Male Sexual Function

A Guide to Clinical Management

SECOND EDITION

Edited by

John J. Mulcahy, MD, PhD

Humana Press

Male Sexual Function

Second Edition

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Preface

The first edition of *Male Sexual Function: A Guide to Clinical Management* was published in 2001. Since that time, two new oral medications for erectile dysfunction (ED), Vardenafil (Levitra®) and Tadalafil (Cialis®), have been introduced.

Links between ED and lower urinary tract symptoms have been postulated, advances in the basic science of erectile physiology have occurred, and the appreciation of ED as a form of endothelial dysfunction and a harbinger of other more potentially lethal forms of vascular disease has become more widespread. In some instances, third-party payers have reduced or eliminated coverage for ED treatments in an attempt to cut costs. They have classified sexual activity as "recreational," "lifestyle," or not medically necessary, but have failed to appreciate the negative consequences of ED, such as depression with all of its ramifications.

Male Sexual Function: A Guide to Clinical Management, Second Edition is a comprehensive overview of the field of male sexual function and includes a chapter on female sexual dysfunction, an emerging field with a very high incidence in the population and an ever-growing following.

The goal is to educate all disciplines in the facts of sexual function and dysfunction in the hope that practitioners will feel comfortable assessing and counseling patients about their sexual needs and concerns and will be able to treat basic problems with easily prescribed therapies and know when and where to refer more complex cases. More money is now spent on advertising ED drugs than any other medical product in the world. Viagra® is the second most recognized product in the world after Coke®. Patients know that treatments are available and, with more openness in discussing sexual matters, are less hesitant to discuss these with their physician. Polls have shown that an overwhelming majority of patients (96%) believe that ED should be treated and 75% feel that physicians should address this area in a comprehensive evaluation. Hence, it behooves practitioners to become familiar with this area and to keep up to date on the latest developments. *Male Sexual Function: A Guide to Clinical Management, Second Edition* should accomplish that goal.

John J. Mulcahy, MD, PhD

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1 Normal Anatomy and Physiology

Paul Milhoua, MD, Daniel Lowe, MD, and Arnold Melman, MD

SUMMARY

This chapter focuses on the human penis and its structure and function. Corporal architecture and vascular anatomy are reviewed in the context of penile physiology and erection. The functional neuroanatomy governing penile erection, flaccidity, emission, and ejaculation is addressed, and attention is given to molecular mechanisms and signal transduction germane to penile erection and flaccidity. Smooth muscle physiology and the major players involved in the regulation of muscle tone are reviewed. This chapter also focuses on the modes of erectile response as well as the relevant central and spinal pathways.

Key Words: Erection; flaccidity; smooth muscle; Rho kinase; Maxi K; nitric oxide; endothelin; norepinephrine.

INTRODUCTION

Normal sexual function in males involves several discrete components: libido, initiating and maintaining erection, orgasm, ejaculation, and the refractory period. The penis is a vascular organ that exists in a continuum from the flaccid to the erect position. Erectile dysfunction is a condition that occurs when penile erection sufficient for vaginal penetration cannot be achieved by normal physiological means. Recent developments in basic science as well as clinical research have led to a better understanding of the physiological mechanisms regulating the erectile function of the penis. Anatomical studies have delineated the veno-occlusive mechanism of the corporal bodies, which is the critical mechanism of restricting blood outflow from the penis. Analysis of corporeal tissue and the use of animal models have further elucidated the mechanisms regulating corporeal smooth muscle tone *(1–4)*.

Penile erection is a neurovascular event that occurs when blood flow to the penis exceeds flow out of the penis. Successful erections depend on precise modulation of neural pathways as well as penile vascular integrity *(1,5–8)*. The relaxation of trabecular smooth muscle results in increased blood flow to the corpora cavernosa, leading to sinusoidal

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expansion. This, in turn, leads to mechanical compression of the emissary veins, thus inhibiting the drainage of blood, which results in an erection *(9)*. Conversely, penile flaccidity results from the release of norepinephrine (NE) from sympathetic nerve terminals and contraction of smooth muscle tissue within the corpora. Corporeal smooth muscle tone is a critical determinant in the control of penile erections *(10,11)*.

Blood flow to the penis is controlled by the autonomic erection center, the source of parasympathetic (S2–S4) and sympathetic (T12–L2) input to the pelvic plexus, as well as the cavernous nerves innervating the trabecular smooth muscle *(11)*. Neural stimulation is transmitted through the Nervi erigentes (i.e., the pelvic autonomic fibers), which release three important neurotransmitters: (a) norepinephrine (sympathetic fibers); (b) acetylcholine (ACh; parasympathetic); and (c) nitric oxide (NO; nonadrenergic–noncholinergic).

High levels of NO within the trabecular smooth muscle results in relaxation. Diffusion of NO through the smooth muscle membrane leads to the activation of guanylate cyclase, which produces cyclic guanosine monophosphate (cGMP). A biochemical cascade results in altered calcium and potassium ion channel permeability; a reduction in cytosolic calcium leads to smooth muscle relaxation and increased blood flow *(12,13)*.

FUNCTIONAL VASCULAR AND MICROSCOPIC ANATOMY OF PENILE ERECTION

Three spongy cylinders comprise the human penis; the paired corpora cavernosa runs dorsolaterally and the corpus spongiosum runs ventrally. Incomplete septa between the corpora cavernosa allow for neurovascular communication, allowing the two bodies to function physiologically and pharmacologically as a single unit. The three corporal bodies are enveloped by a dense fascial structure known as the tunica albuginea. The deep fascia (Buck's fascia) of the penis surrounds the outside of the tunica albuginea and gives off a thin fibrous septum that separates the corpora cavernosa from the corpus spongiosum. Buck's fascia is attached to the perineal membrane proximally; distally, it is tightly attached to the base of glans penis at the coronal sulcus, where it fuses with the end of the corpora. The fascia has a dense structure and is composed of fibers that run longitudinally. It is firmly attached to underlying tunica albuginea and surrounds the deep dorsal vein and the paired dorsal arteries and nerves (*see* Fig. 1).

Surrounding the deep penile fascia is the superficial (Colles') fascia, which is continuous with Scarpa's fascia of the lower abdominal wall and with dartos fascia of the scrotum *(14)*. This fascia is surrounded by skin. The fundiform ligament is the thickening of Colles' fascia, which continues to join the linea alba and splits to surround the body of the penis and then fuses with the septa of the scrotum. Deep to Colles' fascia is the triangular suspensory ligament, which is in continuity with Buck's fascia; its attachment to the pubic bone maintains penile position during erection (*see* Fig. 2).

The proximal penis is anchored to the 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 the perineal nerve). The ischiocavernosus muscles (supplied by the perineal branch of the pudendal nerve) cover the penile crura and proximal part of the penile shaft. These skeletal muscles lie between Colles' and Buck's fascia. The glans penis appears to be spongelike because of a rich venous plexus. It has no fibrous sheath, and it is covered with very thin and firmly adherent skin. A useful mnemonic for the penile layers is ABCD: A = albuginea, B = Buck's fascia, C = Colles' fascia, and D = dermis.

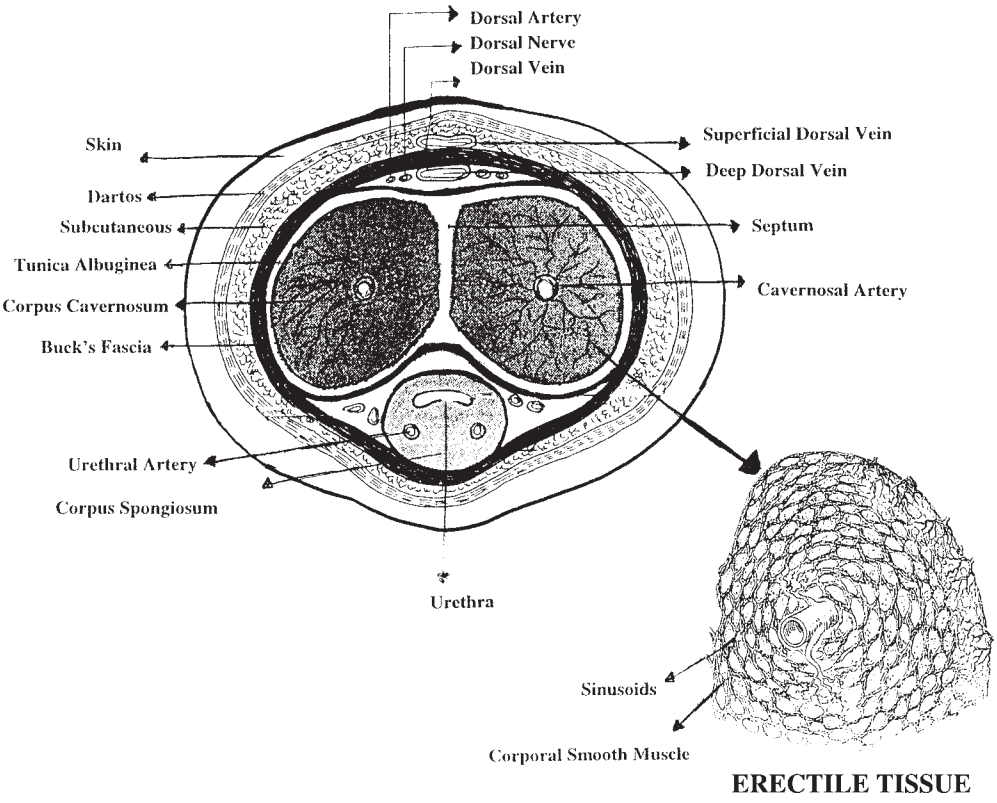

Fig. 1. Schematic representation of a cross-section of the human penis. (Adapted from ref. *282*.)

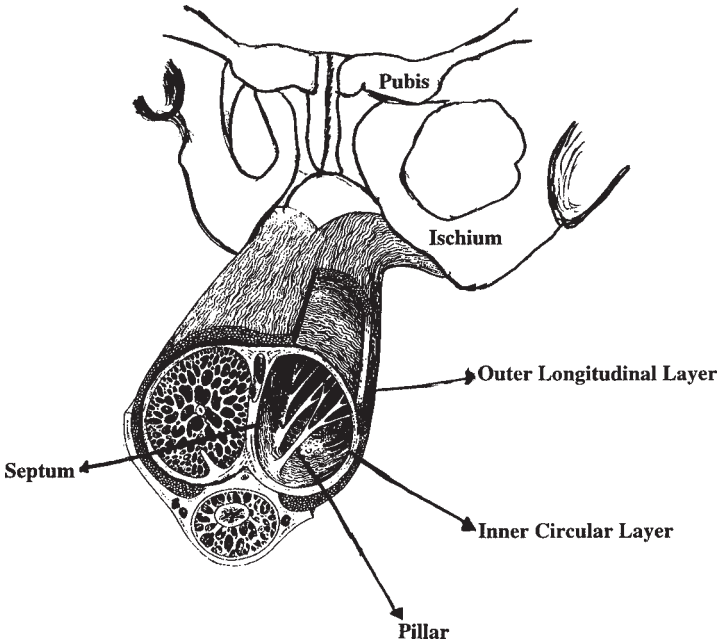

Fig. 2. Schematic representation of a cross-section of the penis that demonstrates the collagen skeleton of the penis. (Adapted from ref. *283*.)

Tunica Albuginea and Fibrous Skeleton of the Penis

The tunica albuginea is composed of elastic fibers forming a tough irregular lattice that is predominantly collagenous (both types I and III), although the detailed histological composition depends on its anatomical location and function *(15)*. In the flaccid state, its average thickness is 2 to 3 mm. The tunica albuginea becomes much thicker ventrally, where it forms the groove to accommodate the corpus spongiosum. Surrounding the corpora cavernosa, the tunica is a bilayered structure. The inner layer is composed of circularly oriented bundles that support and contain the cavernous tissue. Intracavernosal pillars radiate from the inner layer into the corpora and act as struts to support the erectile tissue. The outer layer is oriented longitudinally, extending from the glans penis to the proximal crura, ultimately inserting on the inferior pubic ramus. As the crura diverge proximally, the circular fibers alone provide the support.

The tunica albuginea of the corpus spongiosum is much thinner than that of the corpora cavernosa and contains more elastic fibers. Cadaveric studies have demonstrated that the thinnest portion of the tunica is at the 6 o'clock position over the urethra, which explains the epidemiology of perforation during penile prosthesis implantation. Emissary veins run between the inner and outer bundles obliquely and, therefore, 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. However, dorsal artery branches take a more direct perpendicular route and are protected by compression during erection by a peri-arterial fibrous sheath. The tunica albuginea provides tough uniform backing for engorged sinusoidal spaces.

Corporal Ultrastructure

Cavernosal design provides the penis with flexibility, rigidity, and strength. The cavernosal tissue is spongelike and consists of a meshwork of interconnected cavernosal spaces that are lined by vascular endothelium and separated by trabeculae *(16)*. These structures contain bundles of smooth muscle in a framework of mostly collagen (types I, IV, and, to a lesser extent, type III), elastin, and fibroblasts *(17,18)*. Smooth muscle accounts for 45% of corpora cavernosal volume *(19)*. Alterations in the relative quantities and structure of the cytoskeleton and contractile proteins may be responsible for changes in the active and passive characteristics of penile smooth muscle.

Ultrastructural examination of a smooth muscle cell reveals thin, thick, and intermediate filamentous structures. Thin filaments or light chains are composed primarily of actin (also called LC20 because its molecular weight is 20 kDa). Thick filaments are formed of myosin. Intermediate filaments contain either desmin or vimentin. Each type of filament has a specific function in corporal physiology.

Penile Arterial System

The internal pudendal artery (the terminal branch of the hypogastric artery) is primarily responsible for the blood supply to the deep structures of the penis *(20)*. The internal pudendal runs in a curve along the dorsolateral pelvic sidewall and enters the lesser pelvis through the lesser sciatic notch (*see* Fig. 3A). After entering the ischiorectal fossa, it courses along Alcock's canal along the inferior insertion of the obturator internus muscle. In men, the internal pudendal also gives rise to scrotal and bulbar branches (via the perineal branch) before continuing as the common penile artery. After piercing the urogenital diaphragm, the common penile artery continues along the medial margin of

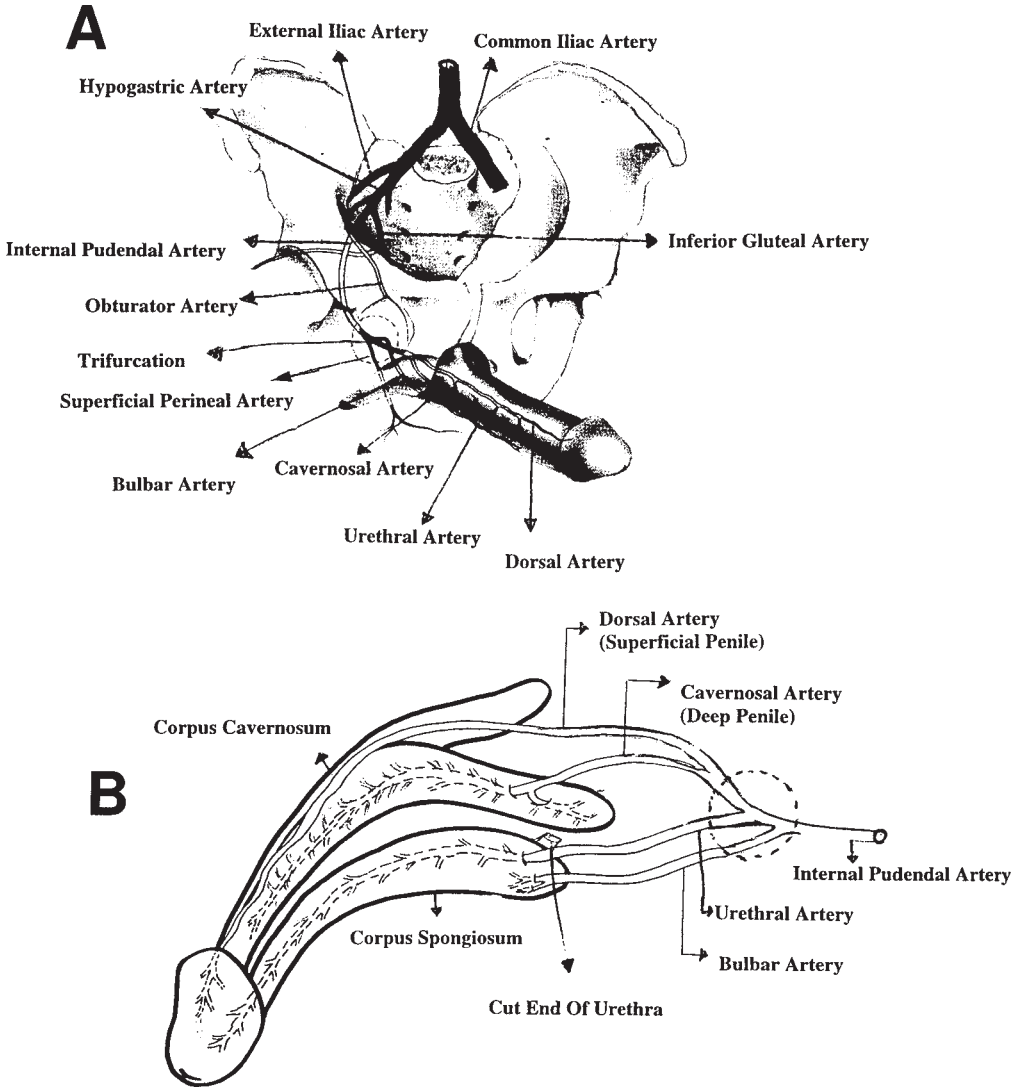

Fig. 3. Schematic representation of the arterial supply to the penis in relationship to **(A)** the bony pelvis and **(B)** the inner portion of the corpora.

the inferior ramus of the pubis. In the anterior perineum near the bulbospongiosus, the penile artery trifurcates; the branches include the bulbo-urethral artery, the cavernous artery (central or deep penile), and the dorsal artery of the penis *(21)*. The glans penis can be separated completely from the corpora cavernosa without compromising blood supply (*see* Fig. 3B).

1. Bulbo-urethral artery. After giving off the bulbar artery, it continues as the urethral artery, which runs on the ventral surface of the corpus spongiosum beneath the tunica albuginea.
2. Dorsal artery. As the termination of the penile artery, it runs over each crus and continues along the dorsolateral surface of the penis distally toward the glans penis. It is situated as part of the neurovascular bundle, lateral to the dorsal vein and medial to the dorsal nerves. The course of the artery is somewhat tortuous; this course accommodates for elongation

Table 1
Penile Arterial System

Penile inflow (arterial)

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) supply smooth muscle and nerve fibers.
- 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.

during erection. This artery gives off circumflex branches to supply the spongiosum before its terminus at the glans. Distally, the dorsal artery runs ventrolaterally near the sulcus before entering the glans. The frenular artery branch of the dorsal artery curves around each side of the distal shaft to enter the frenulum and glans ventrally.

3. Cavernosal artery. The cavernosal artery is responsible for flow to the corporal bodies. It pierces the tunica, entering each cavernosum at the penile hilum, where the two corpora cavernosa come together. It gives off a short branch to the crus and then passes out the cavernous body almost to the tip, running medially toward the midseptum of the cavernous bodies until reaching the distal penis, when it is in the center of the corpus. Two types of branches arise from the cavernosal artery *(22)*. Outer capillaries are responsible for penile nutrition during the flaccid state and supply the smooth muscle and nerve fibers. Inner helicine arteries open directly into cavernous spaces without entering capillaries, which are then emptied into the postcavernous venules. These inner arteries are shaped like corkscrews and allow the penis to elongate and dilate without compromising flow. Multiple layers of smooth muscle surround the helicine branches. This muscle is contracted while flaccid, allowing only small amounts of blood into the lacunar spaces. After the proper stimulus, muscle relaxation occurs and the arteries dilate and straighten, increasing blood flow and pressure to the lacunar spaces *(23)*. Although the cavernosal arteries supply the bulk of the blood delivered to the corpora cavernosa, the dorsal artery contributes to a lesser degree via several circumflex branches to the middorsal corpora cavernosa. Therefore, a bypass into a proximally occluded dorsal penile artery can improve flow into the corpora cavernosa (*see* Table 1).

Anatomical variants are extremely common 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. Iatrogenic

injury to these structures during deep pelvic surgery can lead to vasculogenic erectile dysfunction. Collateral vessels may open in the setting of obstruction, allowing communication between the cavernosal arteries or between cavernosal and dorsal vessels *(24)*.

Penile skin is supplied by the external pudendal artery, a branch of the femoral artery. Each vessel divides to a dorsolateral and ventrolateral branch, which supply the skin of the shaft and prepuce.

Penile Venous System

Corporal Veno-Occlusive Mechanism

There are three sets of veins that drain the penis: superficial, intermediate, and deep systems *(25–28)*. The deep venous system drains both the corpora cavernosa and the corporus spongiosum. The postcavernous 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. 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. This, in turn, 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; therefore, these emissary veins can be easily occluded by the shearing action of the tunical layers during erection (ref. *29*; *see* Fig. 4; Table 2).

FUNCTIONAL NEUROANATOMY OF PENILE FUNCTION

Parasympathetic and Nonadrenergic and Noncholinergic Outflow

Penile Erection

Parasympathetic preganglionic input to the human penis originates in the sacral (S2–S4) spinal cord *(30)*. In most men, S3 is the main source of erectogenic fibers, with a smaller supply provided by 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 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) and are joined by fibers from the inferior hypogastric nerves (sympathetic) to form the pelvic plexus *(31)*. Alternatively known as the inferior hypogastric plexus, these nerves run in the pelvic fascia on the lateral side of the rectum, seminal vesicles, prostate, and posterior bladder. Additional sympathetic contribution arises from the sacral sympathetic chain ganglia via the gray rami.

Not all axons conveyed to 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 in men varies between three and six. The

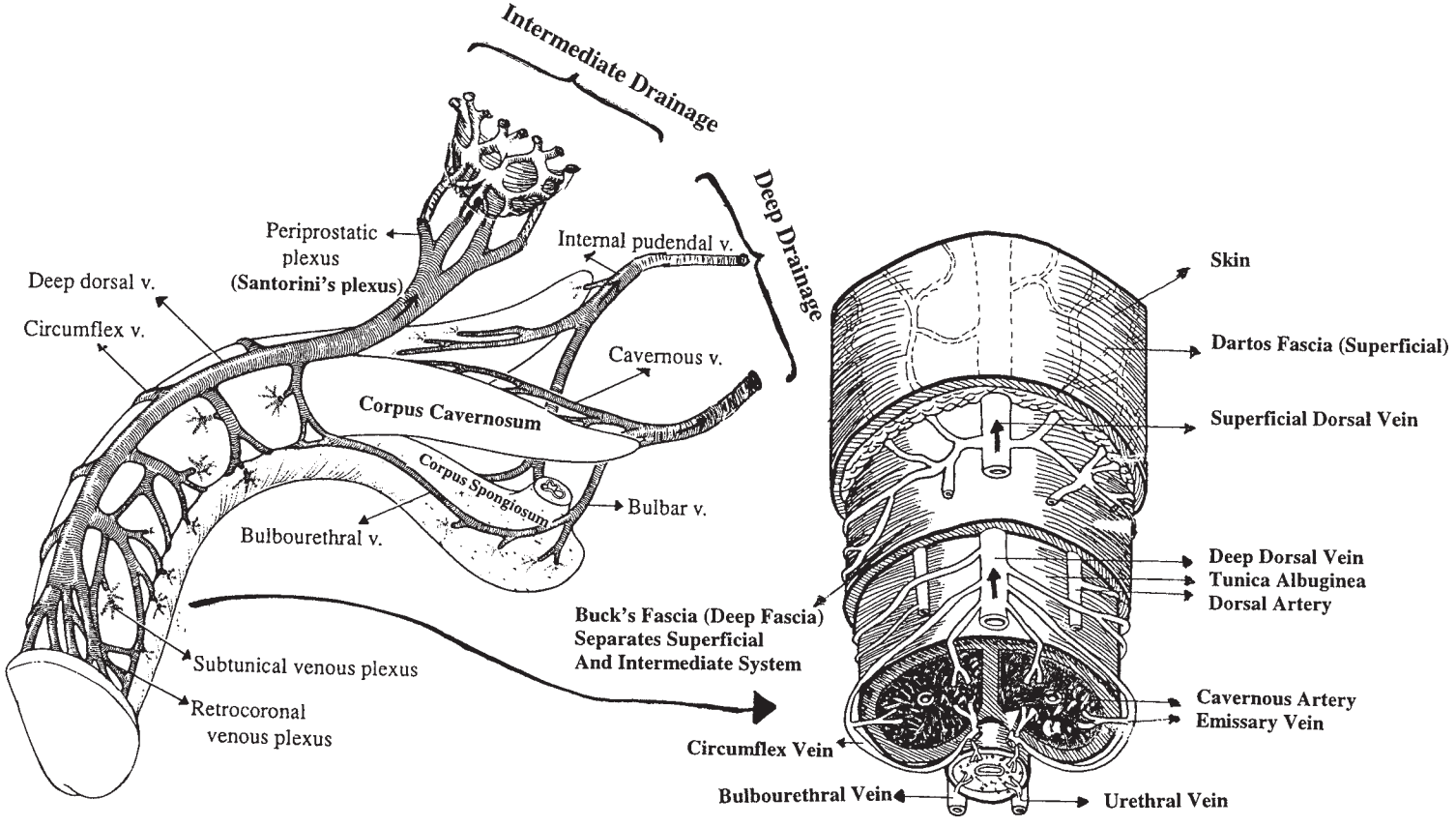

Fig. 4. Schematic representation of the venous drainage of the penis. (Adapted from ref. *282*.)

Table 2
Penile Venous System

Penile outflow (venous)		
Superficial drainage outflow (above Buck's fascia and below Colles's fascia)	*Intermediate drainage outflow: deep dorsal vein and circumflex system (below Buck's fascia and above tunica)*	*Deep drainage outflow: deep penile or cavernous system*
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.

cavernous nerve (parasympathetic and sympathetic postganglionic fibers) leaves the pelvis between the transverse perineal muscles and the membranous urethra, passing between the arch of the pubic bone to supply each corpus cavernosum. The cavernous nerve divides into two branches. One is the lesser cavernous nerve, which supplies the erectile tissue of the corpus spongiosum and the penile urethra. The outer, greater cavernous nerve remains 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 part of the neurovascular bundle of the prostate. After passing the tip of the seminal vesicle and the nerves within the leaves of the lateral endopelvic fascia near its juncture with Denonvilliers' fascia, the cavernous nerve travels at the posterolateral border of the prostate and on the surface of the rectum. Passing posterolaterally to the prostate, the bundle emits 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 *(30,32)*.

Parasympathetic input plays an important role in the case of the prostate, seminal vesicles, vasa deferentia, and bulbo-urethral glands. Parasympathetic efferents stimulate secretion in men from the bulbo-urethral and Littre's glands as well as from the seminal vesicles and prostate *(33)*. Bulbo-urethral and Littre's glands produce mucus, which contributes to penile urethral lubrication. Prostatic and seminal vesicle secretions ensure the viability and motility of the sperm and account for much of the volume of the ejaculate (*see* Table 3).

Table 3
Neuroeffector of Ejaculation

Mechanism	*Autonomic pathway*	*Function*
Afferent		
Touch, vibration, friction	Pudendal center (S2–S4)	Sensory
Efferent		
Secretion	**Parasympathetic center** (S2–S4)	Secretion from prostate, seminal vesicles, ampullary glands, bulbo-urethral 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.

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 spinal 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. The preganglionic fibers leave the cord in the ventral roots of the corresponding spinal nerve, passing via the white rami communicantes to the paravertebral sympathetic chain. At this point, there are two different pathways for axons to reach the penis.

1. Some preganglionic fibers descend to ganglia at a lower lumbar or sacral level and synapse. The fibers then leave the chain at the sacral level and travel through pelvic nerves to the pelvic plexus and cavernous nerve. Alternatively, they travel via the pudendal nerves.
2. Other fibers pass through the corresponding chain ganglia without making synaptic contact and travel in lumbar splanchnic nerves to synapse in the ganglia of the superior hypogastric plexus, or the presacral nerve. This nerve subsequently divides into left and right hypogastric nerves, descending to the inferior hypogastric, or pelvic, plexus. The hypogastric nerves contain postganglionic sympathetic fibers as well as preganglionic nerves, which descend in the pelvis to synapse in the pelvic plexus.

Ejaculation

The process of ejaculation involves two steps: emission and ejaculation proper. Emission consists of the deposition of secretions from the peri-urethral glands, seminal vesicles, and prostate as well as sperm from the vas deferens into the posterior urethra. This results from the rhythmic contraction of smooth muscle in the walls of these organs. The accumulation of this fluid precedes ejaculation proper by 1 to 2 s and provides the sensation of ejaculatory inevitability. Emission is under sympathetic control from the presacral and hypogastric nerves that originate in the T10–L2 spinal cord levels *(33)*. Ejaculation proper (projectile ejaculation) involves sympathetic controlled closure of the bladder neck, the opening of the external urethral sphincter, and contraction of the bulbo-urethral muscles for propulsion of the ejaculate. These are striated muscles innervated by somatic fibers carried in the pudendal nerve. Orgasm can occur despite damage to the sympathetic ganglia; however, it is rarely possible after injury to the pudendal nerve.

Somatosensory Innervation

Pudendal and Dorsal Nerve of Penis

Penile sensation is unique compared to other cutaneous regions. Approximately 80 to 90% of afferent terminals in the glans are free nerve endings, with mostly C or A-δ fibers *(34)*. These sensory fibers belong to spinal segments S2–S4 and travel via the dorsal nerve of the penis, which joins the pudendal nerve *(35)*. The afferent input conveyed from the penile skin, prepuce, and glans through the dorsal nerve is the mechanism responsible for the initiation and maintenance of reflexogenic erections.

The motor neuronal cells of the pudendal nerve form a ventrolateral group in the anterior grey column of S2–S4. The axons of these neurons supply the striated muscles of the penis and perineum. The pudendal nerve leaves the pelvis through the lower part of the greater sciatic foramen and 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 the genitalia, the urogenital diaphragm, and a branch to the spongiosum. The dorsal nerve of the penis runs along the ramus of the ischium, inferior to the pubis with the pudendal artery on the surface of the urogenital diaphragm. It then runs with the dorsal artery, terminating at the glans *(36)*.

Rhythmic movements of the penis are the result of contraction of ischiocavernosus muscles, which compress the crura *(37)*. These periods are brief and are readily observed as rhythmic movements of the penis. It has been suggested that intermittent suprasystolic contraction occurs during pelvic thrusting, when tactile stimulation and friction of the penis triggers the spinal "bulbocavernosus reflex" *(38)*.

PENILE ERECTION AND FLACCIDITY: PHYSIOLOGICAL MECHANISMS

Penile erection is a neurovascular event controlled by corporal smooth muscle tone. In the flaccid state, the corporal smooth muscle of cavernous arteries, helicine arteries, and trabeculae are tonically contracted. This limits the blood flow to the penis at 5 mL/min, which is sufficient for nutritional purposes *(39)*. There are four physiological components necessary to achieve a penile erection:

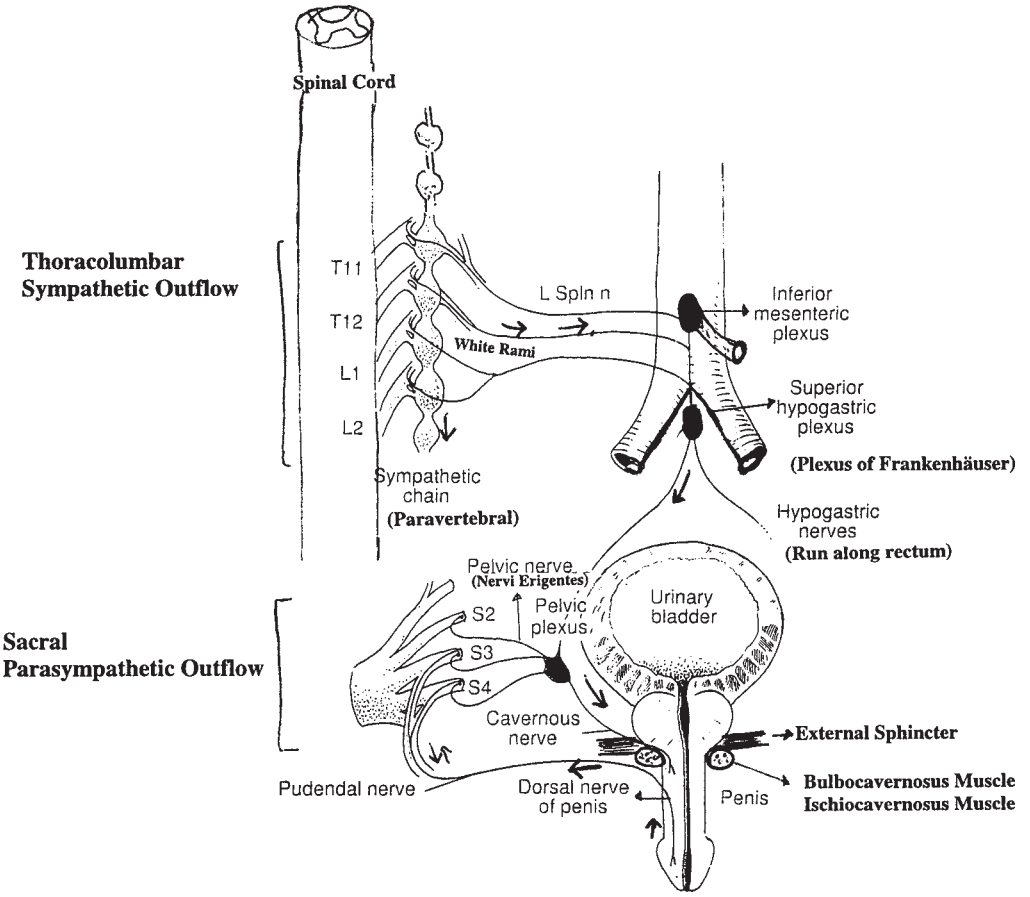

Fig. 5. Schematic representation of neural innervation of the pelvic structures and penile erection.

1. Intact neuronal innervation.
2. Intact arterial supply.
3. Appropriately responsive smooth muscle.
4. Intact veno-occlusive mechanism.

Tactile or psychic stimuli caused by erotic activity initially are processed in the limbic system. The median pre-optic nucleus and the paraventricular nucleus transmit messages coordinated in the midbrain that generate a neuronal signal, which is carried through spinothalamic tracts. The sympathetic signals exit the spinal cord through nerve routes at T11 through L2 to travel via hypogastric nerves. Parasympathetic signals exit at S2 through S4 and travel through the pelvic plexus and cavernous nerve to the penis (*see* Fig. 5). The neural signals cause release of neurotransmitter, which promotes smooth muscle relaxation. The signal that arrives in the penile tissue spreads rapidly through corporal tissue by gap junctions, leading to entire corporal smooth muscle relaxation and expansion of the corporal sinusoids. Corporal smooth muscle relaxation is presumably achieved by a decrease in adrenergic tone, with a simultaneous increase in the release of cholinergic and nonadrenergic, noncholinergic neurotransmitters.

The dilation of cavernosal and helicine arteries is estimated to bring a 5- to 10-fold increase in penile blood flow. This increased inflow of blood temporarily exceeds the

capacity of the veins to drain 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 intercavernous pressure begins to rise. Venules draining the sinusoidal spaces coalesce into a peripheral plexus below the outer fibro-elastic tunica of the corporal bodies. Egress from the subtunical venular plexus occurs via emissary veins exiting obliquely through the bilayer tunica albuginea into the deep dorsal vein in the distal two-thirds and via the short cavernous and crural veins in the proximal one-third of the corporal bodies. As the lacunae fill with blood, expanding sinusoids compress the subtunical venules against the inner layer of tunica albuginea and dampen the drainage of the emissary veins by differential stretching of the two primary layers of the tunica. The increased resistance to venous outflow results in increased turgidity of the corpora (*see* Fig. 6; Table 4).

The unique geometry of the corpora allows for the formation of erection. The following are some of the factors that promote penile rigidity:

1. The intrasinusoidal pressure within the corpora cavernosa distends the tunica albuginea to its maximal capacity.
2. Midline septal fibers are stretched tightly between the dorsal and ventral corpora, thus creating a functional "I-beam" arrangement that accounts for the anteroposterior rigidity of the penis seen with erection.
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. Pressure in the lacunar space during an erection results from the equilibrium between the perfusion pressure in the cavernosal artery and the resistance to blood outflow through the compressed subtunical vessels. Therefore, the penis acts as a reservoir that accumulates blood under pressure. During maximal rigidity, both inflow of blood to and outflow of blood from the corpora cavernosa are practically zero.

Although the glans penis does not have the same hemodynamic structure as the corpora cavernosa, it does experience substantial change in blood flow during erection and detumescence. The glans penis does not possess a tunica albuginea, and the veins draining the glans (the retrocoronal plexus) prevent a pressure rise like that occurring in the shaft of the penis during erection. Blood flow through the glans and corpus spongiosum is increased compared to that in the flaccid penis. The glans maintains a steady and high arterial inflow and venous outflow; therefore, it acts as a large arteriovenous fistula. This enables the glans penis to share in erection but not in rigidity. The deep dorsal vein becomes partially compressed between three expanded corpora and Buck's fascia; this 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 of orgasm and ejaculation. Detumescence is simply a reversal of the events occurring during erection—that is, contraction of the corporal smooth muscle cells and helicine arteries, decrease in arterial blood flow, and resumption of normal venous outflow. Adrenergic nerve activation and release of NE from sympathetic nerve terminals is the primary mediator of this event *(40)*. Norepinephrine has generally been accepted as the principal neurotransmitter in the control of penile flaccidity. However, it has recently been demonstrated that endothelin (ET) may have an important role in the regulation of corporal smooth muscle tone in vivo. Therefore, similarly to erection, the advent of detumescence also may require the concerted efforts of several endogenous substances.

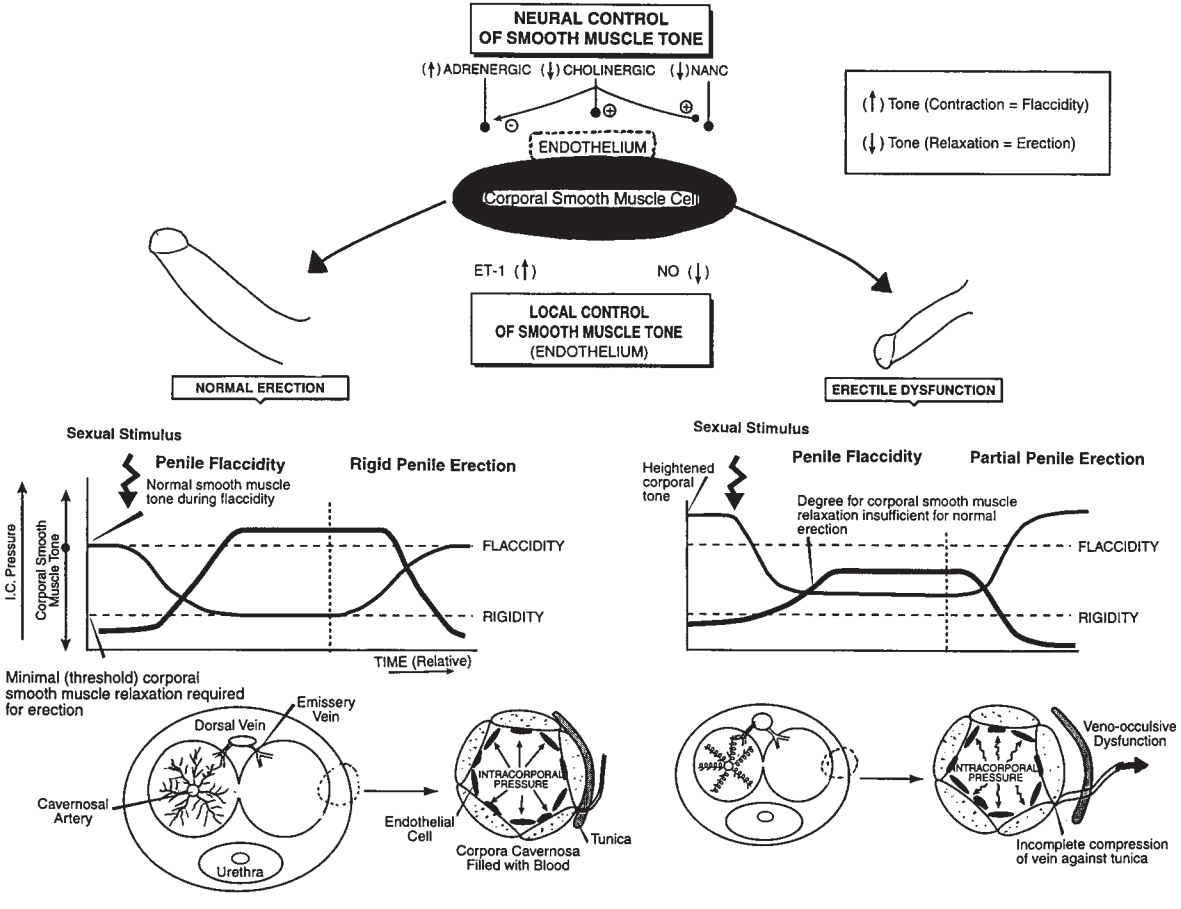

Fig. 6. Mechanism of normal penile erection. Erection is a neurovascular phenomenon initiated by the psychosomatic environment. To obtain penile erection, four physiological events are needed: intact neuronal innervation, intact arterial supply, appropriately responsive corporal smooth muscle and intact veno-occlusive mechanics. Erection involves increased arterial flow, increased venous resistance, and relaxation of sinusoidal spaces. Functional or organic pathologic features at different stages or an individual component will lead to erectile dysfunction.

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 millimeters of mercury for short duration but mainly causes rhythmic movement of the pendulous body of erect penis (throbbing).

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

Ultrastructural examination of a smooth muscle cell reveals thin, intermediate, and thick filaments. Thin filaments are composed of actin; intermediate filaments are composed of desmin or vimentin; and thick filaments are formed of myosin. Each type of filament has a specific function, but the interaction between actin and myosin and their role in smooth muscle contraction and force generation are critically important. The actomyosin cycle begins with phosphorylation of myosin by adenosine triphosphate (ATP), leading to attachments or "cross-bridges" between the regulatory myosin light chain (MLC_{20}) globular heads and actin. These cross-bridges confer contractile tone on the smooth muscle *(41)*. Sustained maintenance of this tone requires a small amount of energy generated from ATP hydrolysis but primarily depends on a high concentration of cytoplasmic free Ca^{2+}.

Modulation of corporal smooth muscle tone is a complex process requiring coordination between a myriad of extracellular signals and intracellular events. Neurotransmitters that participate in erection and detumescence largely modulate smooth muscle tone through their effects on ion channels, activation of downstream second messengers, and gap junctions *(4,42–52)*. The maintenance of adequate calcium homeostasis is extremely important in the regulation of smooth muscle tone. This is achieved by one of three different mechanisms: influx of extracellular Ca^{2+} via voltage-gated channels; activation of membrane-bound receptors, allowing influx of Ca^{2+} through receptor-operated channels; and activation of specific signaling pathways stimulated by the release of Ca^{2+} from the sarcoplasmic reticulum. Initiation, sustained contraction, and modulation of corporal smooth muscle depends on the continuous transmembrane influx of calcium, whereas relaxation (penile erection) is achieved by processes that lower cytosolic calcium.

SMOOTH MUSCLE CONTRACTION AND RELAXATION IS REGULATED BY Ca^{2+}-INDUCED MYOSIN PHOSPHORYLATION AND DEPHOSPHORYLATION

The primary stimulus for corporal smooth muscle contraction (penile flaccidity) again depends on the concentration of intracellular calcium. When the intracellular concentration of calcium increases to 10.5 mol/L, Ca^{2+} forms an active complex with the calcium-

binding protein calmodulin. The Ca^{2+}–calmodulin complex then activates a Ca^{2+}–calmodulin-dependent myosin light chain kinase (MLCK). The activated MLCK phosphorylates the regulatory MLC_{20}, leading to smooth muscle contraction *(53)*. A decrease in intracellular calcium to basal levels (<10.5 mol/L) inactivates MLCK and allows for dephosphorylation of the MLC_{20} by a Ca^{2+}-independent MLC phosphatase, lowering the actin-activated ATPase activity of myosin *(54)*. This allows for the myosin to detach from actin and leads to corporal smooth muscle relaxation (penile erection). It has been demonstrated that activation of both ET-1 and α_1-adrenoreceptors leads to a transient 3- to 10-fold increase in intracellular calcium levels in corporal smooth muscle cells *(44, 55,56)*. Additional mechanisms by which cytoplasmic Ca^{2+} are reduced include cyclic adenosine monophosphate (cAMP) acting through protein kinase A (PKA) and cGMP acting via PKG or directly via activation of potassium channels that lead to cell membrane hyperpolarization. Hyperpolarization prevents the opening of voltage-dependent calcium channels.

Calcium Sensitization and the RhoA/Rho Kinase Pathway

In addition to calcium-dependent mechanisms of activation, recent studies have demonstrated the presence of a calcium-independent pathway that further regulates corporal smooth muscle contraction. Originally described in other smooth muscle types, this process, termed *calcium sensitization*, is regulated by the small, monomeric G protein RhoA and its immediate downstream target Rho-kinase (ROK). Following its activation, ROK inhibits MLC phosphatase (or smooth muscle myosin phosphatase) through phosphorylation of its regulatory subunit (smooth muscle myosin phosphatase-1M), leading to sensitization of myofilaments to Ca^{2+} *(57)*. Both RhoA and ROK have been demonstrated in the corpora of several animal species as well as human corporal tissue *(58,59)*. Furthermore, intracavernosal injection as well as topical application of the ROK inhibitor Y-27632 resulted in an increased erectile response, as demonstrated in an in vivo rat model *(58,60)*. This pathway apparently acts via a NO-independent pathway, because co-administration of NO synthase (NOS) inhibitors to animals injected with Y-27632 did not alter the erectile response. Chitaley et al. *(61)* also demonstrated that transfection of rats with a dominant-negative RhoA enhanced erectile function in rats.

Finally, ROK likely potentiates corporal smooth muscle tone via a common pathway involving ET-1 and noradrenaline-induced vasoconstriction *(62)*. Therefore, agents targeting the RhoA/ROK pathway are potential targets for the treatment of erectile dysfunction.

Second Messenger Signaling (see *Fig. 7; Table 5*)

For corporal smooth muscle relaxation to occur, elevations in both intracellular cAMP and cGMP are important *(4,63–67)*. PKG and PKA activate downstream targets that reduce intracellular calcium levels (Fig. 8). Binding of first messengers to specific receptors on the smooth muscle cell membrane results in the formation of ligand–receptor complexes that interact with downstream G proteins that then stimulate adenylate cyclase. Adenylate cyclase increases intracellular levels of cAMP, which, in turn, activates PKA. Once activated, PKA phosphorylates downstream target proteins, altering their activity. Binding of neuro-effectors, such as prostaglandin E_1 (PGE_1), to their respective receptors leads to activation of the cAMP–adenylate cyclase pathway, as demonstrated by the 3- to 10-fold increase in cAMP levels observed in human corporal smooth muscle cells after activation by PGE_1 *(63)*. Subsequently, cAMP is cleaved back to AMP by the action of

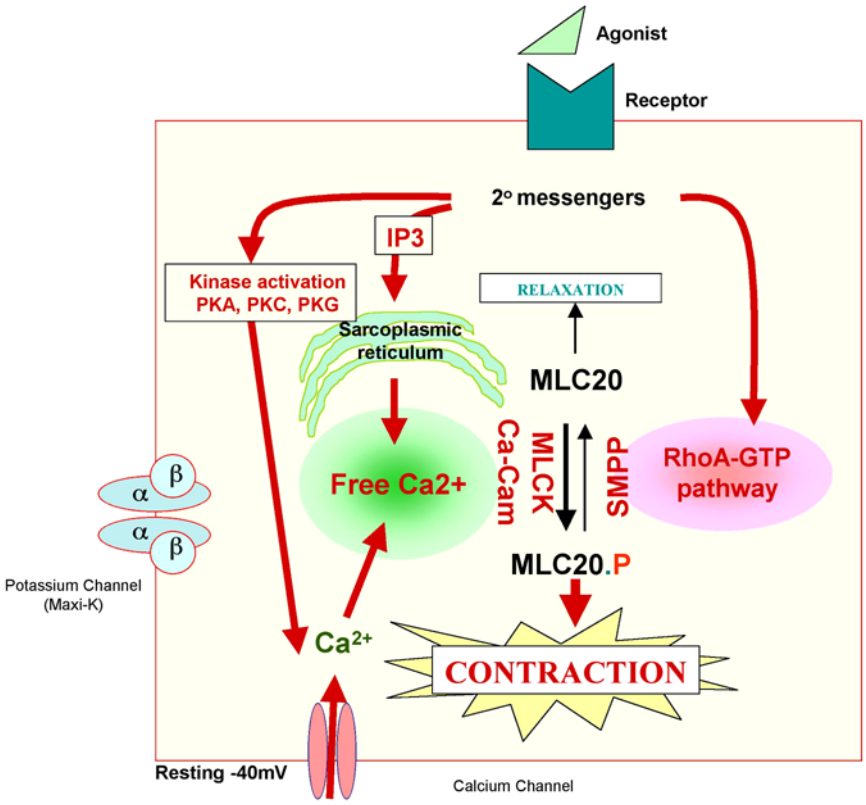

Fig. 7. Major intracellular mechanisms regulating corporal smooth-muscle tone. Pro-contractile ligands (i.e., endothelin-1 and norepinephrine) bind to their respective receptors, leading to activation of second messengers. This leads to the mobilization of calcium via voltage-gated calcium channels and its release from the sarcoplasmic reticulum, resulting in cell membrane depolarization and phosphorylation of MLC20. Corporal smooth muscle relaxation occurs when pro-erectile ligands (i.e., PGE_1) bind to their receptors, or in the case of nitric oxide, diffusion across the cell membrane leads to activation of downstream messengers (PKA, PKG). These molecules lead to corporal smooth muscle cell hyperpolarization and hence relaxation. The effects of second messengers on K channels, Ca^{2+} channels, and gap junctions are thought to be dependent on the phosphorylation of specific amino acid residues within the regulatory elements of these channels. This simplified model illustrates the complex interactions involved in the regulation of corporal smooth muscle tone.

cAMP-binding phosphodiesterases (PDEs). Smooth muscle relaxants such as papaverine exert their effects through inhibition of PDE, thus inducing the accumulation of either cAMP or cGMP, depending on its selectivity *(68)*.

NO acts via guanylate cyclase, which catalyzes the conversion of guanosine triphosphate to cGMP. In turn, cGMP activates PKG, which then phosphorylates downstream targets (e.g., target proteins and ion channels), leading to cell membrane hyperpolarization and corporal smooth muscle relaxation via the opening of potassium channels and thus diminishing intracellular calcium levels by preventing influx and promoting calcium sequestration within the sarcoplasmic reticulum.

Binding of inhibitory ligands (first messengers) to their respective receptors leads to corporal smooth muscle contraction. This occurs via activation of phospholipase C, which generates inositol (1,4,5)-triphosphate (IP_3) and diacylglycerol. Diacylglycerol

Table 5
Primary Effectors of Corporal Smooth Muscle Tone

Neurotransmitter	*Source*	*Receptor*	*Second Messenger*	*CSM Ca^{2+}*	*CSM response*
Norepinephrine (NE)	Adrenergic (NE)	α-Adrenergic (α_1 and α_2)	IP3/DAG/ Ca^{2+}/PKC	Increase	Contraction
Endothelin$_1$ (ET_1)	EC, SMC	$ET_{A,\ B}$	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; EC, endothelial cells; IP3, inositol triphoshate; DAG, diacylglycerol; PKC, protein kinase C; ACH, acetylcholine; CHOL, cholinergic; M, muscarinic; NO, nitric oxide; VIP, vasoactive intestinal polypeptide; PGE_1, prostaglandin E1; NANC, nonadrenergic, noncholinergic; GC, guanylate cyclase; AC, adenylate cyclase; PKA, protein kinase A.

activates PKC, leading to phosphorylation of further downstream targets (e.g., target proteins and ion channels). IP_3 induces the release of calcium from the sarcoplasmic reticulum, leading to corporal smooth muscle cell depolarization and contraction (penile flaccidity). IP_3 also interacts with membrane-bound calcium channels, which further contribute to calcium influx. Several groups have demonstrated that ET and α-adrenergic agents induce smooth muscle contraction via activation of these inhibitory signaling pathways *(8,69–71)*.

Role of Potassium Channels in Corporal Smooth Muscle

Activation of potassium (K^+) channels leads to the efflux of K^+ down its electrochemical gradient, leading to corporal smooth muscle cell hyperpolarization and relaxation. Hyperpolarization results in a decrease in membrane potential (more negative charge) and prevents the opening of L-type voltage-dependent calcium channels *(72)*. Four distinct types of K^+ channels have been identified in corporal smooth muscle: the Ca^{2+}-sensitive potassium (K_{Ca}) channel (e.g., Maxi-K or Slo); the metabolically regulated K_{ATP} channel; the voltage-regulated, delayed rectifier K channel (e.g., K_{DR}); and the fast transient A-type K current *(69,73–75)*.

The Maxi-K and K_{ATP} channels appear to be the most physiologically relevant in modulating human corporal smooth muscle tone. Studies have indicated that the Maxi-K channel mediates the major K^+ current on cultured human and rat corporal smooth muscle cells. The activity of this channel is increased after NOS and cGMP activation, leading to smooth muscle relaxation. Moreover, Maxi-K expression is altered in response to aging and disease-related states, as demonstrated in the rat. Christ et al. *(76)* showed that intracorporal injection of the Maxi-K complementary DNA ameliorated the age-related decrease in erectile function in an in vivo rat model. The same group also demonstrated that Maxi-K/hSlo gene transfer restored erectile capacity in diabetic rats *(77)*. Recent

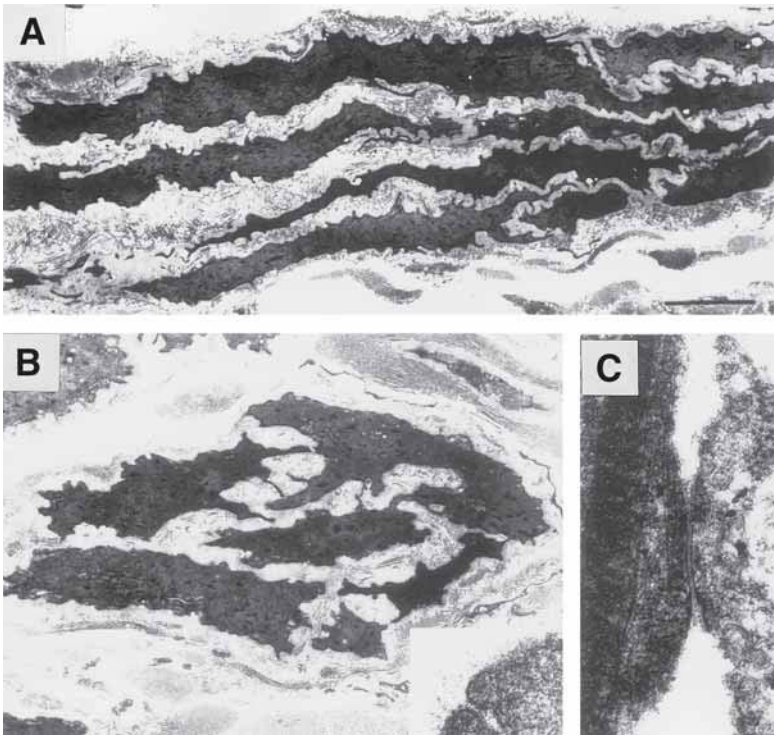

Fig. 8. Electron photomicrographs of the corpora showing the presence of gap junctions. (**A**) Electron micrograph of corpus cavernosum, sectioned longitudinally to show more electron dense smooth muscle cells separated by lighter straining connective tissue. Scale bar = 5 mm. (**B**) Electron micrograph of corpus cavernosum shows region of contact between smooth muscle cells. This region is enlarged in insert to show gap junction. Scale bars represent 5 mm in main portion of **B** and 0.125 mm in insert. (**C**) Electron micrograph of corporeal smooth muscle cells in culture shows larger gap junction between cells. Scale bar = 0.25 mm. (Reproduced with permission from ref. *284*.)

studies have also demonstrated that activation of Na^+/K^+ ATPase by NO is involved in corporal smooth muscle relaxation *(3,78)*. Activation of the Na^+/K^+ ATPase leads to cell membrane hyperpolarization , preventing influx of calcium via voltage-dependent Ca^{2+} channels.

Gap Junctions (Connexins; see *Fig. 8)*

Smooth muscle cell responses are coordinated through gap junctions, which are intercellular communications that allow for the transmission of electrical or chemical signals between adjacent cells (Fig. 8; refs. *43–45, 51, 69, 79,* and *80*). Neighboring cells each contribute a hemichannel (connexon) composed of a hexamer of connexin proteins that constitute the pore-forming units of these aqueous, intercellular channels. Electron microscopic studies have shown that these gap junctions are prominent at areas of membrane apposition between adjacent corporal smooth muscle cells (Fig. 7). Therefore, current-carry-ing ions and second messenger molecules are able to diffuse between adjacent myocytes *(44)*. The connexin family is composed of more than 16 members; however, connexin 43 appears to be the predominant protein found within corporal smooth muscle.

Table 6
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 (PGE_1, PGE_2, PGI_2)

Histological studies on corporal tissue sections have revealed that the autonomic innervation of the human corpus cavernosum consists of widely distributed nerve fibers. Therefore, adjacent myocytes do not receive individual innervation; rather, they are linked by gap junctions that allow for the synchronization of smooth muscle tone. Connexin-43-derived gap junctions appear to modulate the α_1-adrenergic and ET-1-induced contractility as well as NO-induced relaxation responses of corporal smooth muscle *(42)*. Finally, there is significant heterogeneity in connexin 43 expression among corporal tissues excised from patients with organic erectile dysfunction *(81–86)*.

Cholinergic Mechanisms (ACh; see *Fig. 6; Table 6)*

ACh is the main neurotransmitter of the parasympathetic nervous system. For many years, the parasympathetic nervous system was believed to be the sole effector of physiological erections *(87)*; the action of pre- and postganglionic parasympathetic neurons was believed to be mediated in many tissues through the release of ACh *(88)*. However, cholinergic nerve fibers are found in limited numbers within the corpora cavernosa. In humans, intravenous administration or intracavernosal injection of the antimuscarinic blocking agent atropine does not prevent penile erection. In vitro, transmural stimulation of corpus cavernosal strips causes a frequency-dependent neurogenic relaxation that is both resistant to adrenergic and cholinergic blockers and blocked by administration of the neurotoxin tetrodoxin *(89)*. Although cholinergic fibers do not directly mediate relaxation via postjunctional receptors in the corporal smooth muscle, they do act as modulators for other neuroeffector systems. Within the corpus cavernosum, adrenergic nerves receive inhibitory interneuronal modulation from cholinergic nerves. Cholinergic nerves also facilitate nonadrenergic noncholinergic smooth muscle relaxation. Specifically, ACh acting via prejunctional muscarinic receptors inhibits the release of noradrenaline from adrenergic fibers *(90,91)* and facilitates the release of NO from the endothelium via postjunctional muscarinic receptors as well as the release of additional vasoactive peptides.

Nonadrenergic Noncholinergic Nervous System Neuroeffector Systems (Peptidergic, Including Vipergic, and Nitrergic)

The finding that corporal smooth muscle relaxation also occurred in the presence of both parasympathetic and sympathetic blockers led to the search for a nonadrenergic, noncholinergic neurotransmitter responsible for penile erection *(89,92–94)*. This additional pathway is attenuated by pathways interfering with the synthesis and/or the effects of NO.

Immunohistochemical studies have demonstrated the presence of NOS in the autonomic nerves (nitrergic) innervating penile blood vessels and corporal smooth muscle *(95–97)*. The synthesis of NO occurs as a byproduct of the conversion of L-arginine to

L-citrulline by the enzyme NOS. NOS exists as three different isoforms. Neuronal NOS and endothelial NOS are the constitutive isoforms and require calcium and calmodulin for activity. The third isoform, *inducible NOS*, does not require calcium for activation. Notably, NO is not stored in synaptic vesicles within nerve terminals but is synthesized on demand. Therefore, in the flaccid state, NOS activity is minimal.

Experimentally, transmural electrical stimulation of nerves within human corpus cavernosum tissue induces NO production and relaxation *(98,99)*, which are attenuated by the administration of NOS inhibitors. These inhibitors (e.g., NG-nitro-L-arginine) also diminish the erectile response to pelvic nerves in vivo *(95,100,101)*. NO production via neuronal NOS is currently believed to be responsible for the initiation of erection, whereas endothelial NOS facilitates and maintains a full erection. Additionally, recent studies have demonstrated a novel pathway that does not require calcium for NOS activation. In response to shear stress within the penile vasculature, there is activation of phosphatidylinositol-3-kinase, which activates PKB. Once activated, PKB phosphorylates endothelial NOS, leading to the production and release of NO by the endothelium *(102,103)*.

Nitric Oxide

It is well-established that NO is the major regulator of corporal smooth muscle relaxation. This molecule was initially found to be released by endothelial cells and was later found to be synthesized and released by neurons *(104–106)*. These findings have also been demonstrated in the corpus cavernosum *(66,98,107–112)*. Intracavernosal injection of NO donors elicits penile erection in humans *(113–116)*. In vitro, many experiments have shown a relaxant effect of NO on strips of corpora cavernosa and helicine arteries that have been precontracted by noradrenaline *(107,110,117,118)*. Furthermore, smooth muscle relaxation is elicited by NO donors and is inhibited by NO scavengers or NOS inhibitors *(119)*. However, NO activity in response to ACh or bradykinin in penile arteries is only partially reversed following administration of NOS inhibitors. Therefore, the endothelium-relaxing mechanisms appear to differ from those in the corporal smooth muscle.

cGMP is hydrolyzed to GMP by different PDEs, and several PDE isoenzymes (i.e., PDE2, PDE3, PDE4, and PDE5) are localized to the human corpora cavernosum. Some of these PDEs degrade both cGMP and cAMP, whereas others are specific for cGMP or cAMP. Spontaneous contractile activity and noradrenaline-induced contractions are opposed by different PDE inhibitors; quazinone (PDE3 inhibitor) is the most potent. Presently, administration of select PDE inhibitors (i.e., PDE5 inhibitors) is known to facilitate penile erection, an effect expected from a physiological response that depends on the NO–cGMP pathway. Pharmacological inhibition of NOS suppresses penile erection induced by cavernous nerve stimulation in the rat *(95,120)*. NO also mediates ACh- and bradykinin-induced relaxation of corpus cavernosum strips *(90,121)*. Finally, NO-mediated relaxation also appears to be regulated by androgens, because castration reduces NOS expression in the corpora cavernosa of rats *(122,123)*.

NO derived from nitrergic nerve fibers or the endothelium diffuses into adjacent corporal smooth muscle cells *(98,116,121)*, thus activating soluble guanylate cyclase, which results in the generation of cGMP *(107,124)*. As previously mentioned, this cGMP activates second messengers—that is, PKG (or cGK). Following activation, PKG1 (the predominant isoform in smooth muscle) activates K^+ channels and the Na^+/K^+-ATPase pump and inhibits calcium influx, leading to an overall decrease in intracellular calcium

and to corporal smooth muscle relaxation *(4,8,125)*. PKG1 appears to play a critical role in the NO–cGMP pathway, because PKG knockout mice can not obtain normal erections in response to activation of the NO–cGMP pathway *(126)*. Moreover, PKG1 has been shown to phosphorylate and inactivate the RhoA/ROK pathway, providing a regulatory link between these opposing pathways.

Vasoactive Intestinal Polypeptide

Vasoactive intestinal polypeptide (VIP) is a 28-residue polypeptide originally isolated from the porcine gastrointestinal tract. It is a potent vasodilator acting with NO as a possible comediator of penile erection *(127–129)*. This is supported by the observation that a large percentage of corporal trabecular and perivascular nerve fibers stain for both VIP and NOS *(130–132)*. Unlike NO, which acts via cGMP, VIP receptor binding leads to smooth muscle relaxation through an increase in cAMP and PKA activation, resulting in the closure of Ca^+ channels and an opening of K^+ channels *(133)*. Whereas NO is believed to initiate penile erection because of its very short half-life, VIP has been proposed to be responsible for maintenance of relaxation because its half-life lasts 10 min *(134)*. Moreover, conversely to NOS, which has been suggested to be an androgen-dependent neurotransmitter, chemical castration does not influence VIP immunostaining of human corpora cavernosa *(135)*.

VIP fibers also follow the same anatomical course as cholinergic fibers. Cotransmission of VIP and ACh is suggested by the ultrastructural examination of human penile tissue, which demonstrates colocalization of VIP- and ACh-containing vesicles *(136–138)*. Additionally, VIP-induced relaxation is completely abolished by pretreatment with atropine or VIP antibody *(137,139)*. Intracorporal injection of exogenous VIP alone failed to produce erections in many impotent men, indicating that other modulators must be involved in corporal smooth muscle relaxation *(140,141)*. The concentration of VIP has been shown to increase in men during pharmacologically or psychogenically induced erections. Diminished VIP levels may play a role in diabetes- and age-related erectile dysfunction.

Adrenergic Mechanisms

Cavernosal and helicine arteries, as well as corporal smooth muscle cells, receive adrenergic innervation that mediates penile detumescence. Adrenergic fibers outnumber cholinergic nerve fibers within the penis. Penile tissue contains α_1- and α_2-adrenoreceptors. α_1-receptors are the principle mediators of arterial and trabecular smooth muscle contraction; α_2-receptors apparently play a less significant role *(18,21)*. α_1-adrenoreceptors are activated by the local release of noradrenaline (NA or NE) as well as by circulating catecholamines. Recent studies have revealed the presence of multiple α_1-adrenoreceptor subtypes (α_{1A}, α_{1B}, α_{1D}) within human corporal tissue, indicating that NA-induced contraction likely is mediated by more than one receptor subtype *(68,142,143)*. α_{1D} and α_{1A} are the predominant subtypes expressed in the corporal smooth muscle.

Intracavernous drug injection has demonstrated the importance of adrenergic mechanisms in the modulation of penile erection. α-blockers (phenoxybenzamine and phentolamine) induce erection, whereas α-agonists induce shrinkage of both the erect and flaccid penis *(144)*, suggesting that within the flaccid penis, corporal smooth muscle tone is maintained by continuous α-adrenoreceptor stimulation. β-adrenoreceptors also are present within the corpus cavernosum; however, they mediate smooth muscle relaxation and appear to be of little physiological significance *(93)*. Radioligand binding studies have

demonstrated that α-adrenoreceptors outnumber β-adrenoreceptors by roughly 9:1 in corporal smooth muscle cells *(145)*. Furthermore, there is an increase in α-adrenergic tone with aging and disease states *(40)*. Therefore, α-adrenergic vasoconstriction may be the predominant response over β-adrenergic vasodilation resulting from sympathetic nerve stimulation.

α_2-adrenoreceptors (α_{2A}, α_{2B}, α_{2C}) are present on cholinergic nerve terminals in human penile tissue. This is important in maintaining penile flaccidity, because prejunctional NA inhibits nonadrenergic, noncholinergic transmitter release in addition to production of postjunctional vasoconstriction of vascular smooth muscle *(146–148)*. Conversely, activation of muscarinic receptors in addition to α_2-receptors on adrenergic nerve terminals decreases the release of NA in human corporal tissue *(147)*. Therefore, intercommunication exists between adrenergic and cholinergic systems in modulating penile erection.

Finally, α_2-adrenoreceptors distant from adrenergic nerve terminals may be stimulated by circulating catecholamines, suggesting a possible mechanism for impotence associated with high anxiety.

Other Neurotransmitters

Calcitonin gene-related peptide is a potent vasodilator that has been shown to be localized within the cavernous nerves, cavernous arteries, and corporal smooth muscle *(149)*. In sharp contrast to VIP, calcitonin gene-related peptide injection induces a dosage-related increase in penile flow, possibly through the release of NO. Intracavernous injection induces penile erections in humans *(150,151)*.

Neuropeptide Y has both direct and indirect vasoconstrictor actions, and it has been localized with NE in adrenergic postganglionic neurons *(152,153)*. Electrical field stimulation of human cavernosal arteries and corpus cavernosal muscle strips in vitro elicits a biphasic contractile response *(154)*. The second component of the evoked contraction can be abolished adrenergic antagonists; however, the initial contractile component remains refractory, suggesting that contractile neurotransmitters other than noradrenaline are released from these nerve terminals.

Arginine vasopressin contracts human corporal strips and cavernosal artery rings in a concentration-dependent manner. As demonstrated by radio-immunoassay, the concentration of arginine vasopressin is 10-fold higher within human corporal tissue than within plasma.

Substance P has been shown to have an inhibitory effect on cavernosal smooth muscle; however, it is found at smaller concentrations and is localized mainly in the nerves around the corpuscular receptors beneath the epithelium of the glans penis *(138)*.

Angiotensin II has been found within human corpus cavernosum at physiological levels. Moreover, angiotensin II levels are increased during detumescence in humans and have been shown to terminate erections in anesthetized dogs *(155,156)*. Administration of an angiotensin type 1 receptor antagonist was recently shown to restore erectile function in normotensive aged rats, suggesting a role for the renin-angiotensin system in age-related erectile dysfunction *(157)*.

Endothelin-1

ETs are a family of three peptides: ET-1, ET-2, and ET-3. ET-1 is a potent vasoconstrictor and a mitogenic factor that stimulates fibroblasts, smooth muscle, and endothelial cells *(87,116,157–159)*. It is synthesized by the lacunar endothelium and elicits strong,

sustained contractions of the corpus cavernosum smooth muscle in vitro. ET-2 and ET-3 also evoke contractions in corporal smooth muscle; however, they have a lower potency than ET-1 *(160)*. In addition to its vasoconstrictive properties, ET-1 acts as a vasodilator at low doses. ET-3 mainly has vasodilator effects on corporal tissue. This has led to the speculation that ET may contribute to the maintenance of penile flaccidity by providing sustained tone. ET-1-induced contractions are believed to depend on intracellular calcium, whether by influx via voltage-gated or receptor-mediated Ca channels, release from intracellular stores, calcium sensitization, or a combination of these *(161)*. ET also has been shown to potentiate the effect of catecholamines on corporal smooth muscle *(162)*.

Two types of ET receptors have been identified: ET_A and ET_B. ET_A is expressed in the vascular smooth muscle and mediates vasoconstriction, whereas the ET_B receptor predominates in the endothelium and leads to vasodilation via local release of NO *(163)*. Animal studies using ET-selective receptor antagonists have demonstrated enhanced corporal smooth relaxation; however, these agents have failed to show any improvement in erectile response in human clinic trials *(164)*.

Prostanoids

Prostaglandins are synthesized from arachidonic acid via the cyclooxygenase pathway *(65)*. The corpus cavernosum synthesizes PGE (PGE_1 and PGE_2), PGF_{2a}, PGD_2, prostacyclin (PGI_2), and thromboxane A_2. These agents act via G protein-coupled receptors that lead to corporal smooth muscle contraction or relaxation. PGE_1 is the only endogenous prostaglandin shown to elicit human corporal smooth muscle relaxation. However, depending on specific receptor subtype (EP 1–4) interactions, PGE can also lead to smooth muscle constriction. Specifically, the EP_2, EP_{3II}, and EP_4 receptors have been shown to mediate smooth muscle relaxation, whereas the EP_1 and EP_{3I} receptors elicit contraction *(165)*. PGE_1 also acts to inhibit the release of NE by binding to prejunctional EP_3 receptors, thus offsetting corporal sympathetic tone *(140,165)*. Additionally, PGE_1 induces a 3- to 10-fold increase in intracellular cAMP levels *(4,63,166)*, which, in turn, results in the activation of PKA and a decrease in intracellular calcium levels, leading to smooth muscle relaxation *(167)*. Relaxation also occurs through the activation of K_{Ca} channels by PGE_1 via a PKA-mediated mechanism *(168)*.

MODES OF PENILE ERECTION

Penile erections are elicited by local sensory stimulation of the frenulum, glans penis, and perigenital skin (reflexic erections) as well as by central stimuli received by, or generated within, the brain (psychogenic erections). Both types of erectile mechanisms likely act in a synergistic manner and are controlled by the autonomic nervous system (*see* Fig. 6; Table 7).

Reflexic (Spinal) Erection

Reflexic erections are mediated by a spinal reflex pathway whereby sensory information from the penis and genitalia is transmitted by the dorsal nerve of the penis and continues via the pudendal nerve to reach the sacral spinal cord. This constitutes the afferent limb of the sacral reflex arc. The efferent limb arises in the sacral parasympathetic center and contributes fibers to the pelvic nerve, which, in turn, enters the erectile tissue as the cavernosal nerve. These terminal parasympathetic fibers release ACh, VIP, and NO as well as additional vasorelaxant neuropeptides (substance P and calcitonin gene-related peptide).

Table 7
Penile Erectile Reflexes

	Afferents	*Central*	*Efferents*
Reflexogenic			
Tactile stimuli Friction of genitalia	Dorsal nerve of the penis, Pudendal nerve	Spinal (spinal reflex pathway is also modulated by brain, e.g., tactile stimuli ♦ spinothalamic tract ♦ thalamic VLN + ILN ♦ somatic sensory ♦ postcentral gyrus	Pelvic and cavernous N.
Psychogenic			
Special sensory Visual Auditory Olfactory	Thalamic (somatosensory and visual) Rhinencephalon (olfactory)	Supraspinal medial pre-optic area of hypothalamus	Pelvic, hypogastric, and cavernous N.
Psychic Memory Fantasy Construction	Limbic (temporal and frontal lobe) for emotion and memory, Hypothalamic	Paraventricular of hypothalamus	
Sleep erection	Endogenous neurotransmitters	Reticular activating system reticulospinal or spinothalamic ♦	Pelvic, hypogastric, and cavernous N.

Pudendal afferent pathways terminate in the dorsal commissure and medial dorsal horn. In addition to activating the sacral preganglionic neurons that initiate erection, interneurons in these regions presumably are involved in transmitting sensations to the brain and processing supraspinal inputs. The parasympathetic preganglionic neurons are located in the intermediolateral cell column and send dendritic projections to the same regions that receive penile afferent input. Reflexic erections can be observed in men with complete spinal cord lesions above the sacral segments. In such men, there is obviously no sensation; therefore, erection depends on an intact sacral cord mechanism in isolation from the rest of the central nervous system (CNS). Afferent impulses traveling via the dorsal nerve of the penis and pudendal nerve activate spinal interneurons, which then activate preganglionic neurons within the sacral parasympathetic center.

Nocturnal Erections

Multiple areas throughout the brain participate in the sleep–wake cycle. The waking state is maintained by a diffuse collection of neurons within the medulla, pons, midbrain, and diencephalons known as the *reticular activating system*. Electrical stimulation within the reticular activating system leads to a change in electroencephalogram pattern from the sleep state to that of the waking state—that is, cortical arousal. The sleep state does not result from the passive withdrawal of arousal but from two sleep centers that exist

within the brain. One sleep center is responsible for producing slow-wave sleep, whereas the other produces rapid eye movement (REM) sleep.

The slow-wave sleep center is located within the medulla, in a midline area containing the raphe nuclei. Neurons within this nucleus use serotonin (5-hydroxytryptamine [5-HT]) as a neurotransmitter. Administration of 5-HT 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 NE as a neurotransmitter. Lesions within this area eliminate the electrophysiological and behavioral signs of REM sleep. In adults, REM and non-REM sleep alternate through the night. In view of the important role of 5-HT and NE in sleep, it is understandable that drugs may affect the duration and/or content of sleep. Currently, very little is known regarding the neural control of nocturnal penile erection *(169)*. The current opinion is that reduced supraspinal inhibition of the spinal function is partly involved in this process.

Psychogenic (Central) Erection

Erection in response to sexual thoughts or auditory, visual, or olfactory stimuli, without confounding tactile stimulation, occurs in most healthy men and is known as *psychogenic erection (7,33,170)*. Although this response is psychogenic, it appears likely that initiation of an erection also leads a reflexive component through activation of receptors in the penis. These psychogenic erections, initiated supraspinally, are believed to be mediated primarily through the sympathetic thoracolumbar path, with a minor contribution from the sacral parasympathetic system. If the sacral cord is damaged, reflexic erections are lost, but psychogenic erections persist. Although it is generally assumed that the brain exerts both excitatory and inhibitory control on spinal erectile mechanisms, these pathways remain unknown. The finding of increased erections in spinally transected animals has illustrated the inhibitory influence of the brain on spinal mechanisms. 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 the spinal reflex pathways mediating penile erection.

Although the precise anatomic regions are not completely known, it appears that the thalamic nuclei, the rhinencephalon, and the limbic structures play a role in modulating psychogenic penile erections. Messages from these diverse regions are integrated in the medial–pre-optic–anterior hypothalamic area. The limbic system—specifically the cortico–subcortical region—is implicated in the integration of inhibitory and facilitator signals connecting to the medial–pre-optic–anterior hypothalamic area. Efferent pathways from this area enter the medial forebrain bundle (MFB) and then continue caudally into the midbrain segmental region near the lateral part of the substantia nigra. From here, the efferent pathways continue to the ventrolateral part of the pons and medulla, ultimately reaching the spinal centers via the lateral funiculus of the spinal cord.

CENTRAL MECHANISMS OF PENILE ERECTION AND FLACCIDITY

Cerebral Mechanisms

The cortex receives sensory information from the penis and genitalia. Stimulation of thalamic and cortical areas associated with somatomotor pathways elicits sexual feelings

and genital sensations but does not lead to penile erection. Conversely, stimulation of cortical–subcortical areas linked to the limbic system elicit penile erections in response to stimulation, as demonstrated in monkeys *(5,171–173)*. Direct study of the human brain is limited to observations made during neurosurgical procedures. Conversely, stimulation of the amygdala (a limbic structure) can induce erotic emotions similar to those experienced during intercourse. Analogous observations have been made by comparing the experiences of patients suffering from epilepsy with parietal lobe foci to those with mediobasal temporal foci. Animal experiments have shown that damage to the fornix and prefornical area also injures the paraventricular nucleus (PVN) outflow to the MFB, possibly accounting for the impotence associated with these operations.

The current hypothesis of the inhibitory role of the cortex is supported by the findings of hypersexuality and penile erection in the Kluver–Bucy syndrome, resulting from a lesion in the pyriform cortex and amygdaloid complex. The nucleus para gigantocellularis (nPGi) of the brain stem has also been studied for its role in the coordination of erectile control. This region is consistently transneuronally labeled in experiments in which the rat penis is injected with pseudorabies virus *(174,175)*. The nPGi inhibits ejaculatory reflexes, and lesions within this nucleus facilitate copulatory reflexes and male sexual behavior *(176)*. In addition to receiving inputs from the medial pre-optic area (MPOA) and PVN, the nPGi also receives dense projections from the midbrain central gray region *(177–180)*. This region has been demonstrated as an important component in the control of sexual function, and the nPGi likely acts as a relay point for forebrain inputs as they descend to the spinal cord.

The Limbic System

The limbic system has been described inconsistently over recent decades, but there is a general consensus that it includes cortical and subcortical structures. The amygdala, septal nuclei, fornix, thalamus, hypothalamus, and hippocampus are specifically interesting. These structures influence affect, emotional displays, and male sexual behavior *(6,181–187)*. Cortical signals pass through these limbic structures en route to spinal cord targets, thereby adding an additional level of control to penile erections. 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 *(5,173)*. Anecdotal reports from human studies using implanted electrodes have indicated that penile erection may occur in response to stimulation of the MFB or septal region. Thalamic loci induce an ejaculatory response that has been shown to occur independently of erection *(188)*. In neurologically intact men, ejaculation is presumed to involve afferent signals evoked by genital stimulation inputs that reach the thalamus.

Medial Pre-Optic Area

Numerous experiments have shown that the MPOA of the hypothalamus is a key component in the central control of copulatory behavior in male mammals *(189–194)*. Neurotoxin-selective destruction of nerve cell bodies within the MPOA disrupts the male animal's copulatory behavior pattern—that is, mounting and thrusting *(195–198)*—whereas stimulation of the MPOA facilitates male sexual behavior *(189,191,192,199)*. In rats, stimulation of neurons within the MPOA produces rhythmic firing of the perineal muscles in anesthetized animals as well as a rise in intracavernosal pressure *(199)*. The MPOA contains a high density of testosterone receptors *(200)* and has numerous interconnec-

tions with other brain regions, including the limbic system, midbrain, and lower autonomic brain stem nuclei *(177,201–205)*. Therefore, the MPOA is capable of integrating sensory and hormonal signals that initiate sexual reflexes in males. Neuro-anatomical tracing studies have demonstrated that axons exiting the MPOA pass through or terminate in many areas of the brain, including the MFB. Bilateral lesions of the MFB abolish male sexual behavior. Electrical stimulation as well as micro-injection of excitatory amino acids within the MPOA induce rhythmic firing of pudendal motor neurons. Moreover, in conjunction with contralateral MFB lesions, unilateral electrolytic lesions of the MPOA abolish male sexual behavior. This finding of "asymmetrical" damage disrupting male copulatory behavior to the same extent as bilateral lesions to either the MPOA or MFB is consistent with the concept that both of these structures are components of the pathway that regulates male sexual behavior *(176,178–180,205)*. Recent studies have further shown that lesions within the peri-aqueductal gray region block MPOA-induced activation of the ejaculatory response, indicating that these descending pathways pass through, and likely relay within, the peri-aqueductal gray region *(206)*.

Paraventricular Nucleus of the Hypothalamus

Over several recent decades, several groups have contributed to the initial discovery and further characterization of the PVN of the hypothalamus as a sexual response center *(207–212)*. The discovery of a group of oxytocinergic neurons within the PVN was particularly important. In response to sexual stimulation, there is an increase in plasma oxytocin levels, with maximum levels reached at the time of ejaculation. Therefore, oxytocin in the circulation plays a facilitative role in penile erections and male sexual behavior. These oxytocinergic neurons are activated by dopamine, excitatory amino acids (i.e., glutamate), and by oxytocin itself via the NOS pathway *(213,214)*. Dopamine receptor agonists, such as the mixed D1/D2 agonist apomorphine, induce penile erection when injected into the PVN *(210,215)*. These neurons are inhibited by γ-aminobutyric acid (GABA) and opiates that impair erectile function and copulatory behavior. The oxytocinergic fibers run the length of the entire spinal cord, with connections to both sympathetic and parasympathetic targets. These interconnections may account for another aspect of the PVN's role in integrating the neural inputs and outputs that underlie the male sexual response.

Role of the Hippocampus

The hippocampus appears to act in concert with the PVN in the central neural regulation of penile erection. MacLean and Ploog *(207)* found electroencephalographic evidence of an interaction between the hippocampus and its projections to the septum, the MPOA, and thalamus (via the fornix) during experimentally induced erection. Tumescence was frequently associated with after-discharge in the hippocampus, although other areas of the midbrain had been subjected to electrostimulation. During this recorded hippocampal activity, the erections became throbbing in character and reached their maximal size, often waxing and waning in size after discharge for up to 10 min. When certain diencephalic sites were electrostimulated (e.g., the anterior thalamus), erection followed the termination of stimulation rather than occurring with the stimulation. These "rebound" erections were concurrent with hippocampal discharges and provide evidence of the intimate anatomical and functional organization of the inhibitory and excitatory mechanisms involved. Recent investigations have further demonstrated that micro-injection of glutamate receptor agonists within the CA3 hippocampal region leads to a significant

increase in intracavernous pressure in rats, similarly to those occurring after activation of the PVN *(216–218)*.

SPINAL MECHANISMS AND PATHWAYS

The spinal cord is a major site for the regulation of pro- and anti-erectile outflows as well as the coordination of autonomic and somatic pathways. In patients with spinal cord injuries above the sacral segments, erections are triggered via the spinal reflex arc. The patients have poor-quality erections with premature detumescence because of the lack of supraspinal control *(8)*. However, lesions involving the sacral spinal cord, the sacral roots, or the pelvic or pudendal nerves abolish reflexic erections. Psychogenic erections occur in men with complete lesions of the cord as high as T12, suggesting that the sympathetic pathways in these men mediate them.

Additionally, bilateral anterolateral cordotomies in humans result in the complete loss of erectile function and block orgasm-associated sensations. Because touch and two-point discrimination are not altered by this procedure, it appears likely that the erotic quality of genital stimulation depends on the ascending fibers running with the spinothalamic pathways for pain and temperature. In monkeys, electrical stimulation along the course of the spinothalamic pathways at the level of the brain stem elicits erection and ejaculation *(219)*. The relevant fibers could be traced to the caudal thalamic intralaminar nuclei, which may be the receiving area for erotic genital sensation. Stimulation of these nuclei in humans has been reported to cause erotic feelings and orgasm. Under normal conditions, it seems likely that psychogenic and reflexic stimuli act in a synergistic manner to produce erections. Psychogenic erections in paraplegic men are usually short-lived, only partial, and lack the rigidity needed for coitus *(220)*. Further evidence from animal experiments has also shown the presence of an efferent hypothalamospinal pathway running in the dorsal funiculus of the cord *(221)*.

Penile erections remaining after sacral spinal cord lesions or lesions of the pelvic nerve are attributed to sympathetic outflow, suggesting that erections may be elicited by peripheral information integrated at suprasacral levels that activates sympathetic pathways *(222, 223)*. A report of erectile dysfunction caused by lesions of the paravertebral sympathetic chain in humans provides evidence for this hypothesis *(224)*. Furthermore, stimulation of the hypogastric nerve elicits penile erection in patients with spinal cord injury.

PENILE ERECTION AND FLACCIDITY: CENTRAL NEUROPHYSIOLOGY

Table 8 outlines the central neurophysiology of penile erection and flaccidity.

Dopamine

Five dopamine receptor families have been identified (D1–D5). The family of D1 and D2 receptors and their role in the central regulation of penile erection, copulatory behavior, and genital reflexes (with the D2 receptors playing a major role) are particularly interesting *(226)*. Selective D2 agonists cause penile erections that are accompanied by stretch yawning and sedation, which are typical of central dopaminergic stimuli. Moreover, during copulation, studies have shown an increase in the concentration of dopamine within the cerebrospinal fluid. When injected into the cerebral ventricles, the dopamine precursor L-dopa or the mixed D1–D2 receptor agonist apomorphine increased sexual responses in male rats *(227,228)*. Interestingly, low doses of apomorphine facilitate erec-

Table 8
Effects of Central Neurotransmitters on Penile Erection and Sexual Behavior

Transmitters	*Receptor*	*Secondary mediator*	*Pharmacological effect on sexual/erectile behavior*
Dopamine (antipsychotic block D2 receptor)	D_1 D_2	Activate adenylate cyclase (″cAMP♦excitatory) Inhibit adenylate cyclase (∫cAMP♦inhibitory)	Facilitate Facilitate L-DOPA (+) Apomorphine (+)
Epinephrine (found in small neuronal cluster in brain stem especially medulla)	α-1 (Postsynaptic)	″Intracellular ca	Inhibit
Norepinephrine Highest in locus ceruleus rich in β1 β2 receptor that activates adenylate cyclase (excitatory)	α-2 (Pre- and postsynaptic)	Inhibit adenylate cyclase (∫cAMP)	Inhibit Clonidine (+) Yohimbine (−) (Activation of α-2 adrenoreceptor in the MPOA is associated with decrease in sexual behavior)
Serotonin (Found in high concentration in raphe nuclei. Certain antidepressants increase 5HT availability by reducing its uptake)	$5HT_{IA}$ $5HT_{1B}$ $5HT_{1C,2C}$ $5HT_{1D}$ $5HT_2$ $5HT_3$	∫cAMP ∫cAMP ″Phostidylinositol turnover (similar to 5HT1-B) Similar to 5HTC1-C and linked phosphatidyl turnover ″Inflow of Na and Ca	Inhibitory (? facilitatory) 80H-DPAT (+) Inhibit (? facilitate) Facilitatory (direct stimulation of $5HT_{1C\ and\ 2C}$ causes erection) m-CPP/Trazodone (+) Inhibit/facilitate (agonist inhibit erection but facilitate seminal emission and ejaculation) Facilitate/inhibit

Acetylcholine (somatic and visceral nuclei	ACh Nicotinic Muscarinic (M_1–M_3)	Act via G protein	Facilitate
Enkephalins	mu		Inhibit Morphine (+) Naloxone (−) (Inhibitory control on central oxytocinergic transmission)
GABA	$GABA_A$	Open C1 channel	Inhibit Muscimol (+) Bicuculline (−)
	$GABA_B$	⎫Release other neurotransmitter	Inhibit Baclofen (+)
Oxytocin			Facilitate
Prolactin			Inhibit (inhibition of dopaminergic activity in the MPOA)

+, receptor agonist; −, receptor antagonist, L-DOPA, precursor of dopamine; apomorphine, dopamine receptor agonist; 8OH-DPAT, 8 hydroxy-2-(di-*n*-propyl-amino; tetralin, m-CPP, m-chlorophenylpiperazine; GABA, γ-aminobutyric acid; cAMP, cyclic adenosine monophosphate; MPOA, medial pre-optic area.

tions, but higher doses micro-injected within dopaminergic neurons comprising the incertohypothalamic system have been shown to inhibit erections *(215)*. Conversely, lesions within the substantia nigra *(229)* or the administration of dopamine antagonists at doses that do not impair motor function depress the copulatory behavior of male rats *(227)*. The pro-erectile activity of dopaminergic neurons appears to be mediated by the release of oxytocin within the PVN and other areas along the incertohypothalamic pathway. Bilateral lesions of the PVN as well as oxytocin receptor antagonists block the apomorphine-induced erections *(209,230,231)*. Although the exact mechanism of dopaminergic activation of oxytocinergic neurons is not clear, it likely occurs via the NOS pathway.

Serotonin (5-HT)

Seven families of 5-HT receptorsas well as several receptor subtypes (denoted by subscripts A–D) have been identified. 5-HT_3 receptors are unusual because they are coupled to a cation channel, whereas the remaining 5-HT receptor families act via G proteins. There are two serotoninergic paths within the CNS. One pathway originates in the raphe nuclei and has interconnections throughout the brain, whereas the other pathway originates in the brain stem and continues caudally toward the spinal cord. Generally, serotonin acts to depress male sexual behavior. However, peripheral injection of serotonin agonists has been shown to induce tumescence in both humans and rhesus monkeys, likely by stimulation of parasympathetic pathways *(232)*. Therefore, 5-HT compounds appear to have a central inhibitory effect but have a pro-erectile role peripherally that depends specific receptor subtypes.

Micro-injection studies using 5-HT agonists and antagonists have demonstrated that 5-HT_{2c} agonists play a facilitative role that likely is mediated by parasympathetic targets within the spinal cord. Conversely, 5-HT_{1A} receptors have an inhibitory effect on erection and ejaculation, as shown by systemic administration or micro-injection of agonists within the MPOA *(233–237)*. The pro-erectile action of 5-HT may contribute to the induction of priapism in patients treated with the antidepressant trazodone as well as to the noted increase in erectile activity during REM sleep *(238)*.

Evidence for the role of 5-HT in the control of erectile function was first noted from the alteration in sexual function after injection of serotonin within the CNS and from the discovery of areas rich in serotonergic neurons (e.g., the nPGi; refs. *234, 239–241*). As mentioned previously, both facilitative and inhibitory effects have been reported in response to administration of 5-HT, depending on specific receptor subtypes and potential sites of action *(242–245)*. Serotonergic neurons are also found within the intermediate gray matter of the spinal cord and innervate pudendal motor neurons *(246–249)*. Tracing studies have shown that 78% of the ipsilateral cells (15% contralateral) in the nPGi that project to the lumbar cord are immunoreactive for 5-HT *(246,248)*. Intrathecal injection of 5-HT inhibits the urogenital reflex in male rats; however, this is blocked by the preadministration of the 5-HT antagonist methylsergide. Additionally, blockage of descending serotonergic inputs by intrathecal or intracerebroventricular injections of the 5-HT neurotoxin 5,7-dihydroxytryptamine allowed for the urogenital reflex in the nonsignalized male rat *(250)*.

Noradrenaline

Noradrenergic pathways in the brain may exert an inhibitory influence on penile erection. Within the CNS, the most distinct group of noradrenergic neurons is located within

the locus ceruleus. These neurons project through the dorsal noradrenergic bundles to innervate the cortex, cerebellum, and hippocampus. Additional projections travel through the ventral noradrenergic bundles to the hypothalamus, hippocampus, cerebellum, and spinal cord *(251–255)*. Connections between the locus ceruleus and hippocampal formation play an inhibitory role on erection, as demonstrated by electrical stimulation of the locus ceruleus and micro-injection of adrenoreceptor agonists (e.g., NE) within the hippocampus in male rats *(256)*. Additional experiments have demonstrated the presence of α-2a (α_{2a})- and α-2c (α_{2c})-adrenoreceptor subtypes in the sympathetic and parasympathetic preganglionic neurons controlling erection within the rat spinal cord, suggesting that these receptor subtypes play a role in the intraspinal regulation of autonomic outflow *(257)*. α_2-adrenoreceptor agonists such as clonidine inhibit erections, whereas the α_2-receptor antagonist yohimbine increases sexual activity in rats but not in primates. In at least some species, this discrepancy suggests that the male sexual response is tonically inhibited by a central noradrenergic pathway *(258)*. Furthermore, yohimbine increases sexual motivation, likely by blocking the release of NE from presynaptic α_2-receptors.

Endogenous Opioid Peptides and GABA

Administration of opioid receptor agonists to the CNS inhibits—whereas opioid receptor antagonists facilitate—copulatory behavior in male rats *(259)*. Impotence, decreased libido, anorgasmia and the ability to achieve or maintain erection are not uncommon with patients addicted to heroin or methadone *(260,261)*. Spontaneous erections, priapism, and ejaculation occur during withdrawal from narcotics or with the administration of opiate antagonists such as naloxone *(261,262)*. Endogenous opioid production may contribute to impotence *(263)*.

GABA is present at high concentrations within the MPOA in male rats *(264,265)*. This neurotransmitter likely plays an inhibitory role in the control of penile erection. Both $GABA_A$ fibers and $GABA_B$ receptors have been demonstrated in the spinal cord dorsal horn as well as in the vicinity of sacral parasympathetic and bulbocavernosi motor nuclei *(265,266)*. Administration of $GABA_A$ agonists to the CNS reduces apomorphine- and oxytocin-induced erections, whereas $GABA_A$ receptor antagonists facilitate copulatory behavior in rats. Moreover, intrathecal injection of the $GABA_B$ agonist baclofen reduces or abolishes reflexic erections and preserves psychogenic erections in humans. Although the precise mechanism of action remains unknown, activation of $GABA_A$ receptors is believed to inhibit penile erection by reducing the activity of NOS within the oxcytocinergic neurons that mediate penile erection *(267)*. Additionally, the cerebrospinal fluid levels of $GABA_A$ are increased several-fold during the postejaculatory interval, a time when the rats are completely refractory to sexual stimuli *(268)*. GABA has also been shown to have a direct inhibitory effect on sacral preganglionic neurons *(269,270)*. Therefore, it appears that GABA functions as an inhibitory neurotransmitter in the autonomic and somatic reflex pathways involved in erection.

Oxytocin

Micro-injection of oxytocin into the lateral cerebral ventricles, the PVN of the hypothalamus, or the hippocampal formation induces erection *(209,230,231,271)*. Oxytocinergic neurons are found within the descending pathways from the midbrain, brain stem, and spinal autonomic centers. Following sexual activity, serum and cerebrospinal fluid levels of oxytocin are elevated *(260,272)*, suggesting that oxytocin functions as excitatory

transmitter in the control of penile erection within the hypothalamus *(273)*. As mentioned previously, it seems that the activation of oxytocinergic neurons is mediated by the activation of NOS. Studies performed in male rats have shown a concomitant increase in NO within the PVN in rats treated with oxytocin as well as prevention of oxytocin-induced erections by NOS inhibitors *(273)*.

Prolactin

Long-term exposure to elevated prolactin levels suppresses sexual behavior and reduced potency in men. Moreover, prolactin disrupts genital reflexes, leading to decreased frequency of erections in rats *(274,275)*. This reduction in the number of erections is counteracted by spinal transection *(276)*, implying that the disruption of genital reflexes occurs at a supraspinal site. Ultimately, the mechanism through which prolactin inhibits sexual behavior may originate from alterations in brain dopamine levels. Independently of these observations, prolactin may also affect reduction in testosterone levels, which in turn affect neural mechanisms.

Melanocortin System

Melanocortins (MCs) are bio-active peptides that have been shown to play a role in the neural control of penile erection. Derived from the precursor molecule pro-opiomelanocortin, cleavage at several sites within the prohormone results in at least eight distinct peptides. Experiments have demonstrated that intracerebroventricular administration of adrenocorticotropic and α-melanocyte hormones induces penile erection, yawning, and stretching *(277)*. These peptides act via MC receptors, five of which have been identified (MCs 1–5). These receptors are found within the CNS in key areas that regulate erection as well as in the peripheral nervous system (e.g., in the corpus cavernosum and glans penis). Receptor activation leads to an increase in cAMP through the activation of adenylate cyclase. Adrenocorticotropic hormone activates all five MC receptors, whereas α-melanocyte hormone activates all but the MC-2 receptor *(278,279)*. Studies have shown that the pro-erectile function of MCs is mediated by the MC-3 and MC-4 receptors, although it is unclear which is the predominant receptor. Human clinical studies using subcutaneous injection of melatonin-II, a synthetic α-melanocyte hormones analog, or intranasal PT-141 have shown a pro-erectile effect in men with erectile dysfunction of psychogenic and organic origin *(280,281)*.

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2 Epidemiology of Erectile Dysfunction

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Summary

Erectile dysfunction (ED) is a highly prevalent condition among men all over the world. It has a significant negative impact on the quality of life of the patients and their partners. Its prevalence and incidence are associated with aging as well as important comorbidities, such as cardiovascular disease, diabetes, metabolic syndrome, hyperlipidemia, depression, pelvic surgery, side effects of medications, neurological disorders, trauma, symptoms of benign prostate hyperplasia, and psychological and interpersonal problems. Furthermore, lifestyle choices of major public health impact are also associated with ED. These include preventable causes of disease such as obesity, smoking, alcohol abuse, and sedentary lifestyle. Recent studies have revealed that ED is not only a correlate of cardiovascular disease, diabetes, and metabolic syndrome; it is rather an early warning symptom. Studies on treatment-seeking behavior revealed significant barriers to seeking treatment for this condition and its important correlates.

Key Words: Erectile dysfunction; metabolic syndrome; risk factors for endothelial dysfunction; Massachusetts Male Aging Study; global sexual dysfunction.

INTRODUCTION

The treasure of knowledge about the epidemiology of erectile dysfunction (ED) has expanded significantly in the past three decades. Several national and international studies have been performed using population samples that have produced data on the prevalence and incidence of ED. Additionally, large studies have helped in the understanding of the correlates, risk factors, and impact of ED as well as the effect of aging. However, gaps in our knowledge remain in the areas of natural history of ED and risk modification.

PREVALENCE AND INCIDENCE OF ERECTILE DYSFUNCTION

ED is defined by a National Institutes of Health consensus panel as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance *(1)*. Worldwide estimates of ED prevalence range from 2% in men younger than 40 yr to 86% in men 80 yr or older *(2)*. Prins et al. *(2)* systematically reviewed 23 studies (including 15 from Europe, 5 from the United States, 2 from Asia, and 1 from Australia) and reported

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the prevalence of ED in population-based studies. They reported the drawbacks of some studies—namely, prevalence rates without classifying patients with ED into different age groups or without referring to the severity of ED and its nomenclature: mild/partial/minimal, moderate/intermediate, complete/severe. Prevalence rates of ED among specific age groups were not reported in every study. This makes it difficult to draw solid conclusions regarding the prevalence of different degrees of severity of ED among different age groups. ED prevalence and severity increase with age. ED prevalence has been reported as 7% among men aged 18 to 29 yr, 2 to 9% among men aged 30 to 39 yr, 9 to 11% among men aged 40 to 49 yr, 16 to 18% among men aged 50 to 59 yr, 34% among men aged 60 to 69 yr, and 53% among men aged 70 to 80 yr *(2)*.

The large variation in reported prevalence rates reflects differences in methodology, definitions of ED, regional and cultural perceptions of ED, age, and extent of concomitant medical conditions *(2,3)*. Risk factors for ED include aging, comorbid disease, certain medications, obesity, and lifestyle behaviors (e.g., alcohol and tobacco use; ref. *4*). The prevalence of ED is not the same among different countries or continents nor among different ethnic groups. The prevalence rates for mild and severe ED has been reported as 35% in the United States, 26% in Finland, 21% in Italy, 12% in France, and 11% in Spain *(5–9)*. In Malaysia, Low et al. *(8)* reported a difference in the concept of ED and its prevention and treatment among males from three different ethnic groups living in the country (Malay, Chinese, and Indian) without reporting the percentages of each group. Among men consulting for ED in Israel, a multi-ethnic country, 13% were born in Israel, 33% were immigrants from North African (Morocco, Libya, Yemen) or other Middle East countries (Iraq, Iran), and 54% came from North and South America and Europe *(9)*. The Cologne study shows an important difference between an overall ED prevalence of 19.2% among 71.3 to 96% men involved in regular sexual activity and 31.5 to 44% of responders who were dissatisfied with their current sex life *(5)*. The prevalence of ED may be different, depending on the system used to perform the evaluation. ED prevalence has been reported as 12 to 25% on the basis of self-evaluation compared to 19 to 31.6% according to International Index of Erectile Function criteria *(7–9)*.

Although much data exist regarding the prevalence of ED, there is little information regarding the incidence of dropout from treatment programs or discontinuation of follow-up visits. Among 4489 responders in the Cologne study, 46.2% were willing to contribute financially toward the cost of a regular treatment for ED *(5)*. On the other hand, 9 to 25% of sildenafil responders discontinued successful treatment because of medication cost *(10,11)*.

The Massachusetts Male Aging Study (MMAS), the first large-scale, population-based study of ED, found that the prevalence of ED correlated highly with age *(12)*. This study also found that ED correlated with heart disease, hypertension, diabetes, and low levels of high-density lipoprotein cholesterol, independent of age. Using a large claims database of 28 million heath plan members in the United States, Seftel et al. *(13)* found that hypertension, hyperlipidemia, diabetes, and depression were prevalent in men with ED, suggesting that ED shares common etiological risk factors with these comorbidities. Esposito et al. *(14)* showed that lifestyle changes, such as weight loss and increased physical activity, were associated with improvement in sexual function in about one-third of men with ED.

Many of the diseases associated with ED appear to affect the vascular system (e.g., atherosclerosis, hypertension, lipid disorders, myocardial infarction, cerebrovascular accidents, peripheral vascular disease, and diabetes mellitus; refs. *4* and *12*). The erectile

response involves a complex interaction between neurological, vascular, and hormonal processes. Accordingly, disorders that impair processes common to those that underlie the erectile mechanism (e.g., neural transmission, blood flow, or smooth muscle response) may play a role in ED *(4)*. Recently, considerable attention has been given to the correlation between lower urinary tract symptoms (LUTS) and ED *(5,15,16)*. LUTS—frequently caused by benign prostatic hyperplasia—is an aggregate of related voiding symptoms, including urinary frequency, urgency, nocturia, and slow stream. Although the pathophysiological link between LUTS and ED is not understood, the findings from several studies suggest that LUTS is a risk factor for ED, independent of age and other comorbidities *(5,10,17)*.

The Cross-National Survey on Male Health Issues was a population-based, international survey for men regarding their health issues. The study was unique because it primarily measured the prevalence of ED in men who used health care systems. The objectives of the survey were to investigate the prevalence of ED, to evaluate treatment-seeking behaviors among these men, to assess their attitudes toward the condition, and to identify the barriers and motivators of seeking treatment for ED. The treatment-seeking behaviors of men with ED have been reported *(18)*. The results have confirmed other population-based reports that only a minority of men with ED seek treatment. Common barriers to seeking treatment included the belief that the condition would resolve on its own (primarily younger men) and the perception that ED was a normal part of aging (primarily older men). The study also confirmed the association of ED with age, overall health, and comorbidities such as hypertension, hyperlipidemia, diabetes, depression, and LUTS.

Men who currently or formerly suffered from ED comprised 19% of the population in the Cross-National Survey on Male Health study, which is consistent with reports from other population-based surveys*(2,3)*, yielding an overall worldwide prevalence rate of 19%. Age was the primary variable that correlated with ED in this study. Respondents in the oldest age group (70–75 yr) had a 14-fold higher relative risk of experiencing ED than respondents in the youngest age group (20–29 yr). Across the six countries, ED prevalence rates increased from 4 to 6% in men younger than age 40 yr to 39 to 73% in respondents age 70 to 75 yr. These findings are consistent with those from another population-based study *(2)*.

Information on the screening questionnaire allowed the assessment of the correlation between ED and overall health. The results of the analysis showed a significant positive correlation between ED and increasingly poor health, with respondents who reported poor health experiencing a fivefold higher risk for ED than respondents who reported excellent health. The results of the screening analysis showed a significant association between ED and LUTS, which is consistent with findings from other studies. The follow-up questionnaire completed by men who reported ED included several items related to demographics, comorbidities, and medication use. The most frequently reported comorbidities in this sample population of men in the health care system were hypertension and hyperlipidemia. Diabetes was also cited as a frequent comorbidity by a large number of men. These findings are consistent with reports from other population-based surveys *(12, 17,19–21)*. In the MMAS, total serum cholesterol did not correlate with prevalence of ED, but high-density lipoprotein cholesterol was inversely correlated with ED *(12)*. The prevalence of comorbidities for ED in our survey increased with increasing severity of ED when severity was based on either the International Index of Erectile Function or self-report. With the exception of anxiety, depression, and spinal cord injury, the rates of comorbidities increased with age. In our survey of men with ED in six countries, approx

10 to 20% were taking β-blockers. Only a small percentage (2–8%) of men with ED used nitrates for comorbid cardiac disorders, which is important because many men with ED receive phosphodiesterase-5 inhibitors as first-line therapy, and this class of agents is contraindicated with nitrate use. Similarly to all epidemiological studies, there were inherent biases in the survey methodology and data analyses. The analyses performed using the data were *post hoc* and exploratory. As expected, because of the sensitivity of the subject matter and the fact that respondents answered in private and could leave blanks, large amounts of data were missing from the survey.

Results from the Cologne Male Survey of 8000 men in Germany revealed that the prevalence of LUTS was approx 72% in men with ED vs 38% in men without ED (odds ratio: 2.11; ref. *17*). Multivariate analyses showed that the association of LUTS with ED occurred independently of age and other comorbidities such as diabetes, hypertension, and history of pelvic operations. Similarly, the results of the Multinational Survey of the Aging Male, which was conducted on approx 14,000 men in the United States and six European countries (United Kingdom, France, Germany, the Netherlands, Italy, and Spain), found that ED was strongly associated with LUTS severity ($p < 0.001$), independently of age- and vascular-related comorbidities *(15)*.

A noteworthy observation in the Cross-National Survey on Male Health Issues was that the prevalence of comorbidities increased with the severity of ED. This finding, in addition to data showing that ED correlated with overall health, indicates that ED is a prognostic marker of overall health and important diseases. Presentation of diseases such as hypertension, hyperlipidemia, diabetes, depression, and urinary problems should alert the primary care physician, urologist, cardiologist, or endocrinologist to the possibility of ED. For example, practitioners who see men with urinary symptoms have an opportunity to inquire about the possibility of ED, thereby providing a means for overcoming barriers to discussion and treatment. Conversely, the presence of ED should alert practitioners to the likelihood of other common comorbidities. Men with comorbid conditions, such as vascular diseases and LUTS, should be screened for ED, and men with ED should be screened for comorbid conditions. The results from this and similar surveys will improve identification and disease management as well as treatment paradigms for ED.

AGING AND ERECTILE DYSFUNCTION

"A man is as old as his arteries"—Sir William Osler

Because the penis is a vascular organ, it is true that a man is as old as his penis. The classical work by Kinsey *(22)* revealed that aging is a key risk factor for the development of male ED. In his pioneering work, Kinsey showed that the prevalence of ED increased with age from 0.1% at 20 yr to 75% at 80 yr. A half century later, the MMAS *(12)* showed the same trend—namely, the prevalence of ED increased from 39% in men in their 40s to 67% for men in their 70s. Using the same questionnaire as the MMAS study, the Cross-National Epidemiological Study was conducted in four different countries with varying cultures: Brazil, Italy, Japan, and Malaysia *(23)*. The results confirmed the findings of the MMAS with an age-dependent increase in the prevalence of ED in these different countries.

The world is getting older and older, especially in developed countries. Japan is the most aged and still aging country in the world. We see the future of the rest of the world by studying what happens in Japan. The ministry of the Health and Welfare of Japan has

projected that the percentage of the population over 65 yr will represent as much as 20% by the year of 2010. The French, German, and Swedish populations will have a similar distribution based on age by the year 2020. The British and American populations are lagging and, therefore, will not reach 20% of the population over age 65 until the year 2030. Because age has been shown to be a significant risk factor for all types of sexual dysfunction, we anticipate that with the growing population over age 65, there will be an enormous number of patients with either ED or sexual dysfunction *(24)*.

Another key factor is treatment-seeking behavior. The marketing of sildenafil in Japan is a striking example of how aging affects treatment-seeking behavior. Despite the fact that Japan has a significant elderly population, the sales of sildenafil have been disappointing on a per capita basis. Only 800,000 (8%) of the estimated 10,000,000 patients received prescriptions for sildenafil *(23)*. This is especially surprising because neither Caverject nor MUSE® are available in Japan. My colleagues and I *(18)* reported the treatment-seeking behavior in six different countries (the United States, France, Germany, Italy, Spain, and the United Kingdom). They showed that treatment-seeking rate has a peak during middle age, with the exception of in the United States. The most common reason for the older age group to not seek treatment is their impression that "ED is a natural part of aging." Therefore, aging did not directly increase the cost of ED diagnosis and treatment. We have to estimate the cost by combining the age demographics and the treatment-seeking rate in each country or each culture. However, if we manage to eliminate this kind of stigma by educating the medical professionals and the public—especially among the older people—the cost will be much higher.

RISK FACTORS FOR ERECTILE DYSFUNCTION

According to the United Nations, by 2025, there will be more than 356 million men older than age 65 worldwide, an increase of 197 million from the current number. In 1995, the global proportion of men older than age 65 was 4.2%; this is expected to rise to 9.5% by 2025. Because of the correlation between ED and age, global aging will bring an increase in the number of men with ED in the future. ED is commonly associated with aging and age-related health problems, such as vascular, hormonal, neural, psychogenic factors, and side effects of therapeutic drugs. Current data on ED among the healthy population—particularly for physiological and psychosocial variables—is extremely lacking, despite the prevalence and implications of ED on quality of life *(24)*.

ED is common in men with cardiovascular disease and is probably brought about by shared factors that impair the hemodynamic mechanisms *(25,26)*. The majority of patients with ED have at least one significant cardiovascular risk factor (e.g., hypertension, diabetes mellitus, smoking, or hyperlipidemia). Therefore, vasculogenic ED may be the harbinger of a systemic vasculopathic state.

MMAS results showed the age-adjusted probability of the onset of moderate ED increased from 6.7 to 25% as high-density lipoprotein cholesterol decreased from 90 to 30 mg/dL in younger men (40–55 yr) and from 0 to 16% in older men (56–70 yr; refs. *18* and *24*). In the study, heart disease and associated risk factors, hypertension, and low-serum high-density lipoprotein significantly correlated with ED *(25,26)*. Oaks and Moyer reported that 8 to 10% of all untreated hypertensive patients were impotent the time that hypertension was diagnosed *(26a)*. Furthermore, Wabrek and Burchell reported that in a group of 131 men with acute myocardial infarction between ages 31 and 86 yr, 64% were

impotent; additionally, in a study of patients who underwent coronary artery surgery, 57% were mostly impotent *(26b)*. In a study of men in a hypertension center, ED was found to be highly prevalent and severe in men with hypertension *(27)*. Furthermore, ED was found to be a prognostic marker of the complications of hypertension—namely, myocardial infarctions and cerebrovascular accidents *(28)*.

Diabetes is another major illness associated with ED. In the MMAS sample, the age-related probability of complete ED was three times greater in patients with diabetes than in those without diabetes. Other studies using diabetic populations have consistently found a high prevalence of diabetes-related ED, with estimates ranging from 35 to 50% and up to 75%. The prevalence of ED in patients with diabetes has been reported to increase from 15% in men aged 30 to 35 yr to 55% in men aged 60 yr. ED occurs at an earlier age in people with diabetes than in the general population and often follows, or leads to, the diagnosis of either insulin-dependent or non-insulin-dependent diabetes *(24,25)*.

The exact link between ED and depression is not well defined, because its significance is twofold; depression can be both a cause and an effect of ED *(29)*. Depression has numerous ED-correlated symptoms: changes in sleep patterns, decreased interest in and response to pleasurable activities, and anticipation of a negative outcome. However, depression brought on by episodes of ED may perpetuate erectile failure, cause deeper depression, and result in the avoidance of sexual opportunity, even with an effective treatment. In the MMAS study, patients with depression had a 1.82 higher chance of developing ED than patients who did not suffer from depression.

The link between cigarette smoking and ED is not clearly understood *(30–32)*. The MMAS sample did not show a significant difference in cases of ED between current smokers and nonsmokers. However, the association of ED with certain risk factors was greatly amplified in current smokers. According to MMAS data analysis, the age-adjusted probability of complete ED in subjects treated for heart disease was 56% for current smokers compared to 21% for nonsmokers. Furthermore, the Vietnam Experience Study found that the prevalence of ED was 1.5-fold greater in current smokers copared to nonsmokers. A cross-sectional study conducted in Italy comparing nonsmokers and current smokers and exsmokers in 2010 men older than age 18 yr presented an odds ratio of ED of 1.7 and 1.6, respectively. The study also showed that the risk of developing ED is influenced by smoking and that the duration of the habit increases this risk.

Other important factors include heavy alcohol consumption, obesity, and physical activity. Chronic, heavy alcohol consumption may have an irreversible effect on erectile function because of neurological damage; specifically, changes in drinking habits may not influence erectile function. Chronic drug abuse, especially combined with alcohol consumption, can lead to erectile disorders, specifically because of behavioral changes *(32)*. The link between ED and the use of certain medications is underestimated.

A close link exists between ED and pelvic surgery, with rates ranging up to 80%. In this case, radical prostatectomy, cystectomy, and radical pelvic surgery are considered. Transurethral resection of the prostate plays an unclear role *(33)*.

The rise in the prevalence of worldwide ED, coupled with the new high-profile medical treatments, is raising policy issues *(24)*. National health systems that are already underfunded are facing unexpected requests for resources and challenges to current government funding priorities. The wide range of treatment options available since the arrival of new oral drugs effective for the treatment of ED has, above all, re-opened the debate over rationing and funding priorities.

IMPACT OF ERECTILE DYSFUNCTION

ED is highly prevalent, the incidence is strongly age-related, and it is progressive and undertreated *(34)*. The word population is rapidly aging. In 2000, 13% of the world's population was older than 65 yr, and it is estimated that by 2020, this population will increase to 20%. The projections made in 1998—namely, that a fourfold increase in the ED industry would occur by 2002, from about $0.9 to $5 billion—have been proven *(35, 36)*. The impact of a condition with such escalating proportions seems obvious. The economical impact of a medical condition or disease is not limited by the cost of diagnosis and treatment, but it includes the impact on the patient and society in various ways, such as loss of time at work, decreased productivity for the patient, and the effect on the partner, the family, and co-workers. The impact is further confounded by the correlates of ED, which have a high economical impact, such as atherosclerosis, myocardial infarction, hypertension, diabetes mellitus, depression, and conditions of the prostate, such as benign prostatic hyperplasia and cancer of the prostate.

Economical

An attempt was made to estimate the economical impact of ED in the United Kingdom *(24,36)*. In this study (conducted from 1997 to 1998) on the cost of ED in the National Health Service (NHS), it was estimated that £53 million was spent to manage 113,600 patients with ED *(36)*. The main cost driver was outpatient visits, which accounted for 65% of the cost. Drugs accounted for 25% and genito-urinary consultations, and prostheses accounted for only 4% of the cost. It was estimated that the NHS managed 35% of the population with ED. Assuming that this was representative, the total population of individuals in the United Kingdom was estimated to be approximately 325,600. It has been further estimated that these men incur £7.0 million in cost directly attributable to ED (19.63 d/yr to lost work), thus costing the society another £2.2 million in lost gross domestic product. It was concluded that ED imposes a relatively small economical burden on the UK Society (£53 million), of which 83% is borne by the NHS, 13% is borne by patients, and 4% is borne as indirect costs to society resulting from lost productivity. The authors stated that the future burden would depend largely on patient's eligibility to receive treatment under the NHS.

In an attempt to curb expenditure, the NHS imposed prescribing restrictions for ED under Schedule 11. Wilson et al. *(37)* assessed the effect of these restrictions. During the period of the study (1997–2000), a 30% increase in the number of patients (79,800 to 257,984) and a 40% increase in cost (£29.4 million to £73.8 million) were observed. The actual expenditure per patient decreased by 22% from £368 to £286 and the main expenditures were ascribed to specialist consultations (30%) and drug prescriptions (25%). The increased cost mainly resulted from a threefold increase in the number of patients presenting to general practitioners, who then referred patients to specialists because of Schedule 11 restrictions. This led to an increased use of all resources, including sildenafil. The investigators concluded that the cost-effectiveness of transferring prescribing responsibility in cases of severe distress from specialists to general practitioners remained to be determined. In a study on the containment of costs by the implementation of the Department of Health guidelines, following the introduction of sildenafil in Portsmouth and South East Hampshire, researchers observed that specialist care and associated costs fell by 70% in the first year following the introduction of the Department of Health guidelines,

whereas prescribing costs of primary care doubled. Overall costs for providing services in 1999 to 2000 were £232,169 compared to overall costs of £225,108 (uplifted to 1999–2000 values) incurred in 1998 to 1999 *(38)*. These studies indicate that costs can be contained despite the escalation in the number of patients. Potential benefits of the impact of introducing oral treatment for ED have been reported *(39,40)*. Health care systems have generally rejected treatment of ED, despite ignorance regarding the effect of nontreatment *(41,42)*.

Quality of Life

General and disease-specific quality of life in men with diseases such as cancer of the prostate and end-stage renal disease have been evaluated and reported *(43–49)*. In a multicenter European study of men with organic ED, self-administration of intra-urethral prostaglandin E_1 (MUSE) resulted in a 70% improvement in the quality of erections, a 34% improvement in relationships with partners, and statistically significant improvements in personal wellness, contentment, and self-esteem, which translates indirectly to an improvement in quality of life *(50)*. Intracavernosal injection of prostaglandin E_1 also resulted in significant improvement, as measured by the Life Satisfaction Checklist *(51)*. According to the Life Satisfaction Checklist, it was possible to differentiate between patients with organic, psychogenic, and no ED. The study indicated that sexual satisfaction was a major indicator for general life satisfaction. In two further studies of intracavernous injection for ED, a large percentage of patients indicated that treatment improved quality of life *(52,53)*. Most reports from studies on various aspects of quality of life in patients with ED, such as the International Index of Erectile Function (question 13, overall satisfaction with sex life, and question 14, sexual relationship with partner), the Erection Distress Scale, and the Psychlogical General Well-Being Index, showed improvements in quality of life. However, it was unclear why some instruments as measures of self-control and anxiety, such as the Rosenburg Self-Esteem Scale and the Medical Outcome Study, did not detect improvement in quality of life *(54–57)*. Most studies have limited and diverse quality-of-life measurements, but they all support the notion that therapy for ED improves quality of life.

Relationship

Improvement in the quality of life in patients affects their partners. In studies where partners were assessed about their responses, they responded equally as well to treatment and reported significant increases in intercourse frequency, sexual arousal, orgasm, and overall sexual satisfaction *(58)*. The mental and social domains, as measured by the Duke Health Profile, improved significantly after intracavernosal injection of prostaglandin E_1 as treatment for ED *(59)*. A 34% improvement in "relationship with partner" domain was reported in a multicenter European study of 249 men with organic ED who were treated with self-administered transurethral alprostadil *(58)*.

Comorbid Conditions

Comorbid conditions affect erectile function and quality of life negatively, and treatments of these conditions usually improve erectile function and quality of life. Interestingly, symptomatic treatment of ED with sildenafil resulted in an improvement of depression, as measured by depressive scales *(60)*.

In conclusion, ED is a highly prevalent condition, the incidence is strongly associated with age, and it is progressive and undertreated. Although the general impact on a society

is immense, costs may be containable, and the effects on quality of life of patients, their partners, and society are highly favorable.

TREATMENT-SEEKING BEHAVIOR

Behavioral factors significantly influence the behavior of patients with ED as well as their partners. This influence ranges from attitudes toward diagnosis, treatment-seeking behavior, and, ultimately, treatment compliance and dropout. In one study, Althof stated that the high rate of discontinuation for men receiving treatment for ED (50–60%) could not be explained by inefficacy. Althof explored psychological reasons for dropout and proposed seven factors that may explain why men, women, and couples resist continued treatment *(61,62)*. In another study, 30 of 47 patients successfully treated with intercavernous vasoactive agents responded to a self-questionnaire regarding their reasons for dropping out of the program. The authors concluded that discontinuation did not result from treatment-related problems *(63)*.

Another two studies showed a factor that might affect dropout or noncompliance as the tendency to attribute one's problems to external factors (i.e., the partner); therefore, the alleviation of the problem might not be properly attributed to medical intervention *(64,65)*. A Japanese study specifically addressed patient attitudes toward ED treatment through a national mail survey sent to married couples ages 30 to 79 yr. Of the 2034 males and 1820 females who responded to questions about the male's sexuality, 29.9% of males felt they had ED and 30.1% of females felt their husbands had ED. A low percentage of those who responded sought treatment; only 4.8% of male sufferers had consulted a physician. Reasons cited might be include culture ("shyness," "should be covered by insurance," or "not bothered by ED;" ref. *66*).

In a study using questionnaires sent to 108 patients, 100 (93%) responded. Researchers looked at hospital records and data from the survey. Only 32% continued self-injection treatment, about half of those (56%) discontinued within the first year, and patients who stopped therapy were significantly older and had poor initial impressions of therapy. Similarly to other studies, the authors concluded that dropout had little to do with side effects or etiology *(67)*. In a study of 195 men comparing treatment compliance and treatment choice with marital satisfaction using the Maudsley Marital Questionnaire, no differences were found between the four groups tested: patients on intracavernosal injection treatment, patients who dropped out during the trial-dose phase, patients on other treatment, and patients who renounced treatment after first counseling. However, in the patients treated with intracavernosal injections, efficacy was increased by offering information and enabling couple communication *(64)*. Finally, a survey of depressive symptoms in patients presenting with ED suggested that patients suffering from ED who had high depressive scores were more likely to discontinue treatments for ED *(58)*.

In the Cross-National Survey on Male Health Issues *(18,25,65)*, the aim was to describe the motivators and barriers influencing treatment-seeking behavior in men with ED. Screening included 32,644 men. Follow-up questionnaires were completed by 2831 men who suffered from ED. Men were recruited in waiting rooms in general practice offices. Treatment-seeking among men who suffered from ED was highest among Spanish men (48%) and lowest for German and Italian men (27 and 28%, respectively). Rate of current ED medication use among men suffering from ED was quite low across all countries, ranging from only 8% in France and Italy to 14% in the United States.

The top three barriers to seeking ED treatment were the belief that ED was a normal part of aging, the belief that the condition would resolve on its own, and embarrassment. Older men were more likely to view ED as a normal condition, and younger men were more likely to hope that their ED would resolve on its own. Once they perceived an erection problem, men waited many months before seeking treatment, ranging from just over 1 yr in Italy to almost 3 yr in the United Kingdom. Several barriers continue to influence treatment-seeking behavior in men with ED, resulting in low rates of utilization and high rates of dropout for therapies for ED. Further research in this field is urgently necessary.

CONCLUSION

ED is highly prevalent among men, regardless of geography or ethnicity. Its prevalence and incidence are associated with aging, cardiovascular disease, diabetes, hyperlipidemia, lifestyle issues (such as smoking, alcohol abuse, obesity, and sedentary lifestyle), depression, pelvic surgery, neurological disorders, trauma, symptoms of benign prostatic hyperplasia, side effects from medication, and psychological and interpersonal factors. The severity of ED is also a prognostic marker of important medical diseases. ED has a significant negative impact on the quality of life of patients and their partners. Treatment-seeking behavior is influenced negatively by certain barriers, including the belief that ED is a normal part of aging, denial, and embarrassment.

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3 Cardiac Issues Related to Erectile Dysfunction

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SUMMARY

Therapy for erectile dysfunction (ED) has been revolutionized in recent years, since inhibitors of phosphodiesterase-5, such as sildenafil, tadalafil, or vardenafil, were shown to be highly effective in the treatment of ED. Despite theoretical concerns of a reduced tolerance of the myocardium toward ischemia, clinical studies and retrospective analyses did not support an increased cardiac risk with oral treatment of ED. Most importantly, the combination of phosphodiesterase-5 inhibitors with any nitric oxide donor is absolutely contraindicated because of potentially life-threatening hypotension. Before prescribing medication for ED, any patient with cardiovascular disease should be evaluated for a potential risk of a cardiovascular event during sexual activity according to the Princeton Consensus Panel. When a stable cardiac condition can be achieved (low-risk group), oral treatment for ED may be appropriate. On the other hand, a patient presenting with ED should be carefully evaluated regarding cardiovascular risk factors, cardiovascular disease, or other causes of ED, because ED may be a first manifestation of cardiovascular disease. Cardiovascular risk factors should be vigorously treated in these patients.

Key Words: Erectile dysfunction; cardiac disease; phophodiesterae-5 inhibitors; cardiovascular risk factors; sildenafil; vardenafil; tadalafil; nitrates.

INTRODUCTION

In most circumstances, sex is a matter that is near to one's heart; however, when referring to erectile dysfunction (ED), cardiac issues might be similarly important, as reported in an increasing number of epidemiological and clinical studies.

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Table 1
Various Causes for Erectile Dysfunction

Cardiovascular factors	Cardiovascular risk factor: Diabetes mellitus Smoking hypertension Hypercholesterolemia Sedentary lifestyle Obesity Atherosclerosis, vascular surgery Known heart disease
Drug abuse	Alcohol, others
Medical disorders	Renal failure Abnormal liver function Endocrine disorders (hypogonadism, hyperprolactinemia, hypo- and hyperthyroidism) Sickle cell anemia
Neurogenic factors	Neuropathies (diabetes, etc.) Other neurological disorders (spinal cord injury, cerebrovacular insult, multiple sclerosis, nerve damage resulting from prostate surgery, etc.)
Drug treatment (selection)	Thiazide diuretics, spironolactone, digoxin, antidepressants, β-blockers, phenothiazines, carbamazepin, phenytoin, fibrates, (statins), histamine-2-receptor antagonists, allopurinol, indomethacin, tranquilizer, levodopa, chemotherapeutics, and so on
Anatomical–structural abnormalities	Priapism, trauma, and so on
Psychic	Anxiety disorder, depression, problems, or changes in relationship

Generally, ED is a disease of various causes (Table 1). However, from a quantitative perspective, in the majority of cases, ED may be categorized as a primarily vascular disorder *(1)*: Numerous investigations have demonstrated that common risk factors for cardiovascular disease, as well as ischemic heart disease, are associated with ED.

A recent study estimated that 75% of patients attending routine outpatient cardiology visits and suffering from chronic stable coronary artery disease also suffered from ED when evaluated on the basis of a standardized questionnaire *(2)*. The prospective data of the Massachusetts Male Aging Study reported an annual incidence of ED as 2.6 new cases per 100 men (age range: 40–69 yr). In these patients, heart disease, diabetes, and hypertension were identified as major risk factors for ED *(3,4)*. These observations are consistent with various other investigations *(5)*, and a recent study reported a prevalence of 44, 23, 16, 79, and 74% for hypertension, diabetes mellitus, tobacco use, obesity, and elevated low-density lipoprotein levels (>120 mg/dL), respectively, among men with ED.

Consequently, evaluating different diagnostic and therapeutic options of ED in daily practice should be guided by two major questions discussed here:

1. Is the patient presenting with ED a cardiovascular patient; and if so, what does this imply for the medical work-up?
2. What is the adequate recommendation for patients with various types and stages of cardiovascular disease seeking medical help for ED? This question is particularly important with respect to side effects and drug interactions as well as recommendations regarding heart disease and sexual intercourse.

IS THE PATIENT PRESENTING WITH ED A CARDIAC PATIENT?

ED: First Warning Sign of Silent Cardiovascular Disease?

A detailed medical history, including sexual and psychosocial history and an updated list of the medications, should be obtained from any patient seeking help for ED. As mentioned earlier, because of the close association between cardiovascular risk factors and ED, searching for potential cardiovascular disorders in these patients appears worthwhile. In some cases, ED may be a warning sign of silent cardiac disease before symptoms of heart disease are present *(6)*. Among patients with type 2 diabetes mellitus, ED was identified as a highly efficient predictor of silent coronary artery disease apart from traditional risk factors such as smoking, micro-albuminuria, and lipid abnormalities *(7)*. Furthermore, a strong association between endothelial dysfunction of peripheral arteries (measured as vasodilation of the brachial artery) and first symptoms of ED appears to exist even before manifestation of atherosclerotic disease *(8)*. Because endothelial dysfunction generally is supposed to precede the morphological development of atherosclerotic lesions, this association might suggest that the presence of ED can predict the development of atherosclerotic disease in a very early stage of the pathogenesis of atherosclerotic disease. On the other hand, endothelial dysfunction and impaired vascular function may also play a causal role in the development of ED *(9)*.

Notably, a recent retrospective cohort study of more than 24,000 men with and without ED demonstrated a twofold increased risk for acute myocardial infarction among men with ED compared with men without ED after adjustment for age, smoking, obesity, and medication *(10)*. Therefore, detecting the underlying cardiovascular disease in men with ED may bear the potential to treat heart disease or prevent its progression before its clinical manifestation.

If no other obvious cause of ED is present (e.g., structural anatomic disease, hypogonadism, neurological disorders, or prostate surgery), cardiovascular disorders associated with ED should be considered. A complete genitourinary, cardiac/cardiopulmonary exam, including palpation of peripheral pulses, and a neurological exam should be performed. Signs of congestive heart failure, anginal symptoms at rest or after exercise, nonpalpable pulses (Cave–Leriche syndrome) are especially important. It is indispensable to check common atherogenic risk factors—that is, smoking (or history of smoking), diabetes mellitus (fasting blood glucose, hemoglobin A_{1c}), arterial blood pressure, cholesterol (total, low- and high-density lipoprotein fraction), sedentary lifestyle, obesity, and genetic predisposition for atherosclerosis. The patient should always be encouraged to modify his risk profile. A resting electrocardiogram (ECG) should also be recorded. If any of these results are abnormal, a further work-up should be considered (depending on the suspected condition) either by performing an ECG exercise test, Doppler sonographic evaluation of peripheral and carotid/vertebral arteries, or both or by referral to a cardiologist for a detailed examination.

In summary, a patient with ED should be carefully evaluated for potential cardiac or vascular disease and cardiovascular risk factors, because this may initiate adequate treatment for serious conditions before clinical manifestation and may also have special implications for treatment options of ED.

Treating Risk Factors: Treatment of ED?

Because cardiovascular risk factors are closely associated with ED, it is reasonable to conclude that modifying risk factors could favorably influence the severity or progression of ED or even result in reversal of ED. For most of the risk factors, this very suggestive hypothesis has not been conclusively proven. Nonetheless, the potential link between modifiable risk factors and ED should be brought to the patient's attention, which, in some cases, may be a more convincing motivation to reduce the cardiovascular risk profile than the (sometimes) abstract association between cardiovascular disease and risk factors *(11–13)*.

The following sections summarize some findings regarding risk factors and their influence on ED that could be a basis for a discussion with the patient, because the majority of studies suggest that progression of ED can at least be attenuated by risk factor modification.

Smoking

In several investigations, the risk of ED in smokers was reported to be increased 1.5- to 2-fold compared with that of nonsmokers *(14,15)*. Endothelial dysfunction, an early manifestation of arterial disease in smokers, appears to be a potential link in terms of pathogenesis *(12,13)*.

Interestingly, epidemiological data comparing individuals that had never smoked to former smokers *(14)* reported no difference in the prevalence of ED between these two groups, suggesting that cessation of tobacco use could result in reversal of ED. The exception to this finding came from a study in Italy in which the statistical risk of ED among current smokers and ex-smokers did not differ when compared with individuals who had never smoked *(16)*.

Based on the epidemiological data, every patient with ED should be strongly encouraged to quit smoking, even if it is not irrefutably proven that smoking cessation as a therapeutic intervention can completely reverse already established ED. Nonetheless, progression of the vascular pathogenetic process can be attenuated to increasing the chance of successful treatment of ED.

Diabetes Mellitus

ED is a well-known problem in patients with diabetes mellitus, partly because of microvascular, as well as macrovascular and neuropathic, alterations *(17)*. Notably, a patient presenting with ED should be evaluated for potential diabetes *(18)*. In most cases, measurement of fasting blood glucose and hemoglobin A_{1c} should be performed. When the diagnosis of diabetes mellitus is made, the therapeutic goal is effective control of blood glucose. However, this goal must be emphasized even more vigorously in the context of ED, because a very close association exists between glycemic control (measured as hemoglobin A_{1c}) and prevalence of ED *(19)*. In patients with other risk factors or metabolic syndrome, this also means effective control of hypertension, weight loss, and physical activity besides blood glucose control.

Table 2
Erectile Dysfunction as a Potential Side Effect of Medication and Alternative Drugs

Drug class	*Potential alternative*	*Comment*
Thiazide diuretics	Loop diuretics	Thiazide diuretics: higher incidence of erectile dysfunction than β-blockers
Aldosterone antagonists (spironolactone)	As diuretics: *see* above For treatment of congestive heart failure? (Eplerenone?)	Limited information
β-blocking agents	Angiotensin-converting enzyme inhibitors, calcium channel blockers, α-adrenergic blockers	Prognostic benefit after myocardial infarction or in heart failure must be weighed against side effects
Fibrates	Statins	
Angiotensin-converting enzyme inhibitors	Angiotensin receptor blockers	Angiotensin receptor blockers may even slightly improve sexual function.

Some of the alternatives may not be applicable in individual patients.

Hypertension

Another, very frequent risk factor for cardiovascular disease and ED is arterial hypertension. Therefore, (repeated) measurement of arterial blood pressure is part of the initial evaluation of a patient presenting with ED. It is not easy to investigate whether treatment of arterial hypertension can also reduce the risk of ED, prevent deterioration of sexual dysfunction, or even reverse it, because many antihypertensive drugs (*see* Table 2) are reported to induce some degree of ED as a drug-specific side effect. Nonetheless, effective blood pressure control should be achieved in these patients using the broad spectrum of available antihypertensive drugs according to respective guidelines and giving special attention to accompanying diseases. Potential concerns that these drugs might worsen the problem of ED should not result in discontinuation of effective blood pressure control.

The variety of available antihypertensive drugs offers sufficient choices to find a regimen that is effective and also has minimal (side) effects on sexual function. Table 2 summarizes some alternatives when modifying antihypertensive therapy and choosing appropriate substances for the individual patient. Thiazide diuretics are reported to be associated with a higher percentage of ED than β-blocking agents, the most commonly mentioned drugs in this context. Unlike angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists even appear to slightly improve sexual function. Generally, calcium antagonists are associated with a very low incidence of ED, but they may sometimes increase prolactin levels, which could result in ED *(20–23)*.

Lipid Disorders, Physical Exercise, Obesity, Lifestyle

Cholesterol-lowering interventions and treatment of hyperlipidemia can reasonably be expected to attenuate progression and deterioration of the vascular process involved in the development of ED. A recent study evaluating treatment with atorvastatin in 18 males suffering from ED with hypercholesterolemia as the only cardiovascular risk factor

reported that lipid-lowering therapy had already improved sexual function after a mean of 3.7 mo *(24)*. Furthermore, some evidence exists that statines may be more appropriate than fibrates, which, in some cases, also induce ED.

Additionally, Derby et al. *(25)* suggested that modification of lifestyle (especially regular physical exercise, weight loss, reduction of alcohol consumption, etc.) is most likely to have favorable impact on treatment of ED. A study in Italy suggested improvement of sexual function in about 33% of subjects after reduction of body mass index from 36.9 to 31.2 kg/m^2 resulting from reduction of caloric intake and physical exercise *(26)*. However, it was also emphasized that lifestyle modifications should be initiated as early as possible, because changes after atherosclerosis had already developed were too late to effectively reduce the risk of ED.

WHAT IS THE ADEQUATE RECOMMENDATION FOR PATIENTS WITH CARDIOVASCULAR DISEASE SEEKING TREATMENT FOR ED?

Sexual Activity: A Risk Factor for a Cardiac Event?

Statistical Perspective

For the patient suffering from heart disease or myocardial infarction, sexual activity may significantly contribute to quality of life. However, there is substantial uncertainty among patients and doctors regarding whether sexual activity in different cardiac conditions and stages of heart disease can be safely recommended. Therefore, a cardiac patient asking for treatment options for ED, who may have not been sexually active for a certain period of time, needs a competent and realistic estimate of a potential risk of a cardiac event related to sexual intercourse.

Generally, every patient should be given an individualized estimate and recommendation depending on the cardiac (and other) medical condition(s) (*see* section on Risk Stratification of Patients With Cardiovascular Disease According to the Princeton Consensus Panel).

For a nonselected population, currently available data suggest that the risk of myocardial infarction and sudden cardiac death during sexual intercourse (the so-called "coition-induced death") is very low. Fewer than 1% of myocardial infarctions occur during sexual intercourse, and only about 0.6% of sudden cardiac deaths may be related to sexual activity *(27)*. Nonetheless, sexual activity, even if associated with a very low absolute risk, is an established trigger of myocardial infarction *(28)*. Although a 50-yr-old man in the United States is considered to have a baseline risk of myocardial infarction of 1.00% per year, this increases to 1.01% as a consequence of sexual activity. For patients with prior myocardial infarction, the risk may increase to 1.10%.

Muller et al. *(29)* estimated the relative risk of myocardial infarction occurring during and within a 2-h period after sexual intercourse by comparing it to the baseline risk using crossover statistics. Coition-induced myocardial infarction appeared to be associated with a relative risk of 2.5 compared with that of nonsexual activities. Importantly, the relative risk in patients with known cardiac disease was similar (relative risk: 2.1). Interestingly, regular physical activity and risk factor modification may further reduce the risk *(30,31)*. Patients with ischemic heart disease who have undergone successful revascularization (percutaneous transluminal angioplasty or coronary artery bypass surgery) are generally not exposed to an increased risk of myocardial infarction during sexual intercourse compared to the general population *(32)*.

Energy Expenditure During Sexual Activity

Physical activity is regarded as a trigger of cardiac events in susceptible patients *(33)*. With respect to the cardiovascular system, sexual intercourse can be regarded as physical activity, which is not decisively different from other physical exercise in daily life. Therefore, metabolic expenditures during sexual activities may be used to estimate the cardiovascular risk of sexual activity.

Although energy expenditures during sexual intercourse may vary depending on many individual variables, Bohlen et al. *(34)* obtained estimates in a laboratory setting using the metabolic equivalent of energy expenditure (MET) at the resting state (3.5 mL/kg/min of oxygen consumption) as a quantitative parameter. Healthy males attained 2.5 to 3.3 METs during sexual stimulation and orgasm, with some variability (range: 2.0–5.4 METs). Compared with daily activities, 3 METs may be said to equal briskly climbing two flights of stairs, and 5 METs may be equivalent to digging in the garden. Peak heart rate during sexual intercourse ranged between 110 and 127 bpm in these individuals *(34)*.

A possible conclusion derived from these measurements might be that a patient who is able to achieve 5 to 6 METs during exercise testing without signs of ischemia or major arrhythmia may not be at excess risk for a cardiac event during sex. Effort-induced triggering of myocardial infarction is generally believed to be reduced by optimized medical treatment using aspirin, β-blockers, and lipid-lowering strategies *(35,36)*. Additionally, (potentionally unfounded) concerns or fears regarding his cardiovascular risk during sexual intercourse may be dispelled by explaining these facts and performing an exercise test.

Risk Stratification of Patients With Cardiovascular Disease According to the Princeton Consensus Panel

Even if the absolute risk of a cardiac event associated with sexual intercourse is low, advising the patient of whether sexual activity can be safely recommended should be individualized for patients with cardiovascular diseases. The guidelines issued in 2000 by the Princeton Consensus Panel appear to be helpful for both the patient with cardiovascular disease and the physician asked to provide adequate counseling. Furthermore, updated guidelines (Princeton II) were issued in 2005 *(28)*. Because effective oral medication for treatment of ED—namely phosphodiesterase (PDE)-5 inhibitors—has become available and the physician will be asked by an increasing number of patients for these medications, the doctor should review the Princeton Guidelines and adapt them to the individual situation before prescribing these drugs. Additionally, specific attention must be given to potential side effects of the specific agent, accompanying medication for drug interactions, and specific recommendations for the use of these drugs (*see* "Cardiovascular Side Effects: Theory or Clinically Relevant?" e.g., detailed guidelines for the use of sildenafil; *see also* ref. *37*).

The Princeton Consensus Panel suggested a risk stratification of the individual patient by dividing patients with cardiovascular disease into three groups: high risk, intermediate or indetermined risk, and low risk (ref. *28*; Table 3).

Low-Risk Group

The low-risk group comprises all cardiovascular patients that have achieved a stable cardiac condition, either accomplished under medical control, after successful surgery or percutaneous interventions, or both (Table 3). Consequently, patients with fewer than

Table 3
Three Risk Groups of Patients With Cardiovascular Disease According to the Princeton Consensus Panel

Low-risk group
Patients:
with two or less atherogenic risk factors
with medically controlled hypertension
with mild, stable angina (consider exercise test in some cases)
after successful coronary revascularization (without remaining ischemia)
after uncomplicated myocardial infartion[a]
with mild valvular disease
with congestive heart failure: (New York Heart Association I)
Intermediate- or undetermined-risk group
Patients with:
three or more atherogenic risk factors
moderate, stable angina
myocardial infarction (2–6 wk after the acute event)[a]
congestive heart failure: (New York Heart Association II)
stroke, peripheral vascular disease
High-risk group:
Patients with:
unstable angina /refractory angina
uncontrolled arterial hypertension
congestive heart failure (New York Heart Association III–IV)
myocardial infarction (within the last 2 wk)[a]
recent stroke
moderate-to-severe valvular heart disease or hypertrophic obstructive cardiomyopathy
high-risk arrhythmia

[a]For most oral treatment options for erectile dysfunction, a period of 90 d or more after myocardial infarction is suggested.

Modified from ref. *28*.

three cardiovascular risk factors, with controlled arterial hypertension or mild stable angina pectoris, belong to this group. In most cases, for patients with stable angina pectoris, an exercise test should be performed to determine whether physical activity at a level equivalent 3 to 5 METs is possible without symptoms or signs of ischemia (on ECG). When considering PDE-5 inhibitors for treatment of ED, it is absolutely necessary to achieve this level of ischemia-free exercise without use of nitrates (because of potentially life-threatening drug interaction between PDE-5 inhibitors and nitrates; *see* section on Effects in the Cardiovascular System). A few other drug interactions are considered for PDE-5 inhibitors and patients on antihypertensive medication (*see* section on Effects in the Cardiovascular System).

The same guidelines are true for patients after successful revascularization (i.e., percutaneous coronary angioplasty or coronary artery bypass surgery). They should capable of exercise without signs of ischemia at a level of at least 3 to 5 METs. Patients with mild valvular heart disease or mild congestive heart failure (according to New York Heart Association I) are also considered to be at low risk. The Princeton Consensus Panel suggested that patients at a period of 6 wk after uncomplicated myocardial infarction might also be considered as low risk. However, for most options of oral therapy for ED—

particularly PDE-5 inhibitors—a period of 90 d after myocardial infarction should elapse before these drugs can be recommended according to some reports *(37)*.

Patients in the low-risk group may engage in sexual activity and should be assured about the very low risk of a cardiac event. Additionally, respecting special contraindications or precautions for the individual drugs, oral therapy for ED may be prescribed.

Intermediate or Undetermined Risk Group

For patients in the intermediate or undetermined risk group, further diagnostic testing or intensified treatment is necessary before they can be reclassified to the low- or high-risk group. Patients with more than three atherogenic risk factors or moderate angina should be further evaluated to determine whether any of these conditions requires special treatment or an additional work-up (e.g., antihypertensive, lipid-lowering, or antidiabetic therapy; echocardiography; stress testing; etc.) and whether symptoms or signs of ischemia warrant invasive testing or revascularization-procedures. Between 2 and 6 wk after uncomplicated myocardial infarction, patients should be regarded as intermediate risk, and a definite recommendation should not be made before a 6-wk period. Patients with congestive heart failure should be examined closely to determine whether further diagnostic work-ups are necessary or to determine whether to intensify medical treatment to reach a stable cardiac condition if symptoms of heart failure are moderate (New York Heart Association II). For most of these decisions, referral to a cardiologist is necessary.

High-Risk Group

Patients in the high-risk group require further stabilization with either medical or surgical treatment before any sexual activity is advisable. Unstable angina, recent stroke or myocardial infarction, uncontrolled hypertension, and significant symptoms of heart failure or valvular heart disease are reasons that a patient is categorized in this group. Additionally, high-grade arrhythmias require adequate treatment before sexual activity or medical treatment for ED (*see* Table 3). Most of these patients should be seen by a cardiologist and may require referral to the hospital. Decisions regarding treatment of sexual dysfunction should be delayed until the cardiovascular situation is restabilized.

PDE-5 Inhibitors: Mechanism and Potential Source of Side Effects

When the patient and physician agree that ED may be treated (according to the earlier mentioned guidelines), PDE-5 inhibitors are the first choice for therapy, because they were shown to be effective in a high percentage of cases and in ED resulting from a broad spectrum of causes *(38)*. Three agents (sildenafil, vardenafil and tadalafil) are currently available. For few patients and situations, dopamine agonists, such as sublingual apomorphine (which is available in parts of Europe but not in the United States), may be an alternative. Other treatment options, such as vacuum pumps, intracavernosal self-injection techniques, intraurethral application of alprostadil, or penile protheses, have now become second- or third-line treatments and may be reserved for special indications. Therefore, the following section discusses mainly cardiac issues to be considered when using PDE-5 inhibitors.

Sildenafil, Vardenafil, Tadalafil: Basic Mechanism of Action

For the physician interested in cardiovascular issues, PDE-5 inhibitors, now broadly used for the treatment of ED, are a highly interesting class of agents. Sildenafil, the first

available agent for treatment of ED, was initially developed to find a novel anti-anginal concept *(37,39)*. Although its anti-anginal potency was not promising in the first clinical studies, the "side effect" of enhancing penile erections soon became the main target of further clinical research.

In several tissues, smooth muscle cells relax in response to nitric oxide (NO), which stimulates the enzyme guanylate cyclase, resulting in increased intracellular concentrations of cyclic guanosine monophosphate (cGMP). PDE-5, the major target of the PDE-5 inhibitors sildenafil, vardenafil, and tadalafil, catalyzes the breakdown of cGMP. Therefore, in tissues containing significant activity of PDE-5, sildenafil, vardenafil, and tadalafil potentiate smooth muscle relaxation in response to NO by preventing the breakdown of cGMP. Enhanced vasodilation of the vasculature in the corpus cavernosum results in improved erection. However, there is also PDE-5 activity in the systemic arteries and veins as well as in the pulmonary circulation. PDE-5 is also present in platelets *(40)*.

Therefore, the spectrum of effects and side effects of PDE-5 inhibitors in the cardiovascular system may be largely explained by its mechanism of action, the tissue distribution of PDE-5, and potentially on the basis of nonspecific effects on other PDE systems *(28,40–42)*.

Effects in the Cardiovascular System

Because smooth muscle cells of both the arterial and venous system contain significant amounts of PDE-5, blood pressure-lowering effects of the three agents are especially important. In a study by Zusman et al. *(43)*, oral administration of sildenafil resulted in a non-dose-dependent reduction of arterial systolic and diastolic blood pressure of 7 to 10 mmHg. These mild blood pressure-lowering effects were similar in patients with hypertension; small reductions in blood pressure were also observed with vardenafil and tadalafil. Most importantly, combination with a broad spectrum of antihypertensive agents was well-tolerated, as investigated in several studies in normotensive and hypertensive patients *(37,44–49)*. However, there are two important exemptions: Nitrates or any drug serving as a nitric oxide donor must not be combined with PDE-5 inhibitors, because this combination can result in life-threatening hypotension *(37,50)*.

Looking at the mechanism by which PDE-5 inhibitors enhance smooth muscle relaxation, it is obvious that pre-activation of the NO system followed by increasing concentrations of intracellular cGMP can result in uncontrolled accumulation of cyclic guanosine phosphate when its breakdown is inhibited by PDE-5 inhibitors. Therefore, a 24-h time interval is necessary between the use of sildenafil and nitrates and vice versa *(37)*. This safety period is similar for vardenafil, which has a similar half-life (approx 4 h) as sildenafil *(38)*. However, a much longer interval is necessary for tadalafil (half-life: 17.5 h; ref. *38*). After administering 20 mg of tadalafil, 48 h should elapse before any NO donor is administered *(37,50)*.

There is another class of agents requiring special attention: α-blockers (e.g., doxazosin, terazosin, or tamsulosin) used as antihypertensive agents or in the treatment of benign prostate hyperplasia because of potential enhancement of blood pressure-lowering effects. For vardenafil, tadalfil, and sildenafil, the label precaution is used for a combination with α-blockers—especially with higher doses. No more than 25 mg of sildenafil should be taken within a 4-h window with an α-blocking agent *(38,51,52)*.

In summary, the three available inhibitors of PDE-5 are well-tolerated by most of the cardiovascular patients, and blood pressure-lowering effects are mild. Generally, a baseline blood pressure of more than 90/60 mmHg should be a prerequisite for PDE-5 inhibitors (or any vasodilator) to be applied. Various antihypertensive agents can safely be

combined with sildenafil, vardenafil, or tadalafil; however, an NO donor cannot be combined, because hypotension can be life-threatening. Additionally, combination with α-blockers should be used with caution, as described earlier. It must again be emphasized that for PDE-5 inhibitors to be administered, a cardiovascular patient must achieve a stable cardiac condition without use of nitrates up to a level of 3 to 5 METs.

Save these important data, the effects of PDE-5 inhibitors on pulmonary arteries and pulmonary artery resistance are of special interest. There is increasing evidence that these agents may be useful in primary and some forms of secondary pulmonary hypertension *(40,53–55)*. They appear to reduce pulmonary artery resistance and attenuate the effective right-to-left shunting in some conditions. Most interestingly, there might be small, but relevant, differences between the three agents *(55)*. Additional indications for these substances are conceivable in the near future.

Cardiovascular Side Effects: Theory or Clinically Relevant?

Soon after the approval of sildenafil for treatment of ED, several reports of adverse events temporarily related to use of sildenafil raised concerns regarding the safety of PDE-5 inhibitors, particularly in patients with cardiovascular disease *(56,57)*. However, detailed statistical analyses, considering that the patient population using these agents is characterized by a high prevalence of cardiovascular risk factors, did not confirm an increased cardiovascular risk of sildenafil use. Neither prospective clinical trials nor retrospective analyses revealed an increased risk for sildenafil alone or for vardenafil or tadalafil *(58–61)*.

Some theoretical concepts were initially suggested to explain the cardiac events in men taking PDE-5 inhibitors. Direct effects of PDE-5 inhibitors in altering myocardial contractility, altered response of the heart to adrenergic stimulation by potential inhibitory effects of increased cGMP on breakdown of cyclic adenosine monophosphate, reducing tolerance toward ischemia, increasing sympathetic tone, or the susceptibility to arrhythmia *(42,62–66)* were some of the concepts suggested. For most of these concepts, however, it appears to be crucial that significant amounts of PDE-5 are expressed in ventricular cardiomyocytes. However, this remains a matter of discussion. Whereas systematic investigations by Wallis et al. *(42)* did not find evidence of PDE-5 expression in canine cardiomyocytes, Senzaki et al. *(62)* reported evidence for expression of PDE-5 in canine cardiomyocytes. Additionally, in our laboratory, experimental data in the rabbit did not provide evidence for a reduced tolerance toward ischemia under PDE-5 inhibition or promotion of arrhythmia *(42)*. Another hypothesis (referring to a coronary steal phenomenon) involving shifting blood from ischemic to nonischemic myocardium under the influence of sildenafil was not supported in experimental investigations *(67)*. Conversely, the majority of clinical studies have suggested that tolerance toward ischemia, threshold of ischemic reactions during exercise, or parameters hinting at pro-arrhythmic tendencies are not significantly altered or even favorably influenced with PDE-5 inhibition *(68–70)*.

Recently, animal research suggested powerful cardioprotective effects of PDE-5 inhibition, resembling a preconditioning-like effect *(71–73)*. However, these effects remain a matter of debate, and it is not clear how and to what extent they could be transferred into the clinical realm.

In summary, theoretical concepts regarding potential detrimental effects of PDE-5 inhibition in cardiovascular disease were not conclusively established, and neither retrospective epidemiological data nor clinical studies supported any ischemia- or arrhythmia-promoting effect. Therefore, initial concerns about cardiac events after administration

of PDE-5 inhibitors appear to be most likely related to the patient population characterized by a remarkable cardiovascular risk factor profile.

Contraindications regarding drug interactions as well as other contraindications and recommendations according to the Princeton Consensus Panel should be carefully observed when prescribing these substances; however, there is reasonable evidence that PDE-5 inhibitors are also suitable for patients with cardiovascular disease.

Dopamine Agonists and the Cardiac Patient

Although dopamine agonists (e.g., sublingual apomorphine, which is available in parts of Europe) have lower efficacy, they may be an alternative therapy for treatment of ED in some patients, particularly those patients taking nitrates. Side effects are most frequently related to increase vagal tone, leading to nausea, bradycardia, and sometimes syncope resulting from atrioventricular block or sinus pauses. Therefore, baseline hypotension, syncope, bradycardia, and conduction disturbances are a contraindication for use.

CONCLUSION

Therapy of ED has been revolutionized since inhibitors of PDE 5, such as sildenafil, vardenafil, or tadalafil, were shown to be highly effective therapies for treatment of ED. Despite theoretical concerns of a reduced tolerance of the myocardium toward ischemia, clinical studies and retrospective analyses have not supported an increased cardiac risk with these agents. Most importantly, the combination of PDE-5 inhibitors with any NO donor is absolutely contraindicated because of potentially life-threatening hypotension. Before prescribing medication for ED, any patient with cardiovascular disease should be evaluated for a potential risk of a cardiovascular event during sexual activity according to the Princeton Consensus Panel. When a stable cardiac condition can be achieved (low-risk group), oral treatment for ED may be appropriate. On the other hand, a patient presenting with ED should be carefully evaluated regarding cardiovascular risk factors, cardiovascular disease, or other causes of ED, because ED might be a first manifestation of cardiovascular disease. Cardiovascular risk factors should be vigorously treated in these patients.

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4 How a Primary Care Clinician Approaches Erectile Dysfunction

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SUMMARY

Primary care clinicians are recognizing that the longitudinal and personal relationship they have with patients is an asset in discussing and resolving sexual problems. Knowledge of a patient's sexual activities and issues is important to the clinician who is truly interested in the patient's health and happiness. Providing care for sexual concerns can improve patient satisfaction and enhance a primary care practice.

Key Words: Erectile dysfunction; primary care; sex therapy; older men; sexual interview; misconceptions about sex; men's health; treatment of erectile dysfunction.

INTRODUCTION

The language involved in discussing sex is becoming more openly used, and clinicians are learning ways to make these discussions easier in their offices. Because the yield of screening is related to the frequency of erectile dysfunction (ED) in the population, men who should be screened include those over age 40; those with a predisposing comorbidity such as cardiovascular disease, diabetes, or depression; or anyone else the clinician feels may be having difficulty with physical intimacy. Incorporating screening into the primary care practice becomes easier when the clinician adopts a policy of briefly questioning each possibly sexually active patient about his/her sexual activity. Asking sexual partners about each other's sexual function is often very useful.

Early recommendations based on epidemiological studies and increasing recognition of endothelial dysfunction suggest that men with ED should be screened for both cardiovascular risk and depression. The evaluation of ED follows the same pattern as evaluation of any medical disorder, including a pertinent history, physical examination, and laboratory tests. Treatment plans need to be goal-oriented, ideally aimed at satisfying the needs of both the man and his partner and maximizing the chance of achieving patient satisfaction. Determined by the desired outcome, treatment can simply be pharmacological or may require further comprehensive psychosocial and relationship counseling. Follow-up is an essential part of management of ED because reviewing the success or lack of success

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Table 1
Limitations Faced by Primary Care Clinicians

Time
Payer demands
Standards and guidelines
Patient expectations
Reimbursement issues
Personal needs and areas of interest of the clinician

Table 2
Primary Care Clinician Priorities

Problems with high morbidity and mortality
Disabling conditions
Standards of care and guidelines
Improve quality of life
Patient demands
Personal needs areas of interest of the clinician

of treatment, any adverse effects, and considering dose or treatment alterations is more likely to achieve the patient's goal. Consultation with subspecialists may be appropriate at varying intervals when managing a patient with ED.

NATURE OF PRIMARY CARE

For many people, primary care clinicians are the first point of contact with the health care system. Although this care may be episodic or may 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.

At times, it seems that 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 trying to fill this lofty role, primary care clinicians are encumbered by several limitations (Table 1).

Primary care for adults is provided by various 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 are addressed during a visit or a course of care generally are similar for all primary care clinicians (Table 2). Most primary care clinicians 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 patients and the personal interests of the clinician also affect the choice of issues that the clinician addresses.

Issues involving 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 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 regarding 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, aging of patients, managed care, and medical technology have altered demand and actual primary care activity. Results from the National Ambulatory Medical Care Survey 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; a recent study of the length of ambulatory visits to primary care clinicians showed a mean of 16.3 min *(3)*, possibly associated with the availability of nonphysician support personnel and with the prevalence of health maintenance organizations paying medical bills. Other changes in primary care practice include an increase in single- and multispecialty group practice, computerization of the office, more complex reimbursement methods, and an increasingly educated patient population. From the perspective of many people, these changes 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. In the late 1940s, the work of Alfred Kinsey, a nonphysician, also bolstered the social and behavioral sciences as the atmosphere for sexual studies. Between 1960 and 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 some anatomy and physiology, information about acquired immune deficiency syndrome and sexually transmitted diseases, and lectures on "alternative" lifestyles (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, has 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 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. The motivation for primary care clinicians to help patients with sexual dysfunction should be high. General sexual dissatisfaction is very high among men, with 75% noting at least one problem with dissatisfaction, avoidance, infrequency, or noncommunication *(7)*. Specific sexual dysfunction is also prevalent, reported in approximately one-third of men over

Table 3
Reimbursement for Management of Erectile Dysfunction

ICD-9 codes for erectile dysfunction
607.84: Secondary to organic disease
302.72: Related to nonorganic or unspecified causes

ICD, International Classification of Diseases.

age 18 yr, with premature ejaculation as the most common sexual dysfunction reported by men, followed by ED *(7,8)*.

Experiencing a sexual dysfunction is highly associated with numerous unsatisfying personal experiences and relationships. Men with ED experience a diminished quality of life when measured as low physical satisfaction, emotional satisfaction, and 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 the start of 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 and more related to the giving of comfort and security that comes as a result of intimacy.

Primary care clinicians are recognizing that (a) the longitudinal and personal relationship they have with patients is an asset in discussing and resolving sexual problems; (b) the multifactorial issues around ED are appropriately evaluated by the patient's clinician; and (c) the long-term follow-up to be ensure a sexual dysfunction is resolved is well-suited to primary care *(6)*.

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 helps to ensure 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 International Classification of Diseases (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 after having discussions about sexual matters and show such gratitude with increased enthusiasm for better health and increased loyalty to their clinician. They are very appreciative of the clinician's willingness to listen, and a new level of patient–clinician relationship is often reached in which conversation flows more easily and trust allows an enhanced comanagement of other clinical problems. This "affiliative" communication style, which includes friendliness, interest, empathy, a nonjudgmental attitude, and a social orientation, is associated with significantly higher patient satisfaction *(10, 11)*. More overall communication, including social conversation, and greater feelings of

Table 4
Men's Misconceptions About Erectile Dysfunction

Matters relating to sexual dysfunction are taboo
Loss of erection is not a common problem, and their problem is unique
Erectile dysfunction is a normal part of aging
Erectile dysfunction is primarily a psychological problem and not a physical one
Treatment options are generally lacking or are too invasive and risky to be pursued
Erections are indicators of sexual desire
An erection should stay hard until ejaculation
An erection is necessary to have sexual relations

Adapted in part from ref. *10*.

Table 5
Making Discussions About Sex Easier in the Office

Encourage a warm, open, and nonjudgmental atmosphere
Introduce the topic of sexual activity
Initiate and engage in discussion whenever appropriate
Offer help
Be optimistic about resolving sexual problems

partnership have also been related to greater patient satisfaction *(12)*. 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 *(13)*.

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 a discussion about sex (Table 5). An office in which the patient feels comfortable and welcome encourages 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 *(14)*. The office staff also needs to be ready to answer a patient's questions. The staff members need to understand the importance of being sensitive in discussions and the need for privacy during educational sessions.

NOT ALL MEN ARE HETEROSEXUAL

Knowledge of a patient's sexuality is important to the clinician who is truly interested in the patient's health and happiness. "Do you have sex with men, women, or both?" is a common way of demonstrating an acceptance of varying sexual orientations. Using the term "partner" rather than "spouse" or "wife" conveys the fact that the clinician is not making assumptions regarding sexual orientation. Homosexual men are more likely to confide important information and to follow a provider's advice if they feel accepted and understood. Offering to keep information about sexual orientation out of the medical record may encourage open discussion. Patients must be able to involve lovers or other support people in examinations and treatment decisions.

Dr. Marian Dunn, Director of the Center for Human Sexuality at the SUNY-Downstate Medical Center in Brooklyn, New York, has taught many health care clinicians about the

impact of sexual orientation on patients' concerns and their willingness to communicate with health care providers as well as how physicians can improve treatment outcomes. She emphasizes the need to create a welcoming environment even before contact with the health care provider. For example, a physician can post a sign in the waiting room stating, "We do not discriminate on the basis of race, sex, sexual orientation." Additionally, literature may be placed in the waiting room that is targeted at and/or provided by the gay, lesbian, and bisexual community.

Clinicians should be open about any questions they may have about sexual orientation and ask patients for information. Referrals to knowledgeable professionals are appropriate when the situation becomes more complex. Understanding and acceptance of differences does not automatically suggest approval, but failure to deal sensitively with sexual matters predisposes the patient to potential harm by omission or inappropriate treatment.

Dealing with sexual problems is not much different than among homosexual and heterosexual male patients. Issues causing sexual problems remain the same, as do the emotional and relationship consequences. Managing sexual problems among homosexual men involves the same inquiry, evaluation steps, and treatment discussion as with heterosexuals, and partner discussions can be very constructive. The only variations may be differing life stresses, and sensitive and aware clinicians can handle discussion of these stresses.

SCREENING FOR ED

Screening male patients for ED is valuable to minimizing 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.
3. Provide a yield that is higher in value than costs.

Because the yield of screening is related to the frequency of ED in the population, men who should be screened include those over age 40; those with a predisposing comorbidity such as cardiovascular disease, diabetes, or depression; or anyone else the clinician feels may have difficulty with physical intimacy. Incorporating screening into the primary care practice becomes even easier when the clinician adopts a policy of briefly questioning each possibly sexually active patient regarding his/her sexual activity. This develops a habit of discussing sex in the office and helps patients understand that they can raise the topic 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 *(8,15,16)*. Although more than 70% of adult patients in a large sample considered sexual matters an appropriate topic for the generalist clinician to discuss and the rate of sexual dysfunction surveyed was 35% for adult men and 42% for adult women, evidence of discussion about sexual problems was 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 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 an existing problem.

Table 6
Sexual Health Inventory for Men (SHIM)

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 six months:

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

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

No sexual activity	Almost never/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/always
0	1	2	3	4	5

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/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/always
0	1	2	3	4	5

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 diffult
0	1	2	3	4	5

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

Did not attempt intercourse	Almost never/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/always
0	1	2	3	4	5

Score _____

If your score is 21 or less, you show signs of erectile dysfunction, and your doctor can suggest treatment options that can improve your condition.

Adapted from ref. *72*.

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 ease with one of these more active approaches and incorporate

Table 7
Indirect Ways to Engage Patients About Sexual Function

Brochures or Sexual Health Inventory for Men in the waiting room
Posters or displays in the examining room
Ancillary staff discussions
Lapel buttons
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?"

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.
4. During the physical examination of the inguinal area and the testicles.

Making a habit of asking these questions decreases anxiety; encourages the "routine" of sex discussions, thereby reducing possible embarrassment; and makes screening for sexual dysfunction more efficient. Using synonyms such as "getting hard" or "cumming" 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 that are well-known to primary care clinicians. These include appropriate eye contact with the patient, repeating some of the patient's major points, nodding the head up and down to encourage the patient to say more, and expressing optimism that the problem can be resolved.

PATIENTS AND PARTNERS INITIATE DISCUSSIONS ABOUT SEXUAL PROBLEMS

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 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.

If the patient or partner initiates discussion about sex or has a specific question, this requires 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 discuss 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)*.

Partner issues vary widely. Patients may be having sex with one partner, multiple partners, partners of the opposite sex, partners of the same sex, or a combination of these. Issues around partner choice, partner participation in sexual activity, and partner physiology may impact sexual function. All of the emotional components of a good relationship contribute to continued sexual satisfaction. Relationship factors often play a role in men's sexual problems. Early in relationships, partners try to please and be sensitive to one another. After time, these efforts may be abandoned and sex may become perfunctory in both form and function.

Successful treatment of sexual problems is most likely to occur when couples have a good relationship and are able to communicate their positive and negative feelings to each other. Many men may prefer to be evaluated and treated for sexual problems alone, but when a partner is present, patient education may convince the man of the importance of including the partner in further management.

If inadequate time exists to discuss the issue, recognition should be made of the patient's problem or concern and another time should be scheduled to further discuss the issue. Merely 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.

POTENTIAL VALUE OF ED INQUIRY AND MANAGEMENT (TABLE 9)

Linking ED With Cardiovascular Disease

Because risk factors associated with cardiovascular disorder overlap with those for ED, careful cardiovascular risk evaluations following diagnosis of ED may uncover undiscovered risk factors for cardiovascular disease. Abnormal cholesterol profiles were discovered in 60% of men complaining of ED without history of cardiac disease *(22)*. Among apparently healthy men with ED, more than 60% had hyperlipidemia, and 90% of the men with hyperlipdemia had evidence of penile artery disease (as detected by Doppler ultrasound evaluation; ref. *23*).

Up to 15% of previously healthy men presenting with ED have abnormal blood glucose levels *(24)*. In a study of men seeking medical advice for ED, many were newly diagnosed

Table 9
The Potential Value of Inquiry and Management of Erectile Dysfunction

1. Resolution of a prevalent disorder.
2. Successful treatment of ED can improve negative self-image and diminished quality of life resulting from sexual dysfunction for both patient and partner.
3. Improve depression.
4. Identification of occult medical and psychosocial conditions.
   a. Diabetes.
   b. Hyperlipidemia.
   c. Coronary artery disease and peripheral vascular disease.
   d. Neurological disease.
   e. Depression.
   f. Relationship issues.
   g. Environmental issues (e.g., socioeconomic problems).
   h. Other psychosocial concerns.
5. Minimize iatrogenic ED.
6. Better overall health in men.
7. Positively impact on intimate relationships that contribute to psychosocial well-being and physical health.
8. Improve clinician–patient relationship.
9. Increased physician work satisfaction.

Adapted from ref. *73*.

with a comorbid condition after seeking attention for the ED complaint. These included new diagnoses of hypertension (18%), diabetes (16%), benign prostatic hypertrophy (15%), ischemic heart disease (5%), prostate cancer (4%), and depression (1%; ref. *25*).

ED has been suggested as a signal of endothelial dysfunction *(26)*. The penile artery is small; the average cavernosal artery is 0.5 mm in diameter, and the later helicine arteries running to the sinusoids are much smaller. These smaller arteries need to dilate a greater percentage (up to 80%) than larger vessels, which may dilate up to only 15%. The penile vascular bed greatly depends on nitric oxide (NO) for vasodilation to produce rapid increase in blood flow as well as for blood trapping caused by pressure of penile drainage veins against the tunica albuginea, thus enhancing entrapment of blood. Based on the abnormality noted in response to both flow and nitroglycerin, it appears that the abnormality in these men is not only in the endothelium (where NO is produced) but also is present in the smooth muscle response to NO *(27)*. Progressive occlusive disease should be manifested sooner in the microvasculature of the penis than in larger vessels *(28)*.

More answers are needed, but symptoms of vasculogenic ED probably signal systemic endothelial dysfunction with parallel negative effects throughout the cardiovascular system. Because epicardial and microvascular coronary endothelial dysfunction independently predict acute cardiovascular events in patients with and without coronary artery disease *(29)*, vasculogenic ED may have the same predictive value. An intriguing issue is whether or not ED represents a signal of future or merely undiscovered cardiovascular disease. ED stands for more than erectile dysfunction. It is also short for endothelial dysfunction and early detection. ED may be an early marker of oxidative stress and vascular dysfunction *(30,31)*. Vasculogenic ED has been suggested as a risk factor for the presence of occult cardiovascular disease *(30)*.

With endothelial dysfunction as a unifying etiology for many aspects of the metabolic syndrome, especially diabetes and cardiovascular disease, studies have noted that ED is more commonly observed in men with various components of the metabolic syndrome *(32)*. These preliminary epidemiological studies demonstrating the greater prevalence of ED in men with metabolic syndrome confirm the potential value of a healthy lifestyle and possible pharmacological interventions to slow endothelial dysfunction progression and reduce both the prevalence of metabolic syndrome and ED *(33)*.

Additional Benefits of Uncovering ED

Early recommendations suggest that men with ED be screened for both heart disease risk and depression *(23,26,34,35)*. Although the direction of the relationship between depres-sion and ED is unclear, evidence is accumulating that concomitant treatment of both depression and ED in men who suffer from both disorders improves depression scale scores to a greater extent than simply treating the depression and ignoring the ED *(36)*.

Experiencing a sexual dysfunction is highly associated with numerous unsatisfying personal experiences and relationships. Men with ED experience diminished quality of life when measured as low physical satisfaction, emotional satisfaction, and general happiness *(37)*. Reports of low self-esteem and relationship difficulties indicate the effect of ED on function and satisfaction with daily life activities. Naturally, older couples want to continue to share an active sex life—less because of sexual drive but more related to the comfort and security that results from intimacy.

We are also learning that being part of a good relationship is not just a quality-of-life issue but can also promote good health. Clinical studies support the idea that loving, supportive relationships can make you healthier. The breakdown of a significant personal relationship is one of the most stressful life events and impacts general health and quality of life. Although sex is not essential for supportive, healthy relationships, the amount of sexual intimacy in loving relationships has been correlated with relationship satisfaction *(38)*. ED negatively impacts relationships; one survey of ED sufferers noted that 80% of respondents indicated some form of relationship difficulty because of their ED, and 12% stated that the condition prevented them from forming relationships *(39)*. Men with ED often cite ED as the reason for disintegration of a recent relationship. Sexual problems negatively affect intimacy and the desire for intimacy, as do other emotions resulting from ED, such as negative self-image. If "morbidity" is defined as the consequences resulting from an abnormally functioning, diseased organ or body system, then ED clearly has a recognizable morbidity.

Once ED is recognized as more than a simple quality-of-life issue, it will be easier to acknowledge that ED is a very common problem among patients in a primary care office that needs to be addressed.

BARRIERS PREVENTING MEN FROM DISCUSSING ED

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 women, thus reducing the chance of disease recognition and treatment *(40)*. 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 *(40)*.

Research regarding why men do not make visits to family doctors for help revealed several themes to explain this behavior *(41)*, including: (a) support seeking; (b) help seeking; and (c) barriers. Potential barriers to health action also include poor relationships with doctors *(42)*. This research on male reticence to discuss health concerns with a health professional supports the strong role played by the female partner in determining health-seeking behavior. Men often come to a visit with their clinician with no complaints or with only general complaints and wait for the clinician to determine the reason for their visit. 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" *(43)*.

Men need to be offered more comprehensive care and counseling at any visit to a clinician. Men often perceive clinicians as rushed and uninterested in communication. Although 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 yr and older *(44)*.

Disabled patients are another group whose sexual difficulties are often overlooked. Either physical injury or physiological 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 most common sexual problem among disabled male patients *(45)*. Discussion about sexual activity is essential for patients with any type of disability.

THE NEXT STEP AFTER IDENTIFYING ED

The primary care clinician who identifies the patient with ED has accomplished a lot. This information can be used to (a) initiate evaluation for psychological and organic comorbid conditions, including risk factors for neurovascular disease; (b) refer the patient to an appropriate clinician; (c) open further discussion to confirm whether or not ED is the primary sexual problem or whether it is secondary to a difficulty with some other phase of the male sexual cycle, such as libido or ejaculation; and/or (d) work with the patient on a management plan.

The flexibility of response by the primary care clinician to the patient's ED is illustrated by the acronym ALLOW (Table 10). This management plan acknowledges the need for all primary care clinicians to inquire about sexual activity and to recognize the limitations and varied interests of many clinicians in actually managing problems. Step 1 involves "asking" the patient about sexual activity. There are many ways to ask and some were identified earlier. Step 2 includes "legitimizing" the patient's problems and acknowledging that sexual dysfunction is an important issue. An initial impression that his problem is being dismissed can considerably delay or prevent him from seeking further help. Step 3 invites the clinician to evaluate his/her own interest and ability to work with patients who report a sexual problem. Based on this self-evaluation by the clinician, the next step is taken, and the clinician has done it "ALL" for the patient. Step 4 can be a referral to an appropriate subspecialist to further investigate and treat the patient's sexual issues, or the primary care clinician can open up the issues for further dissection and diagnostic evaluation. Step 5 involves working with the patient to identify an appropriate goal and mutually acceptable treatment.

Table 10
"ALLOW" Your Patient to Discuss Sexual Dysfunction: A Management Plan

Step 1: A—Ask

♣

Step 2: L—Legitimize

♣

Step 3: L—Limitations ÷ Refer

♣

Step 4: O—Open up for further discussion

♣

Step 5: W—Work together to develop a treatment plan

♣

Adapted from ref. *74*.

CHARACTERISTICS OF A SEXUAL PROBLEM

If the primary care clinician plans to further manage sexual disorders, it is helpful to obtain further information about the characteristics of the specific problem. These characteristics have been best developed for evaluation of erectile problems but can prove helpful in evaluating and managing other sexual problems. The first characteristic is to determine whether or not the problem is psychogenic or organic. For example, an easy method of distinguishing most psychogenic disorders from potentially organically induced disorders of erectile function is to ask some combination of three questions: (a) Do you ever wake up with an erection before having to urinate? (b) If you experiment and touch yourself when your partner is not around, can you get an erection? (c) Can you get an erection at any time of night or day, during any form of sexual activity, with any partner? A positive response to one or more of these questions indicates stress or anxiety as the trigger of the ED rather than a physical cause or a medication adverse effect. These patients may benefit from sexual counseling by the physician or a knowledgable therapist. Ruling out organic causes requires a history that defines the circumstances of the problem, a physical examination and laboratory tests (which look for clinical disorders that can negatively impact on sexual function), and a careful review for potentially causative medications or drug use.

The second characteristic is to determine if the problem is lifelong or acquired. Dysfunctions that are more recently acquired are more amenable to briefer treatments, whereas those that are lifelong often require further psychotherapy or clinical investigation.

The third characteristic is generalized or situational. Situational problems hint at difficulties with specific partners or in specific situations, implying a psychogenic etiology.

EVALUATING THE MAN WITH ED

A complete evaluation often determines likely etiological factors for ED (Table 11). The evaluation of ED follows the same pattern as evaluation of any medical disorder, including a pertinent history, physical examination, and laboratory tests. However, this history must include a sexual history. A well-organized brief sexual history can be an effective diagnostic tool. It is better not to accept the patient's label for a disorder without first questioning and obtaining a clear picture of the complaint. Often, less educated

Table 11
Causes of Erectile Dysfunction and Diagnostic Clues

Cause	*History*	*Physical examination*	*Possible laboratory findings*
Vascular	Coronary artery disease, hypertension, claudication, dyslipidemia, smoking	Decreased pulses, bruits, elevated blood pressure, cool extremities	Abnormal lipid profile, abnormal penile–brachial index pressure
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
Hyoerthyroidism	Heat intolerance, weight loss, disphoresis, 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

Neurological	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)
Pharmacological	Inquire about all prescription and nonprescription drugs	*See* Table 2	Positive depression inventory

LH, leuteinizing hormone; FSH, follicle-stimulating hormone; CT, computed tomography; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone; T_4, 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 every 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.

From ref. *75*.

Table 12
Phases of Male Sexual Activity

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

patients misuse medical or technical terminology. For example, because some men confuse ED with premature ejaculation, asking if the erection is lost before or after ejaculation can clarify the problem. Learning about the patient's sexual and relationship histories can also be very revealing *(46)*.

Questions generally review the phases of male sexual response (Table 12) 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 communication more clear.

For desire phase disorder, physicians can ask, "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, adverse effects from medication, and depression. It is difficult for most men to sustain an erection if they feel no desire.

For arousal/erection difficulties, physicians can ask, "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 response strongly hints at stress or anxiety as the trigger of the ED rather than a physical cause or medication adverse effect.

For orgasm/ejaculatory phase problems physicians can ask, "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's disease or pain disorders, a physicians can 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 psychological difficulties. A review of medications, 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 *(47)*. Medications have adverse effects on all phases of sexual functioning, making clarification of the patient's complaint a priority before ascribing symptoms to side effects of specific medications *(48)*. Brief screening for depression, including such questions 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, which determines stress surrounding a relationship or substance abuse (including alcohol and cigarettes),

Table 13
Essential Physical Examination Elements

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

is critical. Finally, a review of daily activity and a review of cardiovascular status is important in determining 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 *(49)*.

The physical examination should be comprehensive, with emphasis on several areas (Table 13; refs. *50* and *51*). Evaluation of blood pressure and peripheral pulses may show vascular disease. A neurological exam, including pelvic sensory function and anal sphincter tone, is needed to confirm both sympathetic and parasympathetic function. A prostate exam may help to determine local nerve impingement. A visual and, optimally, manual exam of the penis determines any anatomic defects and aids in identifying Peyronie's disease by the presence of possible tender plaques located in the tunica albuginea surrounding the corpora cavernosa. Immature secondary sexual characteristics, including hair distribution and penile and testicular development, may represent testosterone deficiency. The sexual exam needs to be thorough and sensitive *(52)*. Note that it is good practice to offer the presence of a chaperone to patients undergoing a genital exam. Many patients say that a chaperone is not necessary, but the offer allows the more anxious patient 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 prior to initiating the genital exam.

Laboratory tests useful in evaluating ED look for the risk entities discussed earlier. Physicians should obtain a urine analysis to demonstrate renal disease or infection, complete blood count to note any potential hematological disorder, a chemistry profile to check glucose and renal function, a lipid profile to rule out hyperlipidemia, and thyroid-stimulating hormone (when indicated) to evaluate thyroid function. Prostate-specific antigen should be considered for men over age 50 (40 yr for high-risk patients) to evaluate prostate size and tumor presence, especially if testosterone treatment is a possibility. Some experts recommend a morning serum-free testosterone quantitation and a prolactin level, but the value of routine endocrinological testing is controversial. Testosterone and prolactin have a low yield, but specific therapy is helpful in improving sexual function, whereas glucose and lipids have a higher yield, but specific therapy is not immediately effective for ED *(53)*. If the sexual problem is clearly not a libido problem and the patient has other known major contributing factors that can account for the ED, then these tests can be ordered on an individual basis. If there is any evidence of hypogonadism or the dysfunction is particularly consistent at a young age, then further hormone evaluation becomes a higher priority.

The advanced diagnostic evaluation for ED includes tests like nocturnal penile tumescence studies, vascular evaluation with sonography, biothesiometry, and other tests that

Table 14
Goal-Oriented Treatment Possibilities

Restore sexual function
Improve sexual satisfaction
Improve relationships

These may not be mutually exclusive.

Table 15
Treatment Options

Counseling and education
Lifestyle changes and medication changes
Pharmacological interventions
Physical interventions

can be performed by the urological subspecialist. These tests are somewhat subjective and rarely provide useful information, with the exception of in cases of trauma or other major vascular injury.

If treatment is being considered for a man who has been sexually inactive for a prolonged period, a cardiac evaluation must be done to determine the safety of the patient resuming an actual sex life. Although sexual activity requires only a slight increase in energy expenditure for most men in most circumstances, there is a small absolute increase in risk of an adverse cardiac event occurring during sex or within 2 h of sexual activity *(49)*. The Princeton Guidelines help to evaluate a man's risk for an adverse cardiac event during or shortly after sexual activity *(54)*. These guidelines state that some men with active cardiac risk factors and/or disease fall into a high- or intermediate-risk category for adverse cardiovascular event and require further evaluation. However, the vast majority of men fall into the low-risk category for adverse cardiovascular events with increased sexual activity and can safely be treated for ED *(55)*.

TREATMENT OF ED

Treatment plans need to be goal-oriented, ideally aimed at satisfying the needs of both the man and his partner to maximize the chance of achieving patient satisfaction (Table 14). Based on the desired outcome, treatment can be simply pharmacological 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, thus improving the chance of success.

Educational and Psychosocial Interventions

In most cases, regardless of etiology, the treatment options of the physiological impairment of ED are the same (Table 15). Education is the first step in treatment and is personalized to the needs of the specific patient. The normal changes of aging often are misunderstood by patients and lead to problems. Myths and misunderstandings about sexual activity can directly cause sexual difficulties and can generate anxiety, guilt, and worry that negatively impact sexual response and erectile ability (Table 4; refs. *56* and *57*). Unfortunately, most information people receive about sex comes from mass media, which constantly reinforces the importance of sex without providing the information that ordinary people

can actually use *(58)*. Helping men to have realistic expectations and to better understand healthy function and honest, constructive communication with partners can encourage more satisfactory sexual interaction and a healthier sense of sexual nature. Research has demonstrated that the amount of sexual intimacy correlates with relationship satisfaction *(59,60)*.

The easy erection begins to disappear in older men, especially in 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 the changes that occur during aging can be extremely reassuring.

Partner issues vary widely. Issues around partner choice, partner participation in sexual activity, and partner physiology may impact erectile function. When vaginal 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 information to the man or, ideally, to both partners in a relationship, including factual information about:

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

Emotional and relational factors can play an important role in sexual dysfunction. For example, anxiety can block the production of NO, thus interfering with erectile function. Many couples in which the man has a sexual problem have not had sex for many years. This long period of abstinence often has been coupled with avoidance of all physical affection and intimacy. The relaxed pleasure and sensuality necessary to trigger and maintain good sexual response has been lost.

The physician can help reduce this performance anxiety in several ways. Greater arousal is possible by encouraging sensuality, extended foreplay, and focus on pleasure rather than erection. Couples often need to be encouraged to rekindle the sense of courtship and romance that existed earlier in the relationship. When recommending new treatments, physicians may reduce the patient's anxiety by explaining that treatments often take time to be fully effective and that most couples need time to comfortably integrate the new treatment into their sex lives.

Sometimes a couple's sexual problems serve a function in the relationship. Anger, mistrust, power struggles, and other relationship issues can be expressed through sexual difficulties. When this is the case for one or both partners treatment can be effectively sabotaged. When the physician suspects that this is the case, referral to a marital or sexual therapist is necessary. Lack of communication can also play a role in sexual dysfunction. Even couples in long-term, loving relationships may never have discussed the kinds of touch and caress that are most arousing. Criticism often seems easier than open discussion. It is more effective to guide and encourage the partner in a constructive manner.

The P.LI.SS.IT. model developed by Annon offers a structure that is useful to organizing an approach to brief sex counseling *(61)*. P.LI.SS.IT. is an acronym used to describe

four different levels of counseling: permission, limited information, specific suggestions, and intensive therapy. The model moves from the simplest level of intervention, permission, to the most complex and highly skilled level of intervention, intensive therapy. Any health care practitioner can implement the first three intervention levels. Intensive therapy requires special training in sexual therapy.

Sex therapists can work collaboratively with the physician to resolve the sexual difficulty, tease important history, educate, suggest sexual enhancement techniques, and help couples resolve relationship problems. They can help evaluate and explain varied treatment options so the patient fully understands how to successfully use his chosen option.

More specific suggestions can be offered at 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.

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 all other recreational drug use is critical. 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 increases cardiac output and improves peripheral circulation. These recommendations help men to become healthier and hopefully happier, although their effect on erectile function may not be instantly apparent.

Changing medication regimens to remove causative agents can be attempted when clinically possible. Examples of this might include discontinuing a thiazide diuretic and substitutiing an α-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 alternative antidepressant *(62)*. These substitutions and eliminations may meet with some success, but they need to be individualized depending on clinical circumstances.

Direct Pharmacological 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. The newest Food and Drug Administration approved oral treatments include sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra). The mechanism of action, efficacy, and adverse effects of these three phosphodiesterase type 5 inhibitors are described in Chapter 12.

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. Results are slightly better

in men with primary psychogenic etiologies; men with primarily organic etiologies probably will not be helped by taking this medication. Adverse effects of hypertension and increased heart rate and its prescription with most antidepressants and in patients with vascular disease make Yohimbine significantly less useful than sildenafil. The American Urological Association does not recommend Yohimbine for ED.

Apomorphine, a dopamine agonist that causes central initiation of an erection through specific action in the brain, is available in Europe and offers another approach to managing ED.

Vacuum devices are a reasonable choice for many men who are in a stable relationship in which their partners are willing to accept the inconvenience *(63)*. 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 serum-free 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 *(64)*. Testosterone augmentation requires thorough evaluation and monitoring for prostate cancer.

Second-line therapies for ED include injectable prostaglandin preparations *(65)*. Alprostadil (e.g., Muse) is a prostaglandin-E preparation in a pellet form that is inserted into the urethral opening with a plunger-like mechanism *(66)*. Ideally, the first insertion of alprostadil should be performed in the doctor's office to monitor technique, change in blood pressure, and the response (although this may be blunted in the office environment). Because venous drainage problems may thwart the erection caused by alprostadil insertion because of premature drainage, a ring at the base of the penis may be used to constrict venous outflow. Contraindications include use 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 administered 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 *(67)*. This therapy should be initiated in the physician's office, and caution should be exercised in patients on anticoagulation.

The third-line treatment for ED is penile implant surgery. This is a successful therapy, but it should be reserved for patients who have considered or attempted 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; key recommended nutrients include zinc, essential fatty acids, and vitamins A, B_6, and E. 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.

ISSUES AMONG OLDER MEN

Physiological changes in older men are largely related to a slow, steady decline in bioavailable testosterone, which can result in a decline in sexual interest in a minority of

men and various neurovascular changes that predominantly result in ED caused by penile vascular insufficiency. As men age, sexual organ response becomes slower. These changes can vary widely among individuals, with older men often reporting varying degrees of increased time needed to get an erection and ejaculation, erections that are not as hard and that take longer to achieve a second time (increased refractory time), decreased quantity of lubrication before ejaculation, and decreased volume and force of ejaculation.

Men who have had a radical prostatectomy, even those in whom the nerves are seemingly spared, can develop a decrease in erectile function and/or issues with ejaculation (delayed, retrograde, or anejaculation). Most healthy men retain their interest in sex and their capacity to have erections and ejaculations as they age. A majority of men remain fertile in their 60s, and many 90-yr-old men are still fertile. Unfortunately, the medical issues that occur with age can cause sexual problems.

Diseases that can most negatively affect sexual activity are those that (a) actually affect sexual organ function (e.g., diabetes, poor circulation); (b) affect maneuverability (e.g., arthritis, backache, Parkinson's disease, stroke); (c) cause physical or emotional distress, (e.g., cancer, incontinence); and (d) cause a fear of the result of exertion during sex (e.g., cardiovascular disease). To a limited extent, sex organ functioning can be improved with treatment of the underlying causative disease and use of exercise as well as pharmacological, physical, or surgical interventions. Mobility issues can be eased through education about sexual positions and expanding patients' definitions of sexual activity. Counseling and appropriate pain management can ease the distress of chronic conditions. Patients with cardiac conditions and recent bypass surgery need to know that sexual activity, especially with a familiar partner, requires no more energy than gardening and many other normal activities of daily life. Patients and their partners need to be reassured that the chance of an adverse cardiac event during sex is very low. Other general hints that can improve sexual activity and function for older men include altering potentially offending prescription drugs (when possible), increasing physical fitness through stretching and aerobic exercise, and decreasing alcohol intake and tobacco use.

The absence of a partner and/or various other psychosocial difficulties may add to sexual problems. Emotional and social problems can also negatively impact an older couple's sexual relationship. Table 3 lists some of the more common anxieties, negative feelings, and social changes that occur as adults age.

FOLLOW-UP OF TREATMENT FOR ED

Follow-up is an essential part of management of ED. Patients should be seen 1 mo after initiation of treatment to evaluate progress. Comparison to baseline can be done by verbal exchange or by using the standardized questionnaire measuring erectile function (sexual health inventory for men).

Reviewing the success or lack of success of treatment, any adverse effects, and considering dose or treatment alterations is more likely to help achieve the patient's goal. Further education and/or basic sex counseling can be provided to the patient with or without his partner.

CONSULTATION

Consultation with subspecialists may be appropriate at varying intervals when managing a man with ED (Table 16). The major factors in determining the need for consultation are:

Table 16
When to Get Help

Anytime
Treatment failures
Anatomical or hormonal issues
Complex issues around sex, partnership
Severe psychological problems

1. The primary care clinicians comfort in discussing and managing treatment options.
2. The depth of the psychosocial and sexual issues involved.
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 comfortable about seeking help. The primary care clinician who both has good communication skills regarding sexual activity and is knowledgeable about first-line treatments can plan the initial work-up and treatment. Urologists can be helpful in difficult or complex situations involving ED or when the patient presents with an anatomical problem such as Peyronie's disease. An endocrinologist may be contacted to assist in managing men with diabetes that is difficult to control, hypogonadism, or evidence of pituitary dysfunction.

Sexual 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.
5. Helping couples resolve relationship problems.

The Association of Sex Therapists and Counselors can provide a directory of trained, certified sex therapists (telephone no.: 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's encounter most importantly include delivery effectiveness, that is, will the clinician understand the patient's needs and will the patient receive an effective response? Another dimension of expectations is the "hassle" of getting the information needed. Hassle includes uncertainty and following procedures, which is often more important to the provider than to the patient.

Before the development of specialization, primary care clinicians were the access point to the health care system for patients. With specialization, health care became more

splintered, and the need for coordination and responding to the needs of patients was assumed by health care organizations that view their businesses as customer-responsive organizations. However, these organizations 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 mutually beneficial management of health care resources.

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 minimum hassle *(68)*. Customer-responsive management has two dimensions:

1. Interacting with individual customers to identify their specific needs.
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 creates an infrastructure that allows that relationship to evolve. Relationships are important to obtain maximal beneficial outcomes with minimum of effort. The motivation for a relationship is mutual benefit, with the benefits serving as a measure of how well clinical solutions solve patient needs. In the ideal relationship, both parties totally understand each others' 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 with ease *(69)*.

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 enhances communication and the relationship between clinician and patient. These factors can increase the likelihood of patient satisfaction with medical visits and improve management of other non-sex-related medical issues. Discussing sexual matters can also add a sense of informality and, occasionally, humor to the clinical discussion, thereby helping to level the relationship between clinician and patient. These activities create patient value by solving individual patient problems. 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. Therefore, although paying attention to patient concerns about sexual dysfunction may divert some time and energy from other areas of medical care, it may have the benefit of strengthening the doctor–patient relationship, often resulting in more regularity with repeat visits and referrals of friends and family.

There is demand for ED services regardless of whether they are covered by insurance. Even if coverage for services is not available, patients may be willing to pay for services perceived by them to be high priority. Providing care for sexual dysfunction may be useful to building a medical practice. When management of ED is not reimbursed by insurance, it is considered elective care, and the patient determines the need for the service. If the clinician decides to provide elective care for ED it should be prescribed in an individual manner for the specific patient and in a way that the clinician would prescribe for them-

selves or a family member and be explained honestly with the patient what is involved and how much it will cost *(71)*.

External marketing for 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, and 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 focusing 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. If a clinician is considering spending more time working with patients who are experiencing sexual dysfunction, it might be useful 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 they might think is unimportant to the clinician.

Patient satisfaction results in:

1. Patients who more carefully follow instructions for care.
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.
4. Patients who continue to see one physician for their health care needs *(72)*.

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5 Psychosocial Aspects Related to Erectile Dysfunction

Michael A. Perelman, PhD

SUMMARY

The Sexual Tipping Point™ provides a useful model for conceptualizing etiology and a biopsychosocial combination treatment for all sexual dysfunction. Sexual coaching and pharmaceuticals can be integrated to address the organic, psychological, and cultural issues for men with erectile dysfunction (ED). The clinician's interventions are then focused on the predominant factors, although not ignoring the others. Using this model, the clinician can fully conceptualize ED by understanding the predisposing, precipitating, and maintaining psychosocial aspects of his/her patient's diagnosis and management, as well as organic causes and risk factors. The focused sex history and continuous re-assessment based on follow-up are the foundation of this method. Whether treated by a multidisciplinary team or a solo clinician, restoration of lasting and satisfying sexual function requires a multidimensional understanding of the forces that created the dysfunction. Every clinician must carefully evaluate his/her own competence and interests so that regardless of the method used, every patient or partner suffering from ED receives care designed to optimize sexual function and satisfaction.

Key Words: Combination treatment; erectile dysfunction; impotence; integrated treatment; multidisciplinary; sex therapy; sexual dysfunction; sexual tipping point.

INTRODUCTION

It is clear that both organic and psychosocial factors play a role in the etiology of sexual function and dysfunction and, consequently, in the diagnosis and treatment of erectile dysfunction (ED). Omnipresent psychogenic components exist in most potency problems. Anxiety may exacerbate even a mild organic situation into a seemingly total deficit. The manifest deficit frequently exceeds the actual organic impairment, even in "organically impotent" men. Despite the reality of organic pathogenesis, ED always has a psychogenic component, even if the ED was initially caused by illness, surgery, or other treatment *(1)*. Despite this reality, the treatments most commonly used for ED are overwhelmingly medical.

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Almost 90% of men seeking medical assistance for ED are treated with phosphodiasterase (PDE)-5 inhibitors *(2)*. Generally, PDE-5 inhibitors are safe and highly effective, with an efficacy rate of approx 70%. However, expert clinicians have suggested that the 20 to 50% dropout rate (generally quoted for medical treatments) also holds true for PDE-5 pharmaceuticals *(2,3)*. All three PDE-5 inhibitors approved by the Food and Drug Administration have excellent adverse event profiles, with few patients discontinuing treatment because of adverse events. Whereas some men try PDE-5 inhibitors because of curiosity and never intended long-term use, others become dissatisfied with these pharmaceuticals because of inadequate benefit. Additionally, a certain percentage of men do not experience treatment success with "level one" approaches because their organic pathology is so profound that it overwhelms the beneficial effects of the drug. In particular, men who have survived radical prostatectomy or who suffer from diabetes may require more powerful medical and/or surgical treatments, per the level two and three recommendations of the Process of Care Guidelines *(4)*. However, more than disease severity comes into play.

To fully understand this phenomenon of discontinuation of otherwise effective medications, one must examine the implications of shifting patterns in the health care delivery system. Primary care physicians (PCPs) have become the principal providers of care for men complaining of ED, with urologists typically seeing the more difficult or recalcitrant cases. Unfortunately, the history obtained by these PCPs and urologists is usually end-organ-focused. Significant psychosocial obstacles (PSOs) to restoration of sexual health frequently are neither examined nor uncovered. These PSOs represent an important cause of nonresponse and discontinuation of treatment *(3,5)*. For pharmaceutical treatment to be optimized, the complexity of these obstacles must be understood individually and/or collectively *(2,6,7)*.

Both PCPs and urologists now incorporate sex therapy concepts, and recognize that resistance to lovemaking is often emotional. Clearly, medical and surgical treatments alone are often insufficient to help couples resume a satisfying sexual life. There are numerous biopsychosocial obstacles to recovery that contribute to treatment complexity. All of these variables substantially impact compliance and sex lives *(6)*. Multiple sources of patient and partner psychological resistance may converge to sabotage treatment. Most of these barriers to success can be managed as part of the treatment, but too few clinicians are trained to do manage them *(6,8)*. This chapter focuses on identifying the psychosocial aspects related to the diagnosis and treatment of ED.

A MULTIDIMENSIONAL COMBINATION TREATMENT APPROACH

Combining sexual pharmaceuticals and sexual therapy optimizes treatment for all sexual dysfunctions, including men with ED. Less medication is required when immediate psychological causes of ED are modified *(6)*. Combination treatment is not a new idea, and sexual medicine is not the first specialty to use this broad-spectrum approach to improve satisfaction and efficacy. Psychiatry is now characterized by an emerging literature, demonstrating the benefit of combining both psychological and pharmacological treatments for numerous conditions *(9–11)*. For many medical specialties, including urology, combination treatment only referred to a drug regimen of two or more medications *(12)*.

On the other hand, sexual medicine already had a history of combination treatment. Sex therapists in the 1990s worked adjunctively with urologists when combining intracavernosal injection (ICI), intra-urethral insertion (IUI), and vacuum tumescence therapy *(13–17)*.

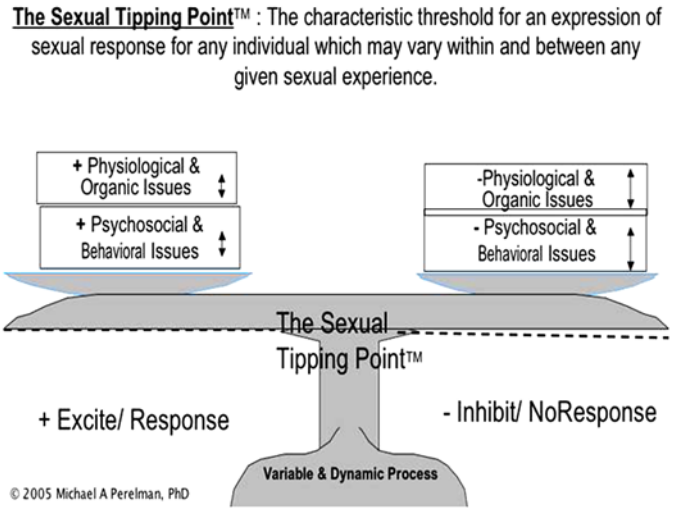

Fig. 1. The multifactorial etiology of sexual function and dysfunction. The Sexual Tipping Point™ is the characteristic threshold for an expression of sexual response for any individual, which may vary within and between any given sexual experience. The arrows symbolize the continuously variable contribution of each of the four categories depicted.

Numerous case reports summarized the benefits of combining sexual pharmaceuticals with various cognitive and behavioral strategies to treat ED *(18–22)*. Later recommendations strengthened the argument for the combination of medical and psychological approaches to the treatment of ED *(2,6,7,17,23,24)*. Perelman *(6)* conceptualized a treatment for integrating sex therapy and sexual pharmaceuticals based on a schema that illuminated the organic and psychosocial factors necessary to understanding the etiological basis of both sexual function and dysfunction.

THE SEXUAL TIPPING POINT MODEL

The mind and body both inhibit and excite sexual response *(25)*, creating a unique dynamic balance, which Perelman named the Sexual Tipping Point (STP; refs. *3* and *25a*). The STP is the characteristic threshold for the expression of a sexual response for any individual and may fluctuate dynamically within and between individuals for any given sexual experience. This response is expressed in a manner that may be inhibited or facilitated because of a mixture of both psychogenic and organic factors. The specific threshold for the sexual response is determined by multiple factors for a given moment or circumstance, with one factor or another dominating, whereas others recede in importance. This etiological model can serve as a foundation to provide a fuller understanding of the interface between psychosocial factors and the medical and surgical treatment of ED (ref. *3*; Fig. 1).

The STP model can also be used to illustrate a combination treatment approach in which sexual coaching and sexual pharmaceuticals are integrated efficaciously into diagnosis and treatment that addresses physiology, psychology, and culture. At any moment in the intervention process, the clinician determines the most elegant solution that focuses the majority of effort on fixing the predominant factor but not ignoring the others. Using the STP model, clinicians can visualize various components of ED by understanding the predisposing, precipitating, and lasting psychosocial aspects of their patient's diagnosis and management, as well as organic causes and risk factors *(3)*.

Sexual coaching integrates sex therapy and other psychological techniques into office practice, improving effectiveness in treating ED. In this manner, the clinician becomes informed about the psychological forces of patient and partner resistance, which impact patient compliance and sex lives beyond organic illness and mere performance anxiety. There is a synergy to this approach that is not yet fully supported by empirical evidence but is rapidly gaining adherents. Medicine and surgery currently emphasize evidence-based research. There is a seemingly inherent tension between this concept and the qualitative "art and science" of psychotherapy. Table 10 of the World Health Organization 2nd Consultation on Erectile and Sexual Dysfunction, Psychological and Interpersonal Dimensions of Sexual Function and Dysfunction Committee report *(26)* provides an excellent summary of the existing evidence for combination treatment—primarily for ED—with a few female sexual dysfunction studies. There is a growing consensus that combination treatment will be the treatment of choice for all sexual dysfunction as new pharmaceuticals are developed for desire, arousal, and orgasm problems in both men and women *(3,7)*.

This chapter discusses the diagnosis and case management of ED from the perspective of combination treatment, including: (a) definition; (b) etiology; (c) a focused sex history; (d) partner issues; (e) pharmaceutical selection, patient preference, and expectations; (f) follow-up that uses sexual pharmaceuticals as "therapeutic probes," illuminating causes of failure or non-response; (g) "weaning" and relapse prevention; and (i) referral.

DEFINITION

The human sexual response cycle can be viewed as four interactive, nonlinear phases: desire, arousal, orgasm, and resolution *(5,27,28)*. Sexual dysfunctions are disruptions of any of these phases, including the sexual pain and muscle spasm disorders *(29)*. Although each sexual dysfunction is defined independently, they may overlap each other. ED is defined as the inability to achieve and/or maintain an erection that is adequate for satisfactory sexual performance *(30)*. Psychogenic ED is defined as the persistent inability to achieve or maintain an erection satisfactory for sexual performance predominantly or exclusively because of psychological or interpersonal factors. Epidemiological studies have demonstrated the prevalence of psychosocial factors in the etiology of ED, with special emphasis on self-reported depressive symptoms. In addition to the clinical generalized versus situational subtypes, psychogenic ED can be characterized as life-long (primary) or acquired (secondary; ref. *31*).

ETIOLOGY

ED was not always presumed to have both organic and psychosocial etiology. For nearly half of the 20th century, the etiology of ED was viewed primarily through a psychogenic lens. Freud highlighted internal conflict and deep-seated anxiety as the root of sexual problems. Later, psychodynamic theorists postulated multiple psychogenic explanations for ED, with unexpressed anger and unconscious aggression as recurring themes. Despite the prevalence of these views, no research ever established any specific psychological trait or style as exclusively associated with ED, although depression and anxiety disorders sometimes manifest as sexual dysfunction. Furthermore, relationship problems and other psychosocial stresses frequently contribute to or result from ED. Men with acquired and/or situational ED should particularly be examined for contextual factors, which play a significant role. For example, pregnancy fears should be explored when the reason for professional referral was related to a female partner's desire to conceive.

By mid-century, Masters *(27)* and Johnson *(32)* and later Kaplan *(5)* nominated limited sexual knowledge, predisposing negative sexual experiences, and anxiety as the primary culprits of ED. Although acknowledging the importance of organic factors, they emphasized cognitive and behavioral prescriptions to improve patient function. Together, they catalyzed the emergence of sexual therapy. Sexual therapists view both intra- and interpersonal factors as causes and consequences of ED. For the next two decades, a psychological sensibility dominated discussions of both etiology and treatment of ED.

Bancroft *(25)* postulated a central excitatory and inhibiting mechanism, adding greater understanding of the role of anxiety and other psychogenic factors in ED. Several investigators and clinicians have described how anxiety's role in initiating or maintaining sexual arousal difficulties was often mediated by cognition. They showed that alterations in perceptual and attentional processes resulted in erectile variation *(31,33)*. Furthermore, performance anxiety led some men to engage in behaviors such as "spectatoring" during intercourse, which focused attention on negative cognitions. The consequence of this "negative" focus away from exciting stimuli dampened erectile capacity and response *(32)*.

Although past literature suggested various psychogenic etiologies, there was also significant evidence of organic determinants of male erectile variability. The increased diagnostic sophistication of the late 1980s triggered a progressive shift toward surgical and, predominantly, pharmaceutical treatments for ED. Urologists established hegemony by the 1990s, with the successful marketing of various penile prostheses, as well as ICI and IUI systems. The apex of biological determinism may have culminated with the extremely successful launch of sildenafil and its subsequent publicity as the 20th century ended. At that time, clinicians and most of the public at large viewed ED and its treatment almost exclusively in organic terms.

The new millennium finds most sexual medicine experts embracing a more enlightened and sophisticated "mixed" paradigm, in which the importance of both organic and psychogenic factors are valued for their role in predisposing, precipitating, maintaining, and reversing sexual dysfunction. Mental health professionals catalyzed this rebalancing of perspective *(6,18,34,35)*. Those mental health professionals successfully advanced an obvious concept once again: psychosocial as well as organic factors are critical to understanding sexual function and dysfunction. Sexual pharmaceuticals can frequently restore sexual capacity, but rewarding sexual activity is only experienced when psychosocial factors also support restored function in the context of an individual's life.

Similarly to all sexual dysfunction, ED is best understood as an interaction of organic and psychogenic factors. Although the exact nature of a biological predisposition is not known, genetic variability in the arousal threshold is probable. It is reasonable to presume that the "threshold" for erectile onset and latency may have a distribution curve similar to numerous other human variables. This view is not unlike theories regarding biologically predisposed thresholds for ejaculation described by Waldinger *(36,37)* and Perelman *(20, 37a)*. Determination of whether the physiological mechanism(s) of this hypothetical "threshold" is central, peripheral, or a combination requires further research. However, this pattern of susceptibility results in manifest dysfunction through interaction with various sexual circumstances, including intra- and interpersonal dynamics as well as environmental and medical risk factors. Therefore, normal variation in the function of the nervous systems could result in a somatically determined variation in both men and women's desire, arousal, and orgasm response in terms of onset, latency, and capacity, and more *(3)*.

Furthermore, it is useful to hypothesize a biological set-point for erectile latency, which is determined by multiple organic and psychogenic factors in varying combinations over

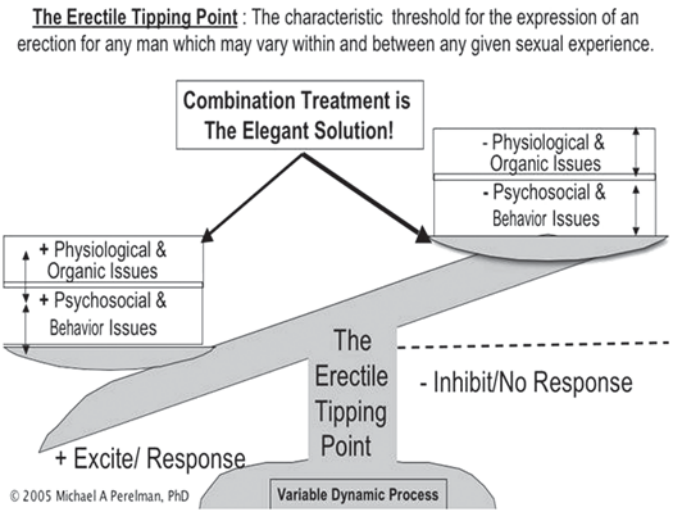

Fig. 2. Combination treatment optimizes response: integrating sex therapy and sexual pharmaceuticals. The Erectile Tipping Point is the characteristic threshold for the expression of an erection for any man, which may vary within and between any given sexual experience.

the course of a man's life. The roles of each of these factors in the endpoint response for an individual at a particular moment in time is illustrated using the STP model. Consequently, each man will have a variably expressed erectile threshold or erectile tipping point (ETP), which may be inhibited or facilitated by a mixture of both psychosocial and organic factors. The specific threshold for erection is determined by multiple factors for any given moment or circumstance, with one factor dominating as others recede. This concept provides a useful heuristic device to describe the various vectors that impact both normal erections and ED. In this manner, the ETP model can be used to illustrate combination treatment, where sexual coaching and sexual pharmaceuticals are integrated together to provide a solution for the treatment of ED (Fig. 2; ref. *3*).

ASSESSMENT

The clinician must determine whether the man has an illness or is ingesting a drug that could cause ED. However, this chapter presumes that the necessary diagnostic procedures, including physical examination and laboratory tests, have been conducted in a manner consistent with recommendations incorporated elsewhere in this text (*see* Chapters 4, 5, and 11). The emphasis of this chapter is the psychosocial balance of the assessment and treatment equation. The psychosocial/sexual history should not be arbitrarily separated from the medical history. An integrated sexual and medical history yields a significant amount of information regarding a man's sexual health and relationships.

A focused sexual history rapidly identifies the numerous causes of sexual dysfunction (e.g., insufficient stimulation, depression) and points toward predisposing and precipitating factors. A broad understanding of the current sexual experience is obtained within the context of a man's life. This "sex status" is an integrated, fluid assessment in which the patient's response is repeatedly re-evaluated through follow-up. Therefore, determining the initial response to the clinician's pharmaceutical and behavioral prescriptions is a critical component of a continuous psychosocial evaluation.

Three key questions regarding diagnosis, etiology, and treatment must be ascertained:

1. Does the patient really have a sexual disorder and what is the differential diagnosis?
2. What are the underlying organic and/or psychosocial factors?
   a. What are the organic factors?
   b. What are the "immediate" maintaining psychosocial causes (e.g., current cognitions, emotions, and behaviors)?
   c. What are potential "deeper" predisposing and precipitating psychosocial causes?
3. Do the underlying factors require direct attention before initiating ED treatment, or can these factors be bypassed or concurrent *(3,38)*?

A focused sexual history is the methodology used to answer these questions. The clinician mastering this method can capture all initial necessary data in less than 10 min, even if additional consultations and/or a later referral are required. The necessary information to answering these three questions should be obtained in a manner that does not sabotage the patient–clinician relationship. ED treatment should be started as soon as possible, with regular re-evaluations of the patient's response. Comprehending psychosocial issues helps optimize patient response and minimizes relapse potential.

The previously mentioned four phases of human sexual response (i.e., desire, excitement, orgasm, and resolution) are rapidly assessed to ascertain the immediate and remote causes of the ED. Obtaining the necessary information to diagnose the ED and to begin developing a treatment plan is the primary goal of the evaluation visit. However, empathy and patient rapport must never be sacrificed in favor of obtaining the critical details. Rapport is strengthened when the patient is asked direct questions in a comfortable, reassuring, empathic manner. Both patient and clinician can obtain an understanding of the problem and benefit from a mutually derived treatment plan. The therapeutic context works best when it is humanistic, emphasizing good communication and mutual respect.

Numerous continuing medical education programs have addressed the problem of encouraging clinicians to initiate discussion of sexual issues by emphasizing the importance of sexual dysfunction as a biological marker of disease. Clinicians should use direct inquiry, using nonjudgmental screening questions. They should inquire directly about any change in the patient's sexual experience and his beliefs regarding the cause of those changes *(39,40)*. Additionally, physicians should allow the patient's story to unfold in the available time. A physician should be carefully guided with a short list of predetermined questions but must be mindful about interrupting in the middle of the patient's explanation.

Whereas most patients are eager to "tell their story" to an accessible knowledgable clinician, others may be ambivalent about discussing details. This anxiety must be appreciated, even as the clinician proceeds. Reciprocally, the interview must be conducted at the clinician's comfort level. The clinician pursuing an analysis of sexual behavior must monitor his/her own comfort to instill confidence and facilitate patient openness.

Evaluation and treatment format partly depends on whether or not the patient is single or in an ongoing relationship. However, most patients visiting a clinician are likely to be seen alone, whether they are single or coupled *(6)*. If time permits, a physician should encourage partner attendance for those patients in a committed relationship, thereby allowing assessment and counseling for both partners. However, this issue should never be forced. Format of treatment is a therapeutic issue, and rapport should never be sabotaged *(6)*. Although conjoint consultation is a good policy, it is not always a practical and/or correct choice. It is usually better to evaluate a man in a new relationship alone,

rather than to stress a new relationship by the clinician insisting on a conjoint visit. The risk–benefit ratio of partner participation is a legitimate issue for both the couple and the clinician. Additionally, sometimes a patient does not have a partner. The current sexual partner may not be the spouse, raising legal, social, and moral issues. Of course, the patient's desire for his partner's attendance may be mitigated by various intrapsychic and interpersonal factors, which should initially be heeded and respected.

It is frequently not necessary to require the partner to attend the office visit, despite Continuing Medical Education program recommendations to the contrary. Although important information can be obtained from the partner's perception of the problem, partner cooperation is more important than partner attendance in the evaluation and treatment of ED *(6,41)*. If the partner is cooperative from the start, sex pharmaceuticals plus sex counseling and education are likely to be effective. Many women cooperate with their partners or facilitate sexual activity even when they do not know the man is using a sexual pharmaceutical. It is critical that the pharmaceutical facilitate capacity and be used in a manner (knowingly or not) that the couples experience as unobtrusive and preferably erotic.

SEXUAL STATUS EXAMINATION

The sexual status examination (SSE) is the most important assessment tool at the clinician's disposal and is most evocative of the "review of systems" common to all aspects of medicine *(6,29)*. A focused SSE critically assists in understanding and identifying the immediate cause of the ED (i.e., the actual behavior and/or cognition causing or contributing to the sexual disorder). The clinician focuses on finding potential physical and specific psychosocial factors relating to the disorder. The clinician pursues a description of the sexual symptom and the history of the sexual symptom in detail. All patients assessed for sexual difficulties should be screened briefly for concurrent psychopathology. This does not need to be in-depth pursuit, unless there is evidence of a significant psychiatric disorder.

Information about the onset and progression of symptoms as well as a detailed description of the patient's sexual symptom should be obtained. The physical and emotional circumstances surrounding the onset of a difficulty are important for the assessment of both physical and psychological causes. If these details are not spontaneously offered, the clinician must elicit them. By juxtaposing detailed questions about the patient's current sexual practices and history, an understanding of the causes of dysfunction and noncompliance can be unveiled.

A detailed analysis of the patient's current sexual behavior and the couple's erotic interaction can help eliminate potential organic causes. Additionally, the sexual information evoked in SSEs helps anticipate noncompliance with medical and surgical interventions. Modifying immediate psychological factors may result in the need for less medication. Generally, urologists and PCPs intervene with pharmacotherapy and brief sexual coaching, which address immediate causes (e.g., insufficient stimulation) directly and intermediate issues (e.g., partner issues) indirectly and are rarely focused on deeper issues (e.g., sex abuse). In fact, a referral is usually appropriate when deeper psychosocial issues are primary *(7)*.

Early in the SSE, a physician should obtain a description of a recent experience that incorporates the sexual symptom. One question helps elucidate many of the immediate and remote causes: "Tell me about your last sexual experience." The clinician can quickly

identify common immediate causes of ED from the patient's response. Several frequently identified contributors to ED include insufficient stimulation (e.g., a lack of adequate friction), a lack of subjective feelings of arousal, fatigue, and negative thinking *(42)*. Sex is fantasy and friction, mediated by frequency *(6)*. To function sexually, men need sexy thoughts and not just adequate friction. Although fatigue is a common cause of sexual dysfunction in our society, negative thinking/anti-fantasy is also a significant contributor *(3)*.

The clinician must determine if the aforementioned "last sexual experience" was a "typical" one. Almost any man can be questioned regarding how his most recent sexual experience differed from those with other partners. A conservative man may presume the clinician was referencing only premarital comparisons, whereas some single and married men may make a current comparison. Sex therapists typically evaluate the quality and pattern of a man's romantic relationships, but PCPs and urologists usually obtain only a brief status of the current relationship.

The clinician should inquire about desire, fantasy, frequency of sex, and effects of drugs and alcohol using focused open-ended questions. Did arousal vary during manual, oral, and coital stimulation? What was the masturbation style, technique, and frequency? Idiosyncratic masturbation and retarded ejaculation are often hidden causes of ED *(43–45)*. When possible, it is useful to inquire about the patient's thoughts during various types of sexual behavior. The following questions may be helpful: Does the patient experience anxiety about sexual failure early in the day before sex is even on the horizon? Does he worry about "getting too soft" and "pulling out" even when he has not "fallen out"? What is the specific content of his negative thinking? Is he fearful of his partner's reaction and worried about what his partner is thinking? Does he judge himself harshly? The mind can interfere with sexual arousal as well as disrupt the restorative benefits of current and future sexual pharmaceuticals. Identifying and modifying cognitions may be key to facilitating sexual satisfaction and recovery *(3)*.

Of course, discovering the reason that a man had intrusive thoughts that impeded his sexual functioning fascinates sex therapists. We want to understand the psychosocial factors maintaining the psychic structure that resulted in the distracting thoughts that implicitly/explicitly reduced sexual arousal? We want to understand the predispositions of the patient to have distressing thoughts and to know his full psychosocial history. However, it is only critical to identify and understand those current psychosocial obstacles that maintain the dysfunctional process. Careful listening frequently provides answers to these questions before they are articulated. If not described spontaneously by the patient, inquiries should be made that are guided by clinical judgment and sensitivity.

EXPLORING OTHER PSYCHOSOCIAL ISSUES

The vast majority of evaluations do not require an exhaustive sexual and family history. Inquiry about these issues should be highly selective so that the interview does not become unnecessarily lengthy. The patient may not experience the difficulty at all times or may indicate ED is manifest only under certain circumstances. This type of fluctuating pattern does not usefully discriminate between psychogenic and organic etiology. In cases of secondary ED, the clinician will hear of an important change from function to dysfunction. This change in function may be preceded by, or concurrent with, major life stress (e.g., loss of a job). The clinician should examine the time period of the sexual change for causation clues, or the patient may identify it spontaneously. Areas known to possibly alter sexual function from the perspective of psychosocial stress may be explored,

including, but not limited to, health, family, and work. However, this process does not need to be completely accomplished during the first visit.

Patients sometimes tell clinicians the exact cause of change. By "interviewing the crisis," the clinician obtains a clear picture of the current situation as well as an understanding of what changes occurred and the patient's response to those changes. A clinician should assess whether the ED progressed slowly with age or whether there was an acute shift in capacity. It is equally important to assess why the patient is seeking assistance at this time.

Some patients provide too much detail that is tangentially relevant but is not primary. Here, the clinician must gently interrupt and refocus the interview and acknowledging the potential importance of the patient's statement. For example, the clinician might say, "That's very interesting, but I wonder if we might postpone that example. We will come back to that, but today we need a broader context." Alternatively, "Okay, but what happened next?" Establishing and maintaining rapport while gathering the relevant details remains the goal.

PREVIOUS TREATMENT APPROACHES

The discussion of the most recent sexual experience and an elaboration on current functioning frequently evokes information about previous treatment approaches. Earlier results, including herbal therapies, folk therapies, and earlier professional treatments, should be obtained. Furthermore, past psychiatric treatment, early sexual experiences, developmental issues, substance use and/or abuse, and partner issues may be mentioned. The clinician should focus on the material that appears most important to understanding the sexual disorder's etiology, which should emerge naturally from the patient's description.

PSYCHIATRIC CONSIDERATIONS

All patients should be briefly screened for obvious psychopathology that would interfere with the initiation of ED treatment. Are any psychiatric symptoms the cause or the consequence of the sexual disorder? ED is associated with a statistically significant increase in depression. The severity of the patient's depression should be clarified, and all patients with major depression should be queried for suicide risk. Depressive symptoms might alter response to therapy of ED, whereas the treatment of ED may improve a reactive depression *(46)*. The history interview must "parse out" whether the ED is causing depression or whether the depression and its treatments (e.g., selective serotonin re-uptake inhibitors) are causing the ED. The reader is recommended to the ref. *26* for a detailed discussion of sexual pharmacology.

When evaluating a patient with various psychopathological states (e.g., stress, phobias, personality disorders), the clinician must consider if the patient's emotional conflicts are so severe that ED treatment should either be postponed for another time or occur concurrently with treatment for the emotional distress. The modal choice is likely to be a simultaneous initiation of the ED treatment along with a referral to a mental health practitioner to improve patient management. However, a person who is addicted to drugs and/or alcohol is not a candidate for ED treatment until he/she is detoxified and no longer taking the drug. It is sometimes appropriate to postpone treating the patient for the ED until psychotherapeutic consultation is available. Subtle personality factors, such as fragile self-esteem, anxiety, and fear of being negatively evaluated by others, are frequently prev-

alent in men with sexual concerns. However, these issues would not typically result in postponing treatment for ED *(28,38)*.

FAMILY AND EARLY PSYCHOSEXUAL HISTORY

The history may provide insight into the deeper causes of the patient's dysfunction and may reveal cultural and/or neurotic origins of the problem. Factors from the past may include losses and/or a variety of traumas, including negative past sexual relationships and negative past interpersonal relationships. Other factors, such as cultural and religious restrictions, may also be significant. However, the physician can usually proceed with "Process of Care" level one treatments *(4)* with confidence and the knowledge that time for further exploration is available at follow-up.

PARTNER–RELATIONSHIP ISSUES

Sexual therapists assess the pattern and quality of the man's romantic relationships, but all clinicians should minimally assess marital status as well as living and dating arrangements. The clinician should clarify difficulties with the current interpersonal relationship and determine whether the partner has any sexual dysfunction. Although the clinician may grasp the couple's interactions from the first interview, it remains to be determined if deeper difficulties in the couple's relationship are the cause of the ED. Many partner-related nonsexual issues can also adversely impact outcome, which may be screened. The physician should monitor the degree of acrimony when the patient describes his complaints. Are the emotions mild manifestations of the frustrations of daily life, or is the anger, resentment, or hurt a maintaining or precipitating factor?

All men need a determination of whether or not the problem is partner-specific. The physician should ask if sexual relations were ever good with the current partner, what changed, and what is the patient's view of causation. The clinician must ascertain which of several categories are etiologically relevant: inadequate sexual technique, poor communication, incompatible sexual fantasies, or no physical attraction. Power struggles, transferences, commitment/intimacy issues, and partner pathology all may have implications for the ED problem. The clinician must decide if the degree of relationship strife is too severe to initiate the ED treatment. Then, relationship counseling can be provided or a referral may be made, and ED treatment can be postponed. However, it will be the bias of many to err on the side of giving the relationship and treatment every possible chance *(3)*.

THE SINGLE PATIENT

A single man's sexual symptom may or may not relate to relationship difficulties. Marital status may be a sensitive issue, and sexual orientation issues require the same, if not greater, sensitivity on the clinician's part. Besides sexual pharmaceuticals, numerous treatments are available for single men with ED, including sexual attitude change, assertiveness training, masturbation exercises, and social skill development in addition to ICI, IUI, and surgery (all per Process of Care Guidelines; refs. *4* and *31*).

QUESTIONNAIRES

In training, questionnaires provide students with a range of diagnosis and treatment foci. Questionnaires in research allow for standardization of diagnostic data collection

and provide recognized treatment endpoints. This topic is reviewed thoroughly in the ref. *26*. Although some clinicians may choose to use current or future instruments to facilitate the history-taking process, such instruments must be incorporated in a manner wherein rapport is maintained, as discussed earlier.

TREATMENT

Treatment is a dynamic process requiring ongoing re-assessment. The previously described "sex status" is used and regularly re-applied during the treatment process. As the degree of treatment intrusiveness increases, there must be a continuing awareness of the intra- and interpersonal forces that interfere with, or enhance, medical and/or surgical outcome *(4,31)*. It is the essence of sexual coaching to optimize pharmaceutical efficacy.

Rosen *(6,18,34,35)* summarized the following approaches used by sex therapists: (a) anxiety reduction and desensitization; (b) cognitive-behavioral interventions; (c) increased sexual stimulation; and (d) interpersonal assertiveness and couples' communication training. Regardless of etiology, most physicians initiate treatment with a PDE-5, even if the ED is primarily psychogenic in origin. This partly results from the extremely high PDE-5 efficacy rate with psychogenic ED *(47)*. There are three highly efficacious PDE-5 inhibitors that have been approved by the Food and Drug Administration as treatments for ED: sildenafil, vardenafil, and tadalafil, all of which are used worldwide. Simple cases respond well to these agents when proper advice on pill use, expectation management, and a cooperative sex partner are provided. Clinicians should provide choice and unbiased, fair-balanced description of treatment options, including pharmacokinetic properties, efficacy studies, and the clinician's patients' experiences. Consequently, the patient will attribute greater importance to the clinician's opinion. Clinicians who provide these important guidelines that incorporate patient preference will experience enhanced healer–patient relationships, minimized PSOs, and improved compliance. Patient preferences may reflect key marketing messages of the respective pharmaceutical companies. Clinicians can take advantage of this hypothesis to increase efficacy. If safety and long-term side effects are a primary concern, sildenafil has the oldest/longest database *(48)*. In vitro selectivity may or may not translate to clinical reality, but some patients believe vardenafil provides the best quality erection with the fewest side effects *(49)*. Tadalafil clearly provides the longest duration of action *(50)*.

The sexual status interview can create awareness of the patient's sexual script and expectations, leading to improved recommendations and management *(6)*. Here, sexual script refers to style and process of an individual's or couple's premorbid sex life *(51)*. A clinician can improve outcome by clarifying whether a patient would perform better by practicing with masturbation or by re-introducing sex with a partner. The first time a recently divorced man (who is using condoms for the first time in years) tries a sexual pharmaceutical, he will probably perform better if he first masturbates while wearing a condom, than if he attempts partnered sex.

Comprehending pharmacokinetics (onset, duration of action, etc.) plus sexual script analysis can optimize treatment by improving the correct prescription selection probability. Pharmaceutical selection can be fine-tuned by understanding the couple's "sexual script," leading to better orgasm and sexual satisfaction *(2,5,7)*. Dosing instructions should focus on returning to previously successful sexual scripts, as if medication was not even necessary. Thus, the patient is likely to receive adequate stimulation, and the treatment will be perceived as partner-sensitive. Recommendations for sexual recovery are improved by

awareness of individual differences. Differences in sexual style (sex script analysis) can determine which medication can be effectively used by a couple, with less change required in their "normal" sexual interactions. Matching the right medication to the individual/couple based on pharmacokinetics and sexual script increases efficacy, satisfaction, compliance, and improved continuation rates. Rather than changing the couple's sexual style to fit the treatment, a physician should try to fit the treatment to the couple *(2,3,5,7)*.

FOLLOW-UP AND THERAPEUTIC PROBE

Follow-up visits vividly illustrate the importance of integrating sexual therapy and pharmacotherapy. The literature emphasizes how PDE-5 nonresponder outcome may be improved through patient education (e.g., food–alcohol effect), repeat dosing, partner involvement, and follow-up *(52,53)*. By scheduling a follow-up the day the prescription is written, clinicians can increase their success. Follow-up is essential to ensuring an optimal treatment outcome. Failures, which can be examined at follow-up, reveal critical information. The sexual pharmaceutical can serve as a therapeutic probe, illuminating the causes of failure or nonresponse *(2,3,5,7)*.

Retaking a sexual status provides a convenient model for follow-up management. During follow-up, the clinician should monitor side effects, assess success, and consider whether an alteration in dose or treatment is required. Until future comparator trials determine which drug works best for which person(s) under which context, clinicians should trust their own judgment and experience. However, they must also provide ongoing education to patients and their partners and involve them in treatment decisions. Encouraging immersion in the sexual experience through fantasy may be helpful to eroticize both the experience and the partner. Although the fantasy could be about anything erotic, masturbatory fantasies are often quite effective. Fantasizing about an earlier time with the current partner may be helpful for men who feel guilty about fantasizing in their partner's presence.

Follow-up also provides an opportunity to confirm whether partner cooperation is present. When not present, a clinician should consider contacting the partner. Active steps must then be taken to evoke the partner's support for successful treatment. When follow-up reveals significant relationship issues, interaction with the partner often increases success rates. If the patient is reluctant, or if the partner initially refuses, a physician should seek contact with the partner via telephone. Most partners find it difficult to resist speaking just once about "potential goals" or "what's wrong with their spouse." This contact provides an opportunity for empathy and potential engagement in the treatment process. It also minimizes resistance and improves outcome. However, this approach depends on the clinician's interest and time constraints. When possible, clinicians should counsel partners, either directly or indirectly. Some partners require direct professional intervention, but many could benefit from information provided by the patient with ED and/or public and private media formats. However, the more problematic the relationship, the less likely that education will be able to successfully augment treatment in and of itself. Although a referral to a mental health professional would not necessarily be accepted, it would then be required *(6,7,54)*.

WEANING AND RELAPSE PREVENTION

The ED literature contains minimal discussion of relapse prevention. However, ED is recognized as a progressive disease in terms of underlying organic pathology. A gradual

alteration in the erectile threshold for response or ETP creates clear potential for a re-emergence of dysfunction. To facilitate success and prevent relapse, a continuing dialogue with patients is critical. Psychosocial issues may evoke noncompliance and are important in differentiating treatment nonresponders from "biochemical failures." Reframe failures into learning experiences and eventual success. McCarthy *(55)* and Perelman *(3,6,7)* have recommended that the clinician schedule follow-up or "booster" sessions. Continuous monitoring keeps the patient on course and provides opportunity for supplemental treatment, as needed. Using sexual therapy concepts in combination with sexual pharmaceuticals offers potential for minimizing the amount of drug needed as well as the opportunity for temporary or permanent weaning from medication, depending on the severity of organic and psychosocial factors *(3,7)*. This is an important benefit to this approach, especially for the patient who prefers to "do it on his own." Over time, the progressive exacerbation of either organic factors (e.g., endothelial disease) or PSOs may adversely impact a previously successful ED treatment regimen. Although there is no current evidence for tachyphylaxis, there is also no long-term evidence to indicate efficacy of PDE-5 beyond 10 yr. Although escalating doses and providing alternative medications may be the initial response of most clinicians, these processes may be modulated and mediated by sexual counseling and education. Sexual therapy techniques and strategies are extremely important in facilitating long-term medication maintenance and continued success *(3,7)*.

COMBINATION THERAPY MATRIX

Sexual medicine clinicians may successfully use two alternative methods for combination treatment. First, PCPs and urologists can work alone and integrate sexual coaching with their sexual pharmaceuticals to treat ED. Second, clinicians may collaborate with sexual therapists through an organized multidisciplinary team approach. The method used varies according to the presenting symptoms, as well as the differing expertise of the health care providers. Use of these two methods is determined by three decisions: (a) the consulted clinician must assess his/her interest, training, and competence; (b) the clinician must evaluate the biopsychosocial severity and complexity of the ED; and (c) patient preference, multidisciplinary availability, and the two previous criteria determine who initiates treatment as well as how and when to refer. Both the solo clinician and the multidisciplinary team are still guided by the treatment algorithms described in "The Process of Care" and other step–change approaches *(4)*.

The decision regarding whether to function as a solo clinician or as a multidisciplinary team is partially determined by the psychosocial complexity of the case *(2,7,26)*. The patient is diagnosed by the health care professional as suffering from mild, moderate, or severe PSOs, which are impediments to successful restoration of sexual function and satisfaction. Althof *(2)* described PSO severity and Perelman adapted and defined it as follows:

1. Mild PSOs: No significant or mild obstacles to successful medical treatment.
2. Moderate PSOs: Some significant obstacles to successful medical treatment
3. Severe PSOs: Substantial to overwhelming obstacles to successful medical treatment *(7)*.

The sexual history forms the basis for this diagnosis. The diagnosis can be modified subsequently to follow-up, because the treatment is continuously re-evaluated. The solo clinician either continues treatment and/or refers according to an outcome matrix described in Table 1.

Table 1
Guidelines for Management of Erectile Dysfunction Based on PSO Severity

	PSO Severity		
Method	*Mild PSOs*	*Moderate PSOs*	*Severe PSOs*
Clinician sexual coach	Frequently	Sometimes	Rarely
Multidisciplinary team	Frequently	Frequently	Frequently

PSO, psychosocial obstacle.

Although a multidisciplinary team including multiple medical specialists and a sexual therapist can treat almost all cases, this type of approach is labor-intensive and often economically unrealistic. Additionally, some geographical regions lack the available manpower and expertise. However, a solo clinician commonly successfully integrates sexual coaching with sexual pharmaceuticals when treating ED. These same clinicians can refer or, possibly, use a multidisciplinary team model when confronted by patients with ED who are suffering from a more recalcitrant psychosocial complexity *(2,5,7)*.

REFERRAL

Active steps must be taken if the partner does not support successful resolution of the ED. Adjunctive treatment by a sexual therapist for the partner or conjoint treatment may be required *(6)*. Profound relationship strife reduces the likelihood that patient–partner sexual education will successfully augment treatment in and of itself. A referral to a mental health professional should then be recommended. There are also many reasons to refer patients to numerous other medical specialists (e.g., gynecologists, neurologists, psychopharmacologists, endocrinologists). Describing these criteria is beyond the limitations of this chapter *(7)*.

Maintaining a multidimensional understanding of ED does not require a clinician to adopt a multidisciplinary team approach to treatment. However, it is critical that more clinicians cultivate a perspective that is consistent with the biopsychosocial consensus initially reflected by the "Process of Care Guidelines" and elaborated on in the published Proceedings of the World Health Organization 2nd International Consultation on Erectile and Sexual Dysfunction. These publications are the result of multidisciplinary cooperation, with collaborative knowledge that is independent of specialty of origin. These consensus reports address the integration of medical, surgical, and psychosocial treatments for ED *(6,26)*.

Models for health care professionals working together vary according to clinician specialty training, interest, and geographical resources. Some expert clinicians work alone, whereas other PCPs, urologists, and gynecologists have set up in-house multidisciplinary teams in which nurses, clinician associates, and master's level mental health professionals provide the sexual coaching *(56)*. This in-house model has obvious advantages and disadvantages. Patients with more severe PSOs are "referred out" for psychopharmacology, cognitive-behavioral therapy, and marital therapy in various permutations, which are provided by doctoral level mental health professionals. However, many clinicians refer within their own academic institution or within their own professional referral network —a kind of "virtual" multidisciplinary team.

Identifying psychological factors does not necessarily mean every clinician should treat them. If PCPs or urologists are uncomfortable or not inclined to counsel, they should consider referring or working conjointly with a sexual therapist. Some PCPs and urologists do not have the expertise to adequately diagnose PSOs, independent of their ability or willingness to treat these factors. Clinicians who are aware of their limitations will refer their patients for adjunctive consultation. When clinicians are uncomfortable discussing sex, many important issues remain unexplored because of anxiety and time constraints. Without a referral, this is detrimental to treatment success. Sexual therapists can effectively educate the patient and enhance his response to the sexual situation. They also help patients adjust to second- and third-line interventions, such as injection and penile prosthesis.

CONCLUSION

Sexuality for a man and his partner is a complex interaction of biology and culture as well as past and current intra- and interpersonal psychology. A biopsychosocial model of ED provides a compelling argument for a combination treatment, which integrates sexual coaching and sexual pharmaceuticals. Although further research is needed, it appears probable that combination treatment is the treatment of choice for all sexual dysfunction as new pharmaceuticals are developed for desire, arousal, and orgasm problems in both men and women *(21,26,42)*. Continuous re-assessment with a sexual status interview is the foundation of this approach. Clinically facilitating sexual satisfaction requires a multidimensional understanding of the patient's STP, whether it is implemented by a solo clinician or a multidisciplinary team. Every clinician needs to carefully evaluate his or her own competence and interests when considering the treatment of a man's ED so that the patient receives optimized care irregardless of the modality used. Often, neither medical nor surgical interventions in and of themselves provide longlasting improvement and satisfaction for a patient or partner suffering from ED. However, this author is optimistic regarding a future using combination treatment that integrates sexual therapy with current and newer medical and surgical treatments to improve sexual function and satisfaction.

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6 Hormonal Evaluation and Treatment

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SUMMARY

Hypogonadism is a problem that has been known about for millennia, both as an endocrine disease and as an age-related phenomenon. Normal aging results in changes in androgen status and alterations in feedback sensitivities, decline in synthetic capacity, changes in serum availability, aging of responder cells, and interaction with other hormone and regulatory systems (e.g., dihydroepiandrosterone, growth hormone, melatonin, leptin). There are significant variations in how hypogonadism develops in terms of timing, the systems involved, and the extent of the changes. Genetic factors may play a part in these variations.

The clinical picture can include alterations in bone mass, energy level and motivation, erectile function, fat mass, hair and skin, hematocrit, low- and high-density lipoprotein, cholesterol, leptin production, mood and cognition, muscle mass, quality of life, sexual desire, sleep, spatial cognition, vasomotor status (hot flushes), and insulin sensitivity. The biochemical diagnosis is made by measuring the total serum testosterone levels, however, in the obese and the elderly, the levels of sex-hormone binding globulin increase, reducing the metabolically active component. The optimal measure is a bioavailable testosterone. Treatment is reserved for men with symptomatic hypogonadism (a combination of clinical and biochemical abnormalities) and is directed at restoring normality. Injections and oral testosterone formulations (non-methylated) are available but transdermal preparations, notably gels, are often preferred by patients for their steady levels. A 3-mo trial may be indicated in borderline cases.

The presence of either prostate or breast carcinoma is an absolute contraindication. At present, it is not thought that testosterone supplementation is responsible for carcinogenesis. All treatment should be adequately monitored for adverse effects.

Key Words: Testosterone; androgen; hypogonadism; treatment; testosterone gel.

INTRODUCTION

Doubts have been raised regarding whether the importance of androgen status to male well-being is a modern, possibly even commercial, construct. However, evidence from ancient Eastern and Western literature points to the importance of gonads in male health *(1)*. More than 50 yr ago, low testosterone levels were recognized as causing the "male

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climacteric" *(2)*, and concern for indiscriminate use of testosterone was gaining increasing awareness *(3)*. Men with low levels of testosterone commonly experience alterations in their sexual function. The other side of this connection is not as frequently seen. Patients who have erectile dysfunction (ED) only rarely have hormonal abnormalities that either contribute to or associate with their presenting complaint. However, the sexual problems of some hypogonadal men may be alleviated by directly addressing their lack of testosterone; thus, an understanding of this reversible cause of ED valuable.

EFFECTS OF TESTOSTERONE ON SEXUAL FUNCTION

It is commonly accepted that low serum testosterone may result in the combination of low sexual desire and erectile difficulties. In many patients, the correlation between sexual function and serum testosterone 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. Hypogonadal men may be capable of sexual erections; for example, only 75% of men who received anti-androgen therapy were unable to develop erections when tested with erotic video challenge *(4)*. Additionally, hormonal supplementation resulting in normal testosterone values does not always result in restoration of libido and quality of erectile function *(5)*. The presence of penile erections has been documented in male fetuses by antenatal ultrasound and *castrati* who have negligible circulating testosterone. Therefore, 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 *(6)*. Low testosterone levels also decrease the frequency, volume, and quality of ejaculation *(7)*. The effect of testosterone on different aspects of erectile function has been studied, and the current belief is that nocturnal penile tumescence and spontaneous erections are androgen-dependent. Audiovisual erotic stimulation predominantly causes erections through androgen-insensitive pathways, but some androgen sensitivity is likely *(8)*. Rapid-eye-movement sleep has been shown to be reduced in hypogonadism, and although androgen reduction adversely affects sleep-related erections, it did not eliminate them over a 12-wk trial in healthy young adult men *(9)*. There are data for supranormal levels of testosterone from the exogenous administration of testosterone to normal males. The patterns of sexual intercourse, masturbation, and sexual interest were not found to change significantly *(10)*. The information in this area has previously suggested compartmentalization, with various functional aspects having different androgen sensitivities; the issue is unresolved but the sensitivities appear to overlap. The prospect that selective androgen modulation may be therapeutically harnessed remains a possibility. Certain types of age-related changes are associated with the length of the *AR* gene CAG repeat. CAG repeat lengths may play a role in setting different thresholds for the various androgen actions *(11)*.

CLINICAL PICTURE OF HYPOGONADISM

There is no doubt that androgens affect male sexual function, in general, and erectile physiology, in particular. ED and hypogonadism co-exist in the same men more frequently than pure causative explanations can justify. Older men have more ED and 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 *(12)*. Clinical practice has verified that older men have

more ED, and age is a variable significantly associated with the finding of ED. Age is also a significant factor in predicting serum testosterone, and lower levels of testosterone are found in older men *(13)*. However, the MMAS found no association between ED and low testosterone, and overall, the prevalence of low serum testosterone in men with documented ED is low *(14)*.

The prevalence of hypogonadism in the older age groups is highest—higher than initially suspected *(15)*. Normal aging results in changes in androgen status and effect through several mechanisms, including alterations in feedback sensitivities; decline in synthetic capacity; changes in serum availability, aging, or responder cells; and interaction with other hormone and regulatory systems (e.g., dihydroepiandrosterone [DHEA], growth hormone, melatonin, and leptin; ref. *16*). There is significant variation in the age at which such changes become apparent as well as in the speed and degree of the changes and the systems that are affected. There is undoubtedly a significant incidence of androgen deficiency in older males when measured by serum levels of bio-available testosterone *(17)*.

The male climacteric is referred to as andropause, androgen decline in the aging male, late-onset hypogonadism (LOH), or symptomatic LOH. Data from the MMAS suggested that each year, biochemical LOH will be present in 481,000 new cases involving US males ages 40 to 69 *(18)*. Similar numbers can be projected for Europe. Although the MMAS was unable to show an association between ED and a decrease in the serum levels of testosterone, a direct correlation was established between ED and a serum deficit in DHEA and its sulfated form, DHEAS. It is possible in a population study to link age and serum testosterone, but the association between low DHEA and increasing age is so strong and predictable that the specific association between DHEA and ED, independent of age, is difficult to demonstrate. However, a recent study pointed to a true finding of lower DHEA in patients with ED compared to controls *(19)*. A diagnosis of hypogonadism can rarely be established on the basis of history and physical examination alone *(20)*.

The changes associated with symptomatic LOH have been recorded many times and include alterations in bone mass, energy level and motivation, erectile function, fat mass, hair and skin, hematocrit, low- and high-density lipoprotein cholesterol, leptin production, mood and cognition, muscle mass, quality of life, sexual desire, sleep, spatial cognition, and vasomotor status (hot flushes). Sexual interest, libido, or desire is a notoriously difficult symptom group that may be depressed in men with normal testosterone levels because of other conditions (e.g., depression; ref. *21*). 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 testosterone *(22)*. The physical appearance of secondary sex characteristics is not sufficiently demonstrative to mark the presence of low testosterone *(23)*. Therefore, the finding of low testosterone depends 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, and luteinizing hormone can provide an indication to distinguish between primary, secondary, or tertiary hypogonadism. From middle age and beyond, however, there is a diminution in function of the pituitary as well as a flattening in the circadian production of gonadotropins *(24)*. Therefore, in men with erectile problems and primary testicular failure, it is not uncommon to observe a low serum testosterone with normal or only minimally elevated gonadotropins.

Hyperprolactinemia is the other common disturbance of endocrine milieu that may be relevant to ED *(25)*. 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. However, if the biochemical hyperprolactinemia is caused by a variant large prolactin molecule known as macroprolactin, these molecules are biologically inert. Hyperprolactinemia may also result from medication *(26)*. The common concept of hyperprolactinemia is that low desire is a reliable marker; however, hyperprolactinemia has been found in patients not reporting major problems with a desire disorder.

Clinically significant hyperprolactinemia may be reliably found with biochemical evaluation and may not be detected in patients with erectile function domain *(27)* scores higher than 10 in assessments done using the International Index of Erectile Function *(28)*.

In summary, although there is much to link androgens and erections, there is little that can be done from a clinical perspective to rule out androgen abnormalities in the specific group of patients suffering from ED. The proof that androgen status is healthy in men with ED depends on biochemical tests. Conversely, the proof required to initiate androgen therapy in men with ED comes from biochemical assessment of androgen status, and the ED provides the clinical symptom that justifies therapy.

OTHER HORMONES

Further hormonal evaluation depends on the interest, expertise, and commitment of the physician and, obviously, the clinical picture. Part of the problem is that andropause is not inevitable and has various clinical presentations *(29)*. 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, 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 *(30)*. Hyperthyroidism may influence testosterone bioavailability.

It should be noted that there are a number of other conditions associated with decreased testosterone including diabetes mellitus, the metabolic syndrome, atherosclerosis, myocardial infarction and chronic heart failure *(31)*. Hypogonadism is linked to the development of insulin resistance and possible progression to type 2 diabetes *(32)*. Insulin resistance is the key finding of the metabolic syndrome (obesity, dyslipidemia, hypertension, atherosclerosis and pro-coagulant state; ref. *33*) and the principle defect in type 2 diabetes, together with compensatory hyperinsulinemia. Studies have shown an increased risk of cardiovascular disease in men with either metabolic syndrome or type 2 diabetes *(34)*.

LABORATORY DETERMINATION OF HYPOGONADISM

There are various recommendations regarding suitable investigations of androgen status *(35,36)*. The standard approach is to measure the total serum testosterone levels, preferably between 8 and 11 AM. In the obese and the elderly, the levels of sex-hormone binding globulin increase, which binds testosterone reducing the metabolically active component (*see* Fig. 1). The optimal measure is probably bioavailable testosterone (the sum of free plus albumin-bound testosterone), measured by an ammonium sulfate precipitation technique at standardized temperature because it determines the amount of testosterone that is readily available to target tissues. Free testosterone may also be considered but only if measured by ultracentrifugal ultrafiltration or dialysis methods. Another option

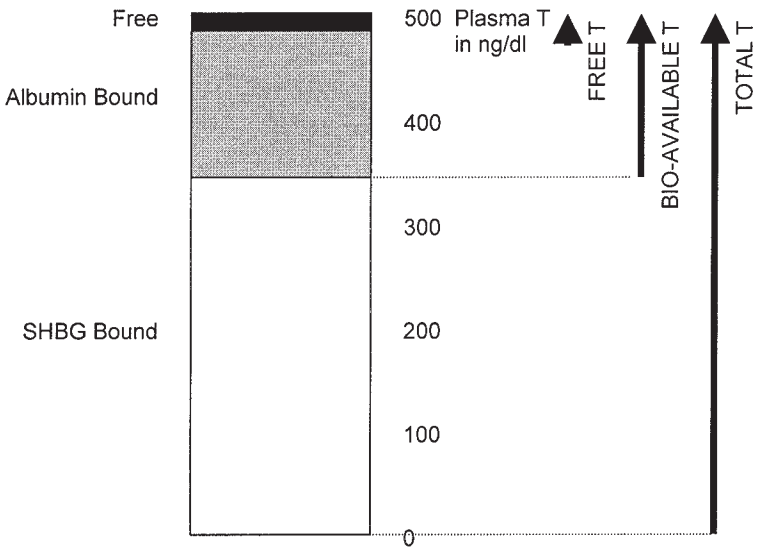

Fig. 1. Conceptual relationship between the various common measures of testosterone along with a general guide to the range of values. The actual values reported for an individual patient should be carefully evaluated as to the exact methods of measurement used in the normal ranges to the laboratory.

is calculated free testosterone determined by measuring testosterone, sex-hormone binding globulin, albumin and using the calculation set at the website www.isam.ch. The direct immunoassay of free testosterone is not considered reliable. In all cases, repeat values are required for diagnosis, together with suitable gonadotropins and also prolactin level.

The range of testosterone 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 testosterone set-point (particularly the longitudinal variation in individuals with age) and this may explain in part some of the difficulty in interpreting testosterone 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 therapy if their clinical symptoms indicate.

TREATMENT OF HYPOGONADISM

There are various treatment options for hypogonadism, and it is common practice to discuss these with the patient and then select an agent that can be tested for individual symptomatic and biochemical effects. The most frequently used testosterone preparations are shown in Table 1.

Oral agents include alkylated (to prevent rapid hepatic metabolism) androgen preparations, which are available in the United States. These generally provide inconsistent androgenic effects and significant changes in lipid profile and have a risk of liver toxicity; they are rarely used. Oral testosterone undecanoate (Andriol™) is commonly used, with the

Table 1
Most Frequently Used Testosterone Preparations

	Trade name	*Generic name*	*Dose*
Oral/buccal	Striant	Buccal tabs	10 mg twice daily
	Metandren Andriol	Methyltestosterone	10–30 mg/d
	Testocaps	Testosterone undecanoate	120–160 mg/d
Transdermal	Androderm	Testosterone patch	5 mg/d
	Testoderm		10–15 mg/d
	Androgen/Testim	Testosterone gel	5–10 g/d
Injectable	Depotestosterone cypionate	Testosterone cypoinate	200–400 mg every 3–4 wk
	Delatestryl	Testosterone enanthate	200–400 mg every 4 wk
	Nebido	Testosterone undecanoate[a]	1000 mg every 12–14 wk[a]

[a]Requires a loading 3 ↔ 1000 mg every 6 wk for naïve patients or 2 ↔ 100 every 8 wk for those switching from a different T formulation.

exception of in the United States, where it is not available. It is not associated with liver toxicity but may result in supraphysiological levels of dihydrotestosterone (DHT; ref. *37*). The mucoadhesive delivery system (Striant™) is placed against the gum above the incisor tooth twice daily. The site of application should be alternated to reduce the incidence of local irritation (~9%).

Transdermal testosterone therapy is applied as patches and gels. Both can produce normal serum testosterone levels and can reproduce its diurnal physiological variations with normal estradiol (E_2) and DHT levels. Disadvantages of patches include visibility and skin reactions *(38)*, whereas gel preparations are better tolerated, with minimal skin irritation. Transdermal testosterone application can result in improved sexual function and mood, increased lean body mass, and muscle strength associated with a decrease in fat mass *(39)*. Testosterone gel (AndroGel™ and Testogel™) have been studied regarding a long-term follow-up of 3 yr *(40)*. Results have shown positive benefits in hypogonadal men, independent of age (19–67 yr), including improvement in bone mineral density—particularly in the spine. Minimal effects were shown on lipid levels. There was a 1.8% incidence of prostate cancer in the study group, although it was not possible to determine whether this was greater than background levels. In terms of dosage of testosterone gel, Meikle et al. *(41)* demonstrated that a dosage of 3 g of 2% gel applied daily produced testosterone levels in the normal reference range (3–11.4 μg/L) in most hypogonadal men. They suggest that dose adjustment to a lower or higher dose may be necessary in certain individuals to achieve the desired testosterone concentration range.

Intramuscular injections of testosterone are long-acting and reach a maximum concentration at about 72 h but do not provide normal circadian patterns of serum testosterone. In some men, levels of E_2 may become excessive, whereas levels of DHT are usually normal. Additionally, supraphysiological serum testosterone levels occur in the first few days following injection. Testosterone injections are commonly administered every 10 to 21 d to maintain normal average testosterone levels; baseline values are reached at approx 21 d. Injectable testosterone preparations are cost-efficient and of proven efficacy *(42)*. Testosterone undecanoate (Nebido™) for injection (1000 mg/dose), which has recently been introduced, results in stable serum levels within the normal range after a loading

dose administration of 1000 mg every 12 wk *(43)*. This product is not yet available in the United States.

The use of DHT as an alternative to testosterone has been suggested *(44)*. The main argument for the use of DHT is that it is not aromatizable and, therefore, may prevent prostate enlargement (believed to require both androgens and estrogens). Although the transdermal DHT preparation is easy to use, long-term studies are lacking and its use outside proper trials is not recommended *(45)*.

There has been considerable interest regarding the use of androgens that spare the most obvious side effects of testosterone supplementation. Although it is not yet commercially available, 7α-methyl-nortestosterone is the most promising of this group of drugs. It has a high biopotency per molecule (about 10 times more than testosterone), does not undergo 5α reduction, but it retains its capacity to be aromatized to E_2. 7α-methyl-nortestosterone has antigonadotropic properties and anabolic effects on muscles. It maintains sexual function in hypogonadotropic men, and its effects on the prostate are less pronounced than testosterone *(46)*.

The therapeutic potential of selective estrogen receptor modulators in women has set the stage for the development of SARMs. The availability of these molecules with their diversity of ligands provides the opportunity to explore the utility and activities of SARMs *(47)*. Various SARMs are being studied, but their availability is not expected in the near future.

CAUTIONS IN TESTOSTERONE SUPPLEMENTATION

The presence of prostate or breast carcinoma are absolute contra-indications for testosterone treatment, but there are several additional adverse events that are particularly significant in the elderly. Although rarely seen, fluid retention in the chronically ill or the frailer older man may pose a problem. Modern testosterone preparations do not give rise to liver toxicity. Testosterone therapy has been reported to exacerbate sleep apnea; however, a recent 36-mo trial of testosterone in older men reported no effect on apneic or hypo-apneic episodes *(48)*. Because of the relatively greater increase in serum E_2 levels, gynecomastia is a rare event that can be overcome with a reduction in the testosterone dose. Benign prostatic hyperplasia and prostate cancer commonly occur in older men, and both are promoted by androgens and, therefore, have been treated by androgen deprivation therapy. It is unknown whether testosterone therapy for an older man places him at increased risk of developing clinically significant prostate disease from a pre-existing but subclinical condition. There have been at least 22 testosterone replacement trials, involving a total of 583 men ages 45 to 89, in which serum prostate-specific antigen (PSA) levels have been measured. Of the 22 studies, 16 showed no increase in PSA with testosterone therapy. In the six studies showing a PSA rise with testosterone, the average PSA change was 0.48 ng/mL, and the average PSA velocity was 0.52 ng/mL/yr. Seven testosterone replacement trials in older men have evaluated prostate size, maximum urine flow rates, and/or International Prostate Symptom Scores. No change in any of these parameters was demonstrated with treatment *(49)*. These data suggest that in the short term (up to 3 yr), testosterone therapy in the older man has little effect on the prostate. Nevertheless, one must consider the longer term effects of testosterone therapy because prostate cancer and benign prostatic hyperplasia are diseases with long natural histories, and the current observation time with testosterone therapy in older men is limited to less than 900 man-years. Testosterone therapy in older men can often result in a significant increase in red blood cell mass and hemoglobin levels. This may lead to either termination of therapy,

a decrease of dose, or a switch to a different formulation of testosterone. The method of testosterone replacement may affect the magnitude of the change in red blood cell mass.

TESTOSTERONE FOR ERECTILE DYSFUNCTION

The specific issue of whether exogenous testosterone 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 has been a meta-analysis *(50)* no studies exist to assess testosterone vs. placebo for therapy of ED of wide-spectrum etiology using good numbers and careful design comparable to modern clinical trials. A double-blind, placebo-controlled trial was conducted to examine whether testosterone therapy could salvage sildenafil failure in men with ED and hypogonadism *(51)*. A total of 75 men were included in the study and were treated with 50 mg/d of testosterone in the form of 1% testosterone gel. Using the International Index of Erectile Function as an assessment tool, following 4 wk of therapy, erectile function was shown to be significantly improved compared with placebo (p = 0.0290). Significant improvements were also reported in orgasmic function (p = 0.009), overall satisfaction (p = 0.02), and the total score of the sexual function questionnaire (p = 0.011). Serum testosterone levels increased from 300 ng/dL at baseline to 500 to 600 ng/dL in the testosterone group. Kalinchenko et al. *(52)* reported similar results.

Testosterone-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 testosterone replacement will not be harmful. The 2nd International Consultation on Erectile Dysfunction (2003) recommended that it is important to screen men who present with ED for low serum testosterone and hypogonadism, particularly if they fail treatment with phosphodiesterase-5 inhibitors or if they are in at-risk populations, such as those with diabetes, metabolic syndrome, or chronic renal failure *(53,54)*.

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. Therefore, biochemical determinations are necessary to establish a firm diagnosis.
2. The most dependable test is a bio-available testosterone.
3. An abnormal testosterone value should be confirmed by a second test.
4. Prolactin may be considered as a routine or after an abnormal testosterone.
5. Testosterone administration must be based on a clear indication (clinical symptom and biochemical information).
6. Borderline levels of serum testosterone 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 co-existing hypogonadism and ED, a 3- to 6-mo trial of hormonal supplementation may be indicated, and failure to respond should halt this test.
8. In men over age 40 yr, a digital rectal examination 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 is an absolute contraindication for androgen therapy.
10. The testosterone 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 testosterone requirements.

POSITION STATEMENT: UNITED STATES

The position statement of the Sexual Medicine Society of North America is that testosterone supplementation is indicated for men who have signs and symptoms of hypogonadism accompanied by subnormal serum testosterone measurements. Testosterone supplementation can provide important health benefits to these hypogonadal men. Although the benefits and risks of long-term testosterone supplementation have not been definitively established, the weight of current evidence does not suggest an increased risk of heart disease or prostate cancer with long-term use of testosterone. Testosterone is not medically indicated in men who do not have hypogonadism. Pretreatment screening must eliminate the possibility of an existing carcinoma, and testosterone supplementation requires medical surveillance to identify early signs of possible adverse effects.

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7 Radical Prostatectomy and Other Pelvic Surgeries

Effects on Erectile Function

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Summary

Preservation of erectile function following pelvic surgery is an important variable in a patient's quality of life. Despite currently available oral and minimally invasive treatments, erectile dysfunction following pelvic surgery and radical prostatectomy challenges most urologists because of the lower-than-anticipated success rates. Postoperative pharmacological penile rehabilitation programs employing oral, transurethral, and intracavernosal vasoactive drugs are suggested to be beneficial for most patients, allowing a faster and more complete recovery of erectile function. New data on cavernous nerve protection and/or regeneration will likely evolve into a new therapeutic avenue for patients who undergo radical pelvic surgery. The ultimate aim is to increase the quality of life in patients undergoing pelvic surgery including radical prostatectomy.

Key Words: Erectile dysfunction; radical prostatectomy; pelvic surgery; treatment; cavernous nerve; neuroprotection.

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent or recurring inability of a man to achieve and/or maintain an erection sufficient for satisfactory sexual performance or intercourse *(1)*. The Massachusetts Male Aging Study provided a detailed epidemiological report on ED, demonstrating the detrimental role of aging and other comorbidities regarding the erectile mechanism *(2)*. In this evaluation, men between the ages of 40 and 70 yr were asked to categorize their erectile function as complete, moderate, or minimal. Overall, 52% of these participants reported a certain degree of ED. Between age 40 and 70 yr, the probability of complete ED tripled from 5.1 to 15%; moderate ED doubled from 17 to 34%; and minimal ED remained at approx 17%. By age 70, only 32% of men studied portrayed themselves as free of any ED.

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Prostate cancer has a significant impact on men's health and quality of life in the United States, with more than 230,000 new cases diagnosed each year, and more than 30,000 annual deaths attributed to this disease *(3)*. Various treatment options are available, including radical prostatectomy, external beam radiation, brachytherapy, and hormonal ablation; for a urologist, however, radical prostatectomy is the optimal treatment option for the majority of men with organ-confined disease. In 2001, approx 80,000 men in the United States underwent radical prostatectomy for treatment of clinically localized prostate cancer *(4)*. Men diagnosed with prostate cancer who elect radical prostatectomy are customarily informed of the potential morbidities, including urinary incontinence and ED *(5)*. The maintenance of a satisfactory quality of life is the principle concern for more than 45% of men who elect treatment for localized prostate cancer *(6)*. Furthermore, sexual dysfunction has been reported to be an independent determinant of a poorer general health-related quality of life at 2 yr after primary treatment for prostate cancer *(7)*. These findings have contributed to an ever-expanding focus on understanding the pathophysiology of post-prostatectomy ED and the new concept of instituting prophylactic measures for prevention and early recovery from ED *(8–10)*.

EPIDEMIOLOGY

The incidence of ED following radical prostatectomy has been reported to range from 16 to 82% *(11–15)*. The Cancer of the Prostate Strategic Urologic Research Endeavor study (CaPSURE), which represented 29 academic and community-based sites across the United States, revealed that only 20% of patients return to their pre-operative baseline potency levels 1 yr after radical prostatectomy *(16)*. The Prostate Cancer Outcomes Study, a population-based longitudinal cohort study using cancer registries from six US geographical regions with up to 24 mo of follow-up, measured changes in urinary and sexual function in 1291 men who had undergone radical prostatectomy for clinically localized prostate cancer *(17)*. At 18 or more months after radical prostatectomy, 59.9% of men reported experiences of ED. Among men who were potent before surgery, the proportion of men reporting ED at 18 or more months after surgery varied according to whether the procedure was nerve-sparing (65.6% non-nerve-sparing, 58.6% unilateral, and 56.0% bilateral nerve-sparing). Importantly, at 18 or more months after surgery, 41.9% of men reported that their poor sexual performance was a moderate-to-large problem. An extension of this study documented 79.6% of men to have ED 2 yr after radical prostatectomy *(18)*.

In a recent population-based cohort study, temporal changes in urinary and sexual function were noted for up to 5 yr following radical prostatectomy in a sample of 1288 men with localized prostate cancer *(19)*. At 60 mo, 28% of the men reported erections firm enough for intercourse, compared with only 22% at 24 mo ($p = 0.003$). Table 1 summarizes the resulting sexual function and bother in 1213 prostate cancer survivors who underwent radical prostatectomy in the Prostate Cancer Outcomes Study *(19)*. Patients undergoing radical prostatectomy may also exhibit other types of sexual dysfunction, such as ejaculatory failure, penile shortening, fibrotic changes in the penis, and orgasmic disorders.

The Scandinavian Prostatic Cancer Group reported that 45% of patients with ED selected watchful waiting compared with 80% who opted for radical prostatectomy *(20)*. Of men undergoing radical prostatectomy, 56% were distressed (moderately or greatly) by the decline in their sexual function, compared with 40% of men assigned to watchful

Table 1
Sexual Function and Bother in 1213 Prostate Cancer Survivors Who Underwent Radical Prostatectomy in the Prostate Cancer Outcomes Study

Measure (level)	*Baseline*	*6 mo*	*12 mo*	*24 mo*	*60 mo*
Sexual activity interest level (%)					
None	7	29	15	17	18
Little/some	53	53	61	63	59
A lot	40	18	24	21	23
Sexual activity frequency (%)					
None	15	62	44	44	46
1/mo or more	37	22	30	30	28
1/wk or more	49	16	26	26	26
Erections firm enough for intercourse (%)					
No	17	89	81	75	71
Yes	81	9	17	22	28
Difficulty maintaining erections (%)					
None	51	2	5	8	9
Little/some	30	8	13	18	21
A lot	11	12	17	17	14
No erections	9	78	65	57	55
How big a problem is sexual function (%)					
No problem	57	12	15	18	23
Small	23	18	24	28	31
Moderate-to-large	20	70	61	54	46

Adapted from ref. *19*.

waiting. Radiation therapy (external beam or brachytherapy) is perceived to be less damaging to erectile function. Recent data suggest that radiation therapy causes progressive damage to the cavernosal tissues for at least 3 yr after therapy; long-term postradiotherapy ED rates are reported to range from 34 to 62% *(21)*. A diverse cohort of patients who underwent external beam radiotherapy from the Prostate Cancer Outcomes Study for clinically localized prostate cancer reported a 61.5% rate of ED 2 yr after treatment *(18)*. Actually, high doses of radiation are delivered to the proximal aspect of the penis in the region of the bulb, where the cavernosal vessels and nerves enter the penile body, even when three-dimensional conformal radiation therapy is employed. Unlike radical prostatectomy, in which ED is immediately apparent postoperatively, patients who receive external beam radiation experience a progressive decline in sexual function over a longer follow-up period *(22)*. Ionizing radiation is postulated to initiate ED by accelerating microvascular angiopathic changes, thereby causing cavernosal fibrosis and endothelial dysfunction. Conversely, radical prostatectomy damages the neurovascular mechanism that initiates erections.

PATHOPHYSIOLOGY

As noted earlier, radical prostatectomy causes ED by damaging the neurovascular mechanism responsible for initiating erections. Following bilateral nerve-sparing radical

prostatectomy (NSRP), erectile function is also impaired in the early postoperative period because of the development of "neuropraxia," a relative trauma invoked to these nerves during surgical dissection of the neurovascular bundles. The mechanism of cavernous nerve fiber injury partly involves Wallerian degeneration, with a loss of normal nerve tissue connections to the corpora cavernosa and associated neuroregulatory functions, both of which cause cavernosal tissue degeneration and atrophy *(23,24)*. The lack of early postoperative nocturnal erections is postulated by many authorities to decrease the amount of regular tissue oxygenation and the development of fibrosis *(25)*. In a recent experimental model, penile tissue from rats undergoing bilateral incision of their cavernous nerves 3 mo after injury showed a significant overexpression of hypoxia-related substances, including transforming growth factor-β and collagen I and III *(26)*.

Temporary bilateral cavernous nerve injury may induce significant apoptosis of smooth muscle cells—particularly in the subtunical area—which, in turn, leads to cavernosal insufficiency and neuro-occlusive dysfunction *(24)*. In a rat model, User et al. *(24)* demonstrated that the wet weight of the denervated penis and its DNA content was significantly decreased after bilateral cavernosal nerve injury. Comparatively, unilateral cavernous neurotomy provided a greater preservation of penile weight and DNA content. Therefore, chronic hypoxia and denervation initiate apoptosis and increase the deposition of connective (scar) tissue *(27–29)*.

Many researchers support the concept that post-prostatectomy ED diminishes the circulation of arterial blood through the corpora cavernosa, which leads to reduced oxygen content, increased production of transforming growth factor-β, and increased corporeal fibrosis *(30,31)*. Postoperative diminishment in penile length and the development of Peyronie's disease may be direct consequences of this increased corporeal fibrosis *(32)*.

Recently, Iacono et al. *(33)* performed corpora cavernosa biopsy to investigate the effect of radical prostatectomy on penile histology. A total of 19 nondiabetic patients with prostate adenocarcinoma and normal erectile function (as reported and validated by testing with Rigiscan, UroHealth Systems, Laguna Niguel, CA) underwent corpora cavernosa biopsy before as well as 2 and 12 mo after radical prostatectomy. Compared with pre-operative biopsies, trabecular elastic and smooth muscle fibers were decreased and collagen content was significantly increased 2 mo after surgery. Furthermore, biopsies performed 12 mo after surgery revealed further deterioration of cavernosal histology compared with early postoperative biopsies. This study reconfirmed the progressive cavernosal fibrosis occurring in humans following radical prostatectomy.

Postoperative NSRP patients who were not enrolled in a pharmacological vasoactive recovery program instituted in the initial year after surgery revealed a progressive increase in venous leakage, varying from 14% at 4 mo to 50% at 12 mo or longer *(31)*. When a vasoactive recovery program was promptly instituted, Montorsi et al. reported a decrease in venous leakage 4 mo postoperatively *(34)*. Using intracavernosal alprostadil injections, only 2 of 12 patients developed a venous leak compared with 8 of 15 patients who did not receive intracavernosal injections. These findings support the role of early penile vasoactive rehabilitation after NSRP to prevent the development of vasculogenic ED.

Molecular consequences of radical prostatectomy are also associated with a reduction in penile dimensions. Fraiman et al. *(35)* investigated the changes in penile morphometrics in men with ED following NSRP. A significant reduction in penile length and circumference was documented during the first 4 to 8 mo postoperatively. A prospective study measuring pre- and postoperative penile lengths in 124 men with prostate cancer reported a significant decrease in penile size following radical prostatectomy *(32)*.

Table 2
Predictive Factors for Postprostatectomy Recovery of Erectile Function

Factors		*Advantages*	*Disadvantages*
Related to prostate cancer	Grade	Low	High
	Stage	≤T2	>T3
	Localization	Organ-confined	Advanced
Related to the patient	Age	≤65 yr	>65 yr
	Associated comorbidities	Absence	Presence
Related to the surgery	Degree of nerve preservation	Bilateral	Unilateral/no
Related to the pre-operative erectile function		SHIM⊕15	SHIM <15

Adapted from ref. *127*.
SHIM, Sexual Health Inventory of Men.

FACTORS ASSOCIATED WITH RECOVERY OF ERECTILE FUNCTION FOLLOWING RADICAL PROSTATECTOMY

Pre-Operative Factors

Pre-operative erectile function correlates with patient age and numerous well-recognized comorbidities, including diabetes, hypertension, atherosclerosis, hypercholesterolemia, smoking, and cardiovascular disease. The recovery rates of erectile function after NSRP correlate inversely with increased patient age. The postoperative potency rates are greatest in men younger than age 65 yr *(36)*. There is a significant effect of age on sexual function following bilateral NSRP, with 61% of men age 39 to 54 yr reporting erections firm enough for intercourse compared to 49% of men age 55 to 59 yr, 44% of men age 60 to 64 yr, and only 18% of men older than age 65 yr ($p < 0.001$; ref. *19*). As noted earlier, associated comorbidities can have an impact on both pre-operative erectile function and postoperative recovery of erections *(37)*. Furthermore, determination of clinical stage, grade, and location of the tumor are recognized factors that predict the likelihood of developing ED postoperatively *(37)*. The International Index of Erectile Function (IIEF; ref. *38*), a validated questionnaire measuring overall sexual function, aids the clinician in objectively assessing erectile function pre-operatively and during convalescence. Men who report some degree of ED or use phosphodiesterase (PDE)-5 inhibitors before surgery are more likely to develop severe ED postoperatively *(37)*. According to the CaPSURE study, household income greater than $30,000 per year and fewer comorbidities are associated with a more likely return to baseline sexual function, whereas race/ethnicity, education, and relationship status have no effect on potency status *(16)*. Table 2 provides predictive factors for the recovery of postprostatectomy ED.

Intra-Operative Factors

Precise visualization and localization of the neurovascular bundles are sometimes problematic during surgery because of variation in the anatomic location of the cavernous nerves, poor exposure because of body habitus, and the ubiquitous presence of overlying tissues and blood during the procedure. Lue et al. *(39)* pioneered intra-operative cavernous nerve electrostimulation as a means of improving the precision and speed with which the

neurovascular bundle may be identified. They noted a significant degree of tumescence in 8 of 11 radical prostatectomy patients who reported pre-operative potency, thereby demonstrating the feasibility of this technique *(39)*. However, the value of cavernous nerve mapping intra-operatively is controversial and requires further study.

The goal of cavernous nerve preservation has led several investigators to consider reconstruction of the nerve at the time of radical prostatectomy. Quinlan *(40)* and Ball *(41)* originally used the genitofemoral nerve as a replacement for the resected cavernous nerve in rats, with promising results. In humans, Kim et al. *(42)* applied the sural nerve as a conduit. These authors demonstrated promising outcomes, with a reported 26% rate of spontaneous, medically unassisted erections sufficient for sexual intercourse in 28 men who underwent radical prostatectomy and subsequent bilateral sural nerve grafting (mean follow-up: 23 mo; ref. *43*). With the addition of four men who had partial erections sufficiently enhanced with sildenafil use, the overall potency rate for sural nerve grafting was reported as 43%. The authors similarly reported the benefit of unilateral grafting, with a potency rate of 78% *(43,44)*. In other clinical studies involving the sural nerve, Chang et al. *(45)* reported a 43% potency rate for bilateral grafting, and Anastasiadis et al. *(46)* demonstrated a 33% success rate for unilateral grafting with mean 23- and 16-mo follow-ups, respectively. Despite modifications, such as electrical stimulation to confirm the function and localization of the recipient nerve, the use of microsurgical instruments and loupe magnification, and grafting without tension, the procedure appears to be technically impractical and is infrequently used *(43–45,47,48)*. Furthermore, the candidates selected for nerve grafting often have high-stage cancer, which, as previously noted, is associated with a low probability of recovery of erectile function after surgery and would likely require adjuvant therapy; all of these factors further decrease the overall success rate *(45,49)*.

Postoperative Rehabilitation

The introduction of the NSRP procedure by Walsh and Donker in 1982 as a means to preserve erectile function has been embraced globally and has inspired greater acceptance of surgical treatment approval for prostate cancer *(11)*. However, time has shown that this technique offers no guarantee that erectile function will be preserved *(14)*. The recovery time for return of erectile function following NSRP is not clear, and most patients do not recover erectile function as quickly as urinary continence. A study by Walsh et al. *(50)* suggested that maximal erectile recovery is not witnessed until a mean period of 18 mo after bilateral NSRP. Because several factors may affect the cavernous nerves during radical prostatectomy (including thermal damage, ischemic injury, mechanically induced nerve stretching, and the local inflammatory effects of surgical trauma), the cavernous nerves may be functionally inactive for as long as 2 yr after surgery—even if the nerve-sparing technique is correctly executed *(50–52)*.

Sexual dysfunction is an independent determinant of a poorer general health-related quality of life following primary treatment for prostate cancer. A restrospective analysis demonstrated that men who underwent non-NSRP reported worse quality-of-life scores for sexual function compared with patients who underwent NSRP *(53)*. However, a significant number of men who undergo NSRP fail to recover true spontaneous erections. The clinical strategy of postoperative penile rehabilitation following radical prostatectomy came from the concept that induced early sexual stimulation and blood flow to the penis can facilitate the return of natural erectile function and the resumption of medically unassisted sexual activity *(54)*.

A consensus has not been reached regarding the implementation of the penile rehabilitation program, its initiation time, the frequency of application, and the type of agents to be used. Some surgeons recommend starting pharmacological erectile therapy during the second postoperative month to achieve optimal recovery of erections at 2 yr *(36)*. Others have suggested that an intracavernous vasoactive agent should be used for at least 6 mo for recovery of spontaneous erections *(34)*. Recently, researchers reported that patients taking sildenafil nightly took 9 mo to regain potency *(55)*. However, others have reported that the natural recovery time of erectile function after NSRP is 2 yr *(37)*. Therefore, penile rehabilitation efforts may only decrease the natural recovery time of erectile function and may not prevent permanent ED.

However, some protocols have claimed to restore erectile function after NSRP. Early postoperative treatment regimens using intracavernosal injections of vasoactive agents or PDE-5 inhibitors are currently recommended by numerous authorities as a means to increase nocturnal erections and oxygenation of the cavernosal tissues. Montorsi et al. *(54)* first demonstrated that men given early injections of intracavernosal alprostadil showed improved recovery of spontaneous erections compared with an untreated control group. These authors recommend that intracavernosal alprostadil injections be started as soon as the catheter is removed, usually before the end of the first postoperative month. The recommended initial dose was 5 μg two or three times per week. Similarly, Brock et al. *(56)* demonstrated that long-term, continuous use of intracavernous alprostadil therapy improved penile hemodynamics and restored spontaneous erections after NSRP. An added psychological benefit is that successful intracorporal injection therapy soon after radical prostatectomy may allow for the resumption of sexual activity and improved couple satisfaction *(37)*.

Raina et al. *(57)* recently demonstrated the feasibility of switching to sildenafil citrate in post-radical prostatectomy patients who had been on long-term intracavernous therapy using various vasoactive agents. In this study, 49 patients with ED (mean age: 60.9 yr) following radical prostatectomy were identified as long-term (3.7 ± 1.9 yr) users of intracavernous injections (70% prostaglandin [PG]E_1 and 30% triple combination of papaverine, phentolamine, and PGE_1). A total of 36 of 49 patients agreed to receive oral open-label sildenafil (50–100 mg) for a minimum of 4 wk in addition to at least five attempts at intercourse. After assessing the Sexual Health Inventory of Men (SHIM) questionnaire, 41% of patients successfully switched to sildenafil and voluntarily discontinued intracavernous injections. Patients taking the triple combination had a poor success rate with switching (7% success rate) compared with men on only PGE_1 injections (67% success rate).

Although PDE-5 inhibitors are popular, the rationale and mechanism for their use in penile rehabilitation programs following radical prostatectomy has not been fully elucidated. Researchers have demonstrated that nightly use of sildenafil significantly increases the overall quality and quantity of nocturnal erections (as recorded by RigiScan; Timm Medical Technologies Inc., Eden Prairie, Minnesota) in men with ED when compared with placebo *(58)*. A recent prospective study showed a significant benefit of either 50 or 100 mg of sildenafil administered every night for 7 mo in men who underwent bilateral NSRP when compared with placebo *(55)*. In this study, the patients who received sildenafil for 36 wk documented a 27% return of spontaneous, normal erectile activity, compared with a 4% return in the placebo group ($p = 0.0156$). These preliminary results suggest a rationale for early prophylaxis with PDE-5 inhibitors to promote early recovery of erectile function after NSRP.

Based on those few available data sets, most researchers recommend either intracavernous injections or a vacuum erection device (VED) as first-line options for the first few months postoperatively, because their mechanisms of action do not require intact neural tissue for erection *(59)*. Thereafter, PDE-5 inhibitor therapy may be a reasonable choice for those patients who can achieve at least partial erections. PDE-5 inhibitors are not likely to be effective when spontaneous erections are absent. The overall concept of penile rehabilitation is to prevent cavernous tissue damage by providing adequate oxygenation to the erectile tissue *(59)*.

TREATMENT OF ED AFTER RADICAL PROSTATECTOMY

Phosphodiesterase-5 Inhibitors

Zippe et al. *(60)* were the first to report on the benefits of sildenafil (Viagra, Pfizer, New York, NY) for patients with postprostatectomy ED. In the bilateral nerve-sparing group, the unilateral nerve-sparing group, and the non-nerve-sparing group, 71.7, 50, and 15.4% of patients achieved successful vaginal intercourse, respectively. Zagaja et al. *(61)*also reported the impact of nerve preservation and the efficacy of sildenafil and found an 80% response rate in men younger than age 55 yr when both nerve bundles were spared and a 40% response when only a single neurovascular bundle was spared. Notably, in the group of men age 56 to 65 yr, the response rate dropped to 45% in the bilateral nerve-sparing group and 0% in the group of men with only one neurovascular bundle preserved. Sildenafil yields the best results in younger men (age < 60 yr), in patients treated with a bilateral nerve-sparing procedure, and in patients who show some degree of early spontaneous postoperative erectile function. Optimal results are anticipated to occur at 12 to 24 mo postoperatively *(51,60,62–64)*. Early postoperative prophylactic administration of alprostadil injections appears to improve subsequent responses to oral sildenafil, requiring lower doses of the drug *(65)*.

In another recent retrospective study, Raina et al. *(66)* reviewed the efficacy and predictive factors for a successful outcome with sildenafil citrate use for ED following radical prostatectomy. The authors reported 76, 53.5, and 14.2% rates of success in the bilateral nerve-sparing, unilateral nerve-sparing, and non-nerve-sparing groups, respectively. These investigators similarly concluded that the factors important for attaining benefit from sildenafil were the presence of at least one neurovascular bundle, a pre-operative SHIM score of 15 or greater, age 65 yr or younger, and an interval from radical prostatectomy to established drug use of more than 6 mo ($p < 0.001$).

The clinical efficacy of vardenafil (Levitra, Bayer/GSK, Pittsburgh, PA) was evaluated in 440 men with severe ED for 6 mo to 5 yr after NSRP *(67)*. Patients were randomized to a 3-mo course of placebo or 10 or 20 mg of vardenafil in a double-blind, multicenter study. After 12 wk of treatment, the global assessment question returned results of 12.5% for placebo, and 59.4 and 65.2% for 10 mg and 20 mg vardenafil, respectively ($p < 0.0001$ vs placebo). For men who underwent bilateral NSRP, 71% who were administered 20 mg of vardenafil responded favorably, compared with only 12% of men given placebo ($p < 0.0001$).

In a large multicenter trial conducted in Europe and the United States using 20 mg of tadalafil, men with ED who underwent a bilateral nerve-sparing procedure demonstrated a 71% subjective improvement rate in erectile function, compared with 24% for placebo ($p < 0.001$; ref. *68*). Administering 20 mg of tadalafil gave patients a 52% rate of success-

Table 3
Treatment Outcomes With PDE-5 Inhibitors After Radical Prostatectomy

Authors	*Assessment*	*PDE-5 inhibitor*	*Nerve preservation*	*Response %*
Zippe et al. (60)	Successful penetration rate	Sildenafil (50–100 mg)	Bilateral	71.7
			Unilateral	50.0
			None	15.4
Zagaja et al. (61)	Mail survey	Sildenafil (50–100 mg)	Bilateral, <55 yr	80
			Unilateral, <55 yr	40
			Bilateral, >56–65 yr	45
			Unilateral, >56–65 yr	0
			None, any age	0
Raina et al. (66)	SHIM	Sildenafil	Bilateral	76.0
			Unilateral	53.5
			None	14.2
Brock et al. (67)	GAQ	Vardenafil (20 mg)	Bilateral	71.1
		Vardenafil (10 mg)	Bilateral	59.7
		Placebo	Bilateral	11.5
Montorsi et al. (68)	GAQ	Tadalafil (20 mg)	Bilateral	71
		Placebo	Bilateral	24

Adapted from ref. *127*.
SHIM, Sexual Health Inventory of Men; GAQ, Global Assessment Question.

ful intercourse, which was significantly higher than the 26% rate observed in the placebo cohort ($p < 0.001$). Table 3 shows the response rates of PDE-5 inhibitors in postprostatectomy ED.

A recent report on the use of oral pharmacotherapy in men who underwent non-NSRP suggested that an oral compound may not be an appropriate first choice for treatment following non-NSRP *(69)*. Instead, the investigators recommend intracavernous injections or VED as the first option, with a change to oral PDE-5 inhibitors suggested no earlier than 1 yr after surgery. The rationale for this suggestion is that only 10% of men who undergo non-NSRP can benefit from oral PDE-5 inhibitors, whereas the overall response rate to VED and intracavernous injections is up to 60% in their study population.

Intra-Urethral/Intracavernous Treatment

Patients who do not respond to PDE-5 inhibitors or who are contra-indicated from using them are candidates for second-line approaches of either intra-urethral or intracavernosal administration of vasoactive agents. In several small studies, a combination of a PDE-5 inhibitor and alprostadil was recommended for patients who failed to respond to a PDE-5 inhibitor alone *(70,71)*. Additionally, intracavernosal or intra-urethral alprostadil administration has exhibited reasonable efficacy in postprostatectomy patients, regardless of the status of cavernosal nerve preservation. To optimize long-term compliance and success with intracavernosal injection therapy, Gontero et al. *(59)* recommended that this form of treatment be initiated within the first 3 mo after surgery.

Vacuum Erection Device

VEDs provide a safe, cost-effective, noninvasive, nonmedical alternative to intracavernosal injection therapy in postprostatectomy patients with ED. Proper instruction in the

use of a VED is crucial to its overall efficacy. A VED can also be alternatively recommended for the initiation of programmed cavernosal oxygenation to accelerate penile erection recovery. Patient satisfaction with VEDs varies significantly. In a group of 115 patients with a mean follow-up of 29 mo, Cookson and Nadig *(72)* reported a continuance rate of 70%, with 84% of patients satisfied with VEDs. Other series have not reported such high success rates.

Penile Prosthesis Implantation

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 less invasive pharmacological therapies.

Another novel concept is the simultaneous placement of a penile prosthesis at the time of non-NSRP. Khoudary and colleagues *(73)* published the first account of immediate sexual rehabilitation with a penile prosthesis. In a two-team approach, this group performed a non-NSRP procedure followed by penile prosthesis placement infrapubically in 50 patients. The majority of these patients (48 of 50 [96%]) reported participating in sexual intercourse within 3 mo of surgery. Surgical revision was required in four cases (8%) because of curvature or mechanical failure. A comparison of this group to a group comprised of 72 patients who underwent radical prostatectomy alone during the same 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 a Foley catheter make prosthesis infection the principal concern following simultaneous prosthesis placement. Surprisingly, the Boston group *(73)* reported no infections in their experience and attributed the success to the liberal use of antibiotics and strict sterile techniques. It appears that for men who undergo prosthesis placement, the psychological benefits of immediate sexual rehabilitation outweigh the risks of a potentially unnecessary procedure. Further evaluation of this technique is necessary to validate the merit of this practice in men with normal erectile function pre-operatively.

The ease of the trans-scrotal approach for the implantation of an inflatable penile prosthesis (IPP) and the proximity of the urethra have paved the way for the new strategy of dual implantation of the artificial urinary sphincter and the IPP. Concerns regarding increased infection rates and poor outcomes have prevented widespread acceptance of the simultaneous implantation technique. A multi-institutional evaluation of synchronous dual prosthesis implantations in 22 patients between 2000 and 2003 revealed two urethral erosions and a reservoir migration but no postoperative infections *(74)*. Risk factors included diabetes in seven patients (32%), hypertension in six (27%), and history of radiation therapy in six (27%). The overall revision rate was 14%. All patients reported a mean of 1 pad or fewer per day of urinary leakage. High-risk patients with complex urological issues are predisposed to a higher complication rate; however, the inherent advantage of a single anesthetic event for patients employing a single trans-scrotal incision should encourage more widespread acceptance of this technique.

ED AFTER PELVIC SURGERY

The protection of the pelvic bones, close proximity of the pelvic organs, and vast array of nerves and blood vessels contribute to the complexity of pelvic surgery. ED was an

accepted complication during extirpation of a pelvic malignancy or revascularization of pelvic blood vessels. Walsh's *(11)* neuro-anatomical description of the cavernosal nerves during prostatectomy has revolutionized all forms of pelvic surgery; because modifications in technique can improve ED without compromising cancer control or interfering with vascular surgery, a greater emphasis is now focused on quality of life. Although erectile function preservation via aortoiliac, colorectal, bladder, and/or transplant surgery has not received much attention compared with preservation via prostate surgery, postoperative ED has been studied and the literature describes strategies to improve ED.

Aortoiliac Surgery

As mentioned earlier, hypertension, diabetes mellitus, hyperlipidemia, smoking, and age are risk factors for the development of ED as well as aortoiliac disease. Not surprisingly, 29% of patients report ED before abdominal aortic aneurysm repair *(75)*. The increased prevalence of ED postoperatively can be explained by injury to the superior hypogastric nerve plexus and the hypogastric arteries *(76)*.

Prior to 1990, few studies had objectively investigated ED following aortoiliac surgery. Early reports have suggested that the incidence of postoperative sexual dysfunction following open abdominal aneurysm repair is 20 to 40% using nonstandardized techniques *(77–79)*. Using the IIEF questionnaire, however, a more recent study has revealed that the rate of ED after open abdominal aortic aneurysm repair is alarmingly high. This retrospective review of 68 married male patients followed-up with the IIEF surveys based on their recall of pre-operative and 3-mo postoperative sexual function revealed that 83% of patients with normal erectile function before surgery developed ED postoperatively *(75)*.

Recognizing the importance of the autonomic nerves overlying the aortic bifurcation, in the 1970s, DePalma et al. *(80)* developed a nerve-sparing approach. They noticed that the lumbar splanchnic nerves supplying the superior hypogastric plexus were more voluminous on the left. Therefore, nerves from the inferior mesenteric artery to the aortic bifurcation were spared on the left. A thin fascial plane between the aorta and the subperitoneal tissue was dissected to mobilize the nerve plexus without damaging the aortic wall. Improved potency rates were reported compared with the traditional approach, but the means of characterizing erectile function was mainly subjective *(80–82)*.

Compared to open aortoiliac surgery, endovascular techniques have resulted in considerably less ED. Karkos reported that 50% of patients undergoing endovascular repair recorded a decrease in their IIEF score; however, none of the patients with some degree of erectile function (IIEF > 11) developed complete postoperative ED *(83)*. Although dissection along the superior hypogastric plexus is no longer incorporated in the procedure, the endovascular approach may result in occlusion of the hypogastric arteries, which eventually branch to form the internal pudendal and, subsequently, cavernosal arteries. Occlusion of the hypogastric arteries may be intentional or inadvertent from positioning of the graft over the hypogastric ostium or embolization of aneurysmal components. Sexual dysfunction can be related to the degree of pelvic ischemia following endovascular repair; approx 10% of patients with unilateral hypogastric occlusion and 20% of patients with bilateral hypogastric occlusion develop postoperative ED *(76)*.

Cystectomy

Following the success of the anatomical NSRP, Schlegel and Walsh *(84)* modified the technique for radical cystoprostatectomy to avoid injuring branches of the pelvic plexus

that innervate the corpus cavernosum. A detailed dissection in nine male cadavers revealed the midpoint of the pelvic plexus, which closely approximated the lateral margin of the seminal vesicle. Using the seminal vesicle as an intra-operative landmark, nerve-sparing radical cystectomy has improved potency rates measured by subjective questioning to 42 to 71% *(85,86)*. Furthermore, the percentage of patients subjectively reporting reduced or normal erections (compared with no erections) was evaluated in 331 patients who underwent attempted bilateral, unilateral, or non-nerve sparing cystoprostatectomies. Approximately 60% of the bilateral nerve-sparing group, 30% of the unilateral group, and 10% of the non-nerve sparing groups reported normal or partial erectile function *(87)*. Although the results may not be as dramatic as the nerve-sparing approach to radical prostatectomy, preservation of the neurovascular bundle is paramount for potency in management of bladder cancer.

Very few studies have objectively studied erectile function and pharmacotherapy following radical cystoprostatectomy. Zippe et al. *(88)* used pre-operative, postoperative, and postsildenafil SHIM questionnaires to evaluate 49 potent males who underwent radical cystoprostatectomy. Only 9% of the patients with postoperative ED responded to sildenafil therapy. These patients also underwent nerve-sparing procedures; none of the patients with ED who underwent non-nerve-sparing cystoprostatectomy responded to sildenafil.

Spitz et al. *(89)* reported four cases involving young men who underwent cystectomy and anterior prostatectomy while sparing the vas deferens, seminal vesicles, posterior prostate, and neurovascular bundles. None of the pathologies in these four men involved a urothelial malignancy. An orthotopic urinary diversion was then anastomosed to the posterior prostate, and all four patients were potent postoperatively *(89)*. Colombo et al. *(90)* applied a similar technique to 27 patients with urothelial malignancy. Transurethral resection of the prostate was performed pre-operatively. Patients were evaluated at 6 and 12 mo postoperatively and showed no significant difference in pre- and postoperative IIEF scores. Rigiscan testing further documented near equivalent values compared to pre-operative measurements *(90)*. Meinhardt et al. *(91)* reported 80% potency with a similar procedure. Although it may be too early to determine if the oncological control compares to standard cystoprostatectomy, the erectile function observed in these studies is promising.

Urethrectomy also predisposes the patient to decreased erectile function. Several groups revealed that the quality of erections was inferior to similarly matched patients who did not undergo urethrectomy *(84,92)*. It may be hypothesized that the additional dissection near the proximal urethra/prostatic apex iatrogenically injures the neurovascular bundles where they enter the pelvic diaphragm.

Finally, urinary diversion produces postoperative anxieties associated with hygiene and altered body image. Patients do not only avoid sexual encounters because of decreased erectile function; decreased libido, partner refusal, and feelings of diminished sexual attractiveness contribute significantly to a decrease or cessation in coitus *(93,94)*.

Rectal Surgery

Colorectal surgeons have recognized a significant incidence of ED following rectal surgery. Kim et al. *(95)* used the SHIM questionnaire to confirm several previous reports in the colorectal literature based on subjective questioning. All five measured variables were significantly decreased in 68 men following mesorectal excision.

Lindsey *(96,97)* proposed four zones of risk and correlated each step in the technical procedure to a neuroanatomical area of risk. First, the sympathetic hypogastric nerves are

adjacent to the aorta and are at risk for injury following ligation of the inferior mesenteric artery. Second, the hypogastric nerves may be injured during initial posterior rectal dissection high in the pelvis before integration of the nervi erigentes to form the pelvic plexus. Third, traction on the rectum to facilitate the lateral dissection may lead to injury of the pelvic plexus. Finally, dissection of the anterior rectum adjacent to the prostate and seminal vesicles can be a source of iatrogenic injury to the cavernosal nerves. Lindsey hypothesized that this region is very similar in its landmarks to that of radical prostatectomy and is the zone of greatest risk. The increased incidence of ED following abdominoperineal (typically used for lower colonic lesions) versus anterior resection (more proximal, sphincter-sparing procedure) involves a deeper rectal dissection posterior to the prostate and portends added risk. When patients who underwent anterior resection had very low lesions, they had an increased risk of ED, reaching comparable levels to those who underwent abdominoperineal resection *(98)*. Similarly, the laparoscopic approach for low rectal cancers resulted in a 10-fold increase in ED compared with the open approach, without a concurrent increase in bladder dysfunction *(99)*. The dissection of the anterior rectum in the area of the prostate is one of the more technically challenging steps of this procedure, secondary to visualization and retraction.

Lindsey *(96,97)* described three planes amenable to dissection on the anterior rectum. First, the close rectal plane lies immediately on the rectal mucosa; although this plane is furthest from the cavernosal nerves and is the most useful for inflammatory disease resections. It is not a natural plane and, unfortunately, may lead to increased bleeding. Second, the mesorectal plane is directly outside of the fascia propria of the rectum and is posterior to Denonvillier's fascia. It is the standard region for dissection of the rectum. Finally, the extramesorectal plane is closest to the cavernosal nerves and is typically used when tumor threatens the anterior rectal margin. In patients who underwent rectal dissection for inflammatory bowel disease, there were no significant differences in ED (characterized by the postoperative IIEF) when the close rectal plane was used instead of the mesorectal plane.

Lindsey *(100)* has published the only known study of pharmacological therapy in 32 men with ED following rectal excision. All men were randomized to sildenafil or placebo groups. Of men responded to sildenafil, 79% significantly increasing their IIEF score and erectile function domain score compared with the placebo group. The excellent response to sildenafil can be explained by the mere partial injury to the cavernosal nerves in these patients, compared with the complete transection of the cavernosal nerves in patients who undergo radical prostatectomy who, therefore, may not respond as well to the medication.

Renal Transplant

About 50 to 85% of patients with end-stage renal disease have ED *(101)*. A functioning renal allograft resulted in improved, deteriorated, or unchanged erectile function in 44, 12.5, and 43.5% of patients, respectively *(102)*. A vasculogenic cause is often suspected in patients who develop ED following transplantation surgery. Revascularization of the transplant is typically accomplished via an end-to-end anostomosis with the internal iliac artery or end-to-side with the external iliac vessel. The incidence of ED following a first transplant anostomosed to the internal iliac artery is 10% and transient; however, following a second transplant to the contralateral internal iliac artery, ED increases to 65% and remains permanent *(103)*. A more recent study documented a decrease in postoperative cavernosal artery blood flow using penile duplex Doppler ultrasound. Although

the pathogenesis of ED in this population is multifactorial, a vasculogenic cause likely plays a role in any new-onset cases of postoperative ED.

Several studies have demonstrated improved IIEF scores in patients who are medicated with pharmacologic therapy following renal transplant. Sildenafil was shown to be effective in treating ED in posttransplant subjects *(104,105)*. Although sildenafil does not affect cyclosporine levels*(104)*, occasional reduction of antihypertensive medications is required. PGE_1 has demonstrated efficacy in treating ED in transplant patients *(106)*.

BASIC SCIENCE AND FUTURE PERSPECTIVES

There are numerous documented research initiatives employing methods of neural protection and stimulation of neurogenesis to restore cavernous nerve function after radical prostatectomy. In rat studies, various neurotrophic factors, such as nerve growth factor, acidic fibroblast growth factor, and basic fibroblast growth factor, have been studied alone or in combination with nerve grafting to hasten recovery of erectile function *(40,107–109)*. Several potential neurotrophic effectors in the penis, including neurtrin, immunophilins, growth hormone, sonic hedgehog protein, vascular endothelial growth factor, brain-derived neurotrophic factor, insulin-like growth factor-1, and PGE_1, have documented improvement in erectile function after nerve injury using the rat erection model *(110–116)*. Gene therapy with adeno-associated and herpes simplex virus vectors, tissue reconstruction, and tissue engineering have recently been employed for transfer of neurotrophic factors *(117,118)*. Current studies are focusing muscle-derived stem cell injections at the site of cavernous nerve injury *(118)*, intracorporeal autotransplantation of pelvic ganglia *(119)*, and cavernous nerve replacement using Schwann cell transplantation to improve cavernosal nerve activity *(120,121)*.

The immunophilins (e.g., FK506) appear to be the most promising of these candidates. FK506, which is expressed in neurons in high concentrations, regulates nitric oxide toxicity and neurotransmitter release and mediates a neurotrophic effect *(122,123)*. Using a rat model of cavernous nerve injury, which mimics the partial nerve injury associated with NSRP, Sezen et al. *(111)* demonstrated the protective effect of FK506 in preventing cavernous nerve degeneration and thus preventing ED. The same investigators also demonstrated the expression of FK506 binding protein 12 in rat penile nerves *(124)*. In a rat model with extensive cavernous nerve injury, Burnett et al. *(125)* demonstrated the neuro-regenerative effects of FK506 and GPI1046 (an FK506 derivative) on penile innervation and erectile tissue histology. The potential clinical efficacy of immunophilins in men who undergo bilateral NSRP is currently underinvestigation in a multicenter, randomized, placebo-controlled study.

Poly(ADP-ribose) polymerase (PARP) activation during neuronal injury plays a role in the development of neurotoxicity and neurodegenerative disorders. The role of the PARP pathway in the pathogenesis of neurogenic ED has not been fully explored. Our center investigated the effects of PARP activation on erectile function following cavernous nerve injury and evaluated the neuroprotective effects of a PARP inhibitor in a rat model of cavernous nerve injury *(126)*. Bilateral cavernous nerve-crush injury in rats caused significant impairment in erectile function and increased PARP activation, upregulation of inducible nitric oxide synthase, and nitrotyrosine levels. Our study demonstrated that PARP inhibitors reduce the degree of nitrosative stress, exhibit significant cavernosal neuroprotection, and preserve erectile function. It is anticipated that these

basic science studies will not only increase our understanding of the pathophysiology of postprostatectomy ED but will open new avenues in the area of neuroprotection and treatment of ED that occurs with prostate cancer therapy.

CONCLUSION

NSRP is the "gold standard" surgical approach for men with organ-confined prostate cancer. Other pelvic surgical procedures have adopted the nerve-sparing technique to improve postoperative erectile function. ED following pelvic surgery and radical prostatectomy challenges most urologists because of the lower-than-anticipated success rates, despite currently available oral and minimally invasive treatments. Postoperative pharmacological penile rehabilitation programs employing oral, transurethral, and intracavernosal vasoactive drugs are suggested to be beneficial for most patients, allowing a faster and more complete recovery of erectile function. PDE-5 inhibitors provide improved postoperative prostatectomy erectile function in approximately half of men who undergo NSRP. Alternatives include VEDs and the implantation of an IPP. New data on cavernous nerve interposition grafts, peri-operative nerve protection procedures, and prophylactic agents that promote neuro-regeneration will likely evolve into a new therapeutic avenue for patients who undergo radical pelvic surgery. The ultimate aim is to increase the quality of life in patients diagnosed with prostate cancer.

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8 Drugs That Affect Male Sexual Function

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SUMMARY

Many drugs are known to alter normal male sexual function. In most instances, this is an undesirable effect and every effort is made to minimize the sexual adverse effects of therapeutic pharmacological agents. The effort to use medications that have minimal risk for disruption of sexual function is complicated by the development and introduction of multiple medications for chronic vascular and neurological disease. Patient compliance can be problematic when a therapeutic agent interferes with sexual function and serious complications have been seen when patients discontinue their medications because, in their minds, the medications are interfering with their sexuality. This chapter attempts to enhance the practioners knowledge of the sexual adverse effects associated with multiple classes of therapeutic agents commonly used in medicine today.

Key Words: Medication side effects; sexual function; erectile dysfunction.

INTRODUCTION

The introduction of sildenafil citrate, the first phosphodiesterase (PDE)-5 inhibitor for male erectile dysfunction (ED), ushered in a period of medical renaissance. No longer viewed as an issue of personal embarrassment, sexual dysfunction—particularly ED—is viewed and treated as a medical issue. In the United States alone, the prevalence of any degree of ED in men is estimated to be between 15 and 30 million *(1)*, with more than 610,000 expected new cases annually *(2)*. As awareness of this medical problem increases, the incidence of ED and the number of men seeking assistance from their physician rise accordingly. In response, the American Urological Association convened the Erectile Dysfunction Clinical Guidelines Panel in 1996 (updated in 2003) to develop specific practice recommendations for managing this rapidly growing problem.

One of the most common, and easily reversible, causes of male sexual dysfunction is the adverse effect of the proper use of prescribed or recreational drugs. Data from the National Center for Health Statistics demonstrated that the number of noninstitutionalized Americans age 65 yr and over who reported using three or more prescription drugs in the past month increased from just over one-third in 1988 to 1994 to almost one-half in 1999 to 2000 *(3)*. The current percentage is certain to be higher as medications continue to become a greater component of contemporary health care. The likelihood that sexual side effects may lead to drug noncompliance and the persistence of disease and

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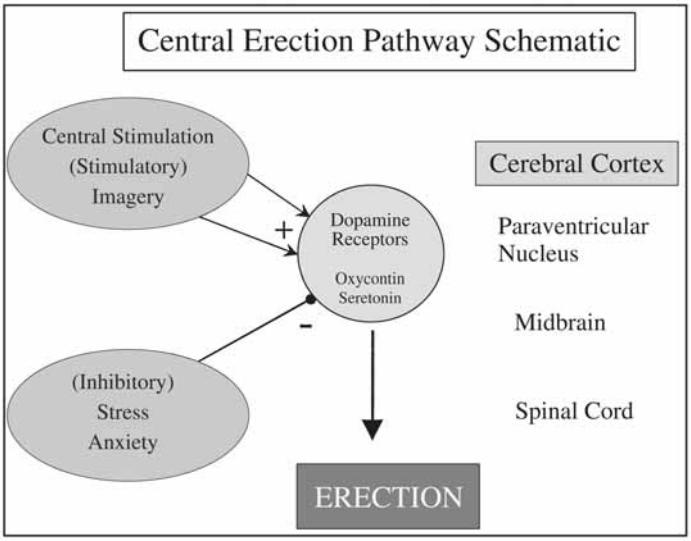

Fig. 1. Depicts the central neurological pathways that affect ED.

all of its attendant morbidities is equally important *(4,5)*. Therefore, it is imperative that the work-up of male sexual dysfunction begin with a thorough history and physical, including a complete medications and drugs list. Proper management of sexual dysfunction may be as simple as adjusting or switching to an alternative medication, and this chapter assists in this standard of care by delineating the common classes of prescription and recreational drugs that can impact male sexual function.

PATHOPHYSIOLOGY

Male sexual dysfunction can be broadly divided into three major entities: (a) dysfunction of erection; (b) dysfunction of ejaculation; and (c) dysfunction of libido, by which sexual dysfunction caused by side effects from medication can materialize. Previous chapters delineated the complex neuronal and hormonal pathways controlling sexual function in detail, and Fig. 1 illustrates these pathways. As demonstrated, interruptions at several areas of both the central and peripheral pathways by various medications can cause the circuit to break down.

Briefly, the penis is innervated by both autonomic and somatic nerves. A complex play of autonomic (sympathetic and parasympathetic) and somatic (sensory and motor) nerves along with supraspinal processing comprise the normal physiology of erection, ejaculation, detumescence, and sexual drive.

The typical awake erection is initiated by either tactile or psychogenic stimuli. Tactile sensory information is delivered sequentially via primarily cholinergic neurons that make up the dorsal nerve of the penis, known as the pudendal nerve, and then continues through ascending spinal pathways to the cerebral cortex and thalamus, where sensory perception forms. This information is then processed in several supraspinal centers, including the medial pre-optic area (MPOA) and the paraventricular nucleus of the hypothalamus, which are critically important in facilitating male sexual behavior *(6)*. The processed neuronal signal then descends through thalamospinal tracts to the spinal cord. Dopamine, noradrenaline, and serotonin appear to be the main neurotransmitters involved in this central circuitry. Dopaminergic and noradrenergic neurons promote sexual function and can be

lowered by sympatholytic antihypertensives, antidepressants, lithium, antipsychotics, and benzodiazepines. Conversely, serotonin has a primarily inhibitory effect and can be raised by all classes of antidepressants, especially the selective serotonin re-uptake inhibitors (SSRIs). Neural hormones—notably prolactin—also play a role in sexual function, and levels can be altered by H_2-blockers.

A normal male erection results from neural output from the parasympathetic nerves that originate in the sacral spinal cord (S2–S4). As a part of the cavernous nerves, parasympathetic end terminals release acetycholine and nitric oxide (NO) when activated to cause relaxation of arteriolar smooth muscles and dilation of the cavernosal sinusoids, leading to engorgement of the penis. Simultaneously, motor neurons arising from Onuf's nucleus in the sacral cord (S2–S4) travel via the pudendal nerve and induce contraction of the ischiocavernosus muscle to contribute to the rigid erection phase. PDE inhibitors, such as sildenafil, increase the level of NO in the cavernosal smooth muscle cells to improve erectile function. On the other hand, several drugs can interfere in this mechanism on both a neural (by antagonizing cholinergic effects, including tricyclic and SSRI antidepressants, phenothiazines, and butyrophenones) and vascular level (by decreasing peripheral vascular resistance and flow of blood into the penis, including all classes of antihypertensives, especially thiazides, nicotine, and narcotics).

The culmination of male sexual function is typically marked by ejaculation. This is a two-part process involving emission of seminal fluid and sperm into the posterior urethra and propulsion of the semen out of the urethra. Emission is mediated by noradrenergic sympathetic nerves originating from T12–L2, whereas propulsion is controlled by an interplay of sympathetic nerves to close the bladder neck and to prevent retrograde flow as well as somatic nerves (Onuf's nucleus) to cause rhythmic contraction of the bulbocavernosus muscle. Therefore, adrenergic receptor blockade can result in ejaculatory dysfunction, either primarily or secondarily, and can include medications such as nonselective α-blockers, sympatholytics, all classes of antidepressants, thioridazine, chlorpromazine, haloperidol, opiates, and cocaine.

Following ejaculation, detumescence occurs as the events leading to an erection are reversed. Sympathetic activation resulting principally from the release of norepinephrine produces a tonic state of smooth muscle contraction and resultant penile flaccidity *(6)*. Other neurotransmitters contributing to this state include endothelin, prostaglandins, leukotrienes, and angiotensin II. Consequently, pharmacology that disturbs this normal milieu of vasoactive agents, such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and nonsteroidal anti-inflammatory drugs, can lead to erectile difficulties.

Sexual drive, or libido, is the final aspect of sexual function that can be altered by pharmacology, because it is critically dependent on the level of male sexual hormones, such as testosterone and dihydrotestosterone (DHT). Testosterone has been shown to enhance sexual interest and increase the frequency of sexual acts in males *(7)*. The hypothalamic–pituitary–gonadal axis is responsible for maintaining normal levels of androgens; an interruption anywhere along this pathway can lead to hypogonadism and decreased libido, including inhibition of androgen binding (diuretics, especially spironolactone, cimetidine, and anti-androgens), reduction of testosterone levels (β-blockers, thioridazine, luteinizing hormone-releasing hormone agonists, progestational agents, anabolic steroids, fibrates, digoxin, alcohol, opiates, and marijuana), and induction of hyperprolactinemia (methyldopa, antipsychotics, cimetidine, ranitidine, and opiates). Sedation side effects in numerous drugs, notably, antidepressants, anticholinergics, phenothiazines, benzodiazepines, and opiates, can also decrease libido and cause sexual dysfunction.

ANTIHYPERTENSIVES

High blood pressure is a major public health challenge and represents the most prevalent risk factor for atherosclerotic vascular disease *(8)*. Like sexual dysfunction, hypertension increases with age, with an incidence of more than 50% in US men in their 60s and 75% of men age 70 yr and older *(9,10)*. Although the effects of hypertension and atherosclerosis on peripheral vessels (including the pudendal artery) can decrease arterial flow into the penis and, therefore, disrupt sexual function, treatment with antihypertensive drugs has been widely implicated in causing sexual dysfunction independently of the disease process. Centrally acting sympatholytic agents, β-blockers, and diuretics are the most commonly cited antihypertensives that negatively affect sexual function. Meanwhile, calcium channel blockers and ACE inhibitors may be neutral, whereas α-blockers and angiotensin II_1-receptor antagonist may be associated with an improvement of sexual function.

Sympatholytics

Antihypertensives in this class include methyldopa, reserpine, guanethidine, and clonidine. The former three were among the earliest antihypertensive drugs developed and widely prescribed and were among the first drugs suspected to negatively affect male sexual function *(7)*. Because of their extended use, significant research and clinical data are available, which reveal often contradictory and inconsistent conclusions. With the exception of clonidine, the use of this class of medications has significantly declined with the advent of newer antihypertensives. Nevertheless, they remain an existing option in the management of hypertension in specific circumstances and possess certain favorable characteristics, including an absence of metabolic side effects, favorable effects on systemic hemodynamics, and low cost *(11)*. Generally, sympatholytics functionally block α_1-adrenoreceptors or stimulate inhibitory α_2-adrenoreceptors, thereby decreasing vasomotor outflow. Sexual side effects arise from diminished central sympathetic outflow from the supraspinal sexual control centers as well as altered signal transmission of the seminal vesicles, vas deferens, ejaculatory ducts, and bladder neck, resulting in erectile—especially psychogenic—and ejaculatory dysfunction.

Use of methyldopa has decreased in recent years but remains the antihypertensive of choice for pregnant women because of its established low risk for fetal harm *(12)*. Several, but not all, studies have demonstrated that methyldopa causes ED in approx 20 to 30% of men who use the medication *(13–16)*. A lower incidence of ejaculatory dysfunction has been reported in approx 10% of men. In a multicenter, randomized, double-blind clinical trial, patients who received methyldopa and a diuretic reported significantly worse total sexual distress symptoms than than those who took placebo and noted specific problems in maintaining erection and ejaculation *(15)*. Methyldopa also causes a net decrease in dopamine, which can lead to hyperprolactinemia and decreased libido *(17)*.

Guanethidine and reserpine are sympatholytic agents that decrease the amount of norepinephrine released at peripheral sympathetic nerves. Both have been reported to cause significant ED in up to 40% of patients who take either drug *(14,18,19)*. Guanethidine and a related agent, guanadrel (which has a faster onset, shorter duration, and less frequent side effects) have been discontinued in the United States secondary to their significant side effect profiles, which include pronounced postural hypotension. Previously, guanethidine was indicated in the management of moderate and severe hypertension and renal hypertension from pyelonephritis, amyloidosis, and renal artery stenosis *(20)*. Its potent

α_2 stimulation is reflected by a significant 40% rate of ejaculatory disturbance *(20a)*. Reserpine disrupts catecholamine storage vesicles and depletes not only norepinephrine but also dopamine and serotonin neurotransmitters, leading to sedation and depressive states *(21)*. Decreased libido results from the hyperprolactinemia that arises from dopamine depletion. These adverse central nervous system (CNS) effects combined with the expected disruption of emission and ejaculatory processes make it difficult for normal sexual processes to occur. The use of newer alternative antihypertensives with less sexual side effects should improve or completely reverse these problems in affected men.

Clonidine is an effective and versatile drug used to treat not only conventional hypertension and hypertensive crises but also opiate and nicotine withdrawal and refractory cancer pain *(22)*. As an agonist of central presynaptic α_2-adrenoreceptors, the inhibition of sympathetic outflow theoretically leads to both impotence and ejaculatory dysfunction. Nevertheless, the published literature raises some controversy regarding these adverse effects. In the Veterans Administration Cooperative Trial, clonidine was one of six randomized single-drug therapies for which no significant increase in the frequency of impotence was demonstrated over placebo *(23)*. Meanwhile, other studies cite sexual dysfunction varying from 10 to 25% *(24–27)*. Switching from oral to transdermal clonidine may help reduce typical side effects without compromising blood pressure control *(28)*.

Diuretics

As recommended by The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the first choice for drug treatment of most uncomplicated hypertension should be a diuretic, either alone or in combination with drugs from other classes *(9)*. Because of the long-term and widespread use of this class of antihypertensive, its relationship with sexual dysfunction is well-reported. Because of the diuretic-induced decrease in peripheral vascular resistance, blood flow to the usually well-perfused corporal bodies is hypothesized to diminish, leading to organic impotence *(29)*. CNS and anti-androgen side effects also contribute to problems of decreased libido. The most commonly cited diuretics associated with sexual difficulties include the thiazide diuretics, chlorthalidone, acetazolamide, indapamide, and spironolactone.

Thiazide diuretics, including hydrochlorothiazide, bendroflumethiazide, and trichlormethiazide, are some of the most commonly prescribed agents for the treatment of hypertension. Although the Veterans Administration Cooperative trial concluded that hydrochlorothiazide (12.5–50 mg/d) was one of six randomized drugs "not associated with a significant increase in the frequency of impotence" compared with placebo *(23)*, most other trials have demonstrated associated significant ED with use of thiazide and have reported an incidence between 4 and 32% *(14,25,30–33)*. Moreover, the addition of hydrochlorothiazide to other antihypertensive agents may exacerbate existing sexual side effects *(15)*. Studies have demonstrated that thiazides specifically impact sexual quality of life, including libido, erection, and ejaculation issues, but do not adversely affect other aspects of quality of life compared with either placebo or other antihypertensive agents *(34,35)*.

Chlorthalidone is a thiazide-like diuretic used in the management of hypertension and edema and is unique because of its long duration of action (48–72 h; ref. *36*). Historically, chlorthalidone appears to be the worst offender among diuretics and has been implicated to cause sexual dysfunction in several studies, including two large-scale, randomized, placebo-controlled studies: the Treatment of Mild Hypertension Study (TOMHS) and the Trial of Antihypertensive Interventions and Management (TAIM; refs. *37* and *38*). In both of these studies, erection-related problems worsened in men who received chlor-

thalidone compared with the problems in those who received placebo (in the TOMHS at 24 mo: 17.1 vs 8.1%; in the TAIM at 6 mo: 28 vs 3%).

In middle-aged men, the incidence of erectile problems is around 10 to 15%, whereas the proportion of older men affected is unknown *(39)*. Symptoms appear relatively early after administration, and new onset of adverse effects after 24 mo is rare *(37)*. Another study cited a 42% incidence of sexual dysfunction (compared with 16% in the control group) and detected no difference in serum testosterone levels to explain the effects *(40)*. Management of sexual dysfunction arising from chlorthalidone may require cessation and substitution for another diuretic, because the lowest therapeutic dose (25 mg) has been shown to cause high incidence rates *(38)*.

Acetazolamide is a carbonic anhydrase inhibitor and has been used as a diuretic for edema caused by congestive heart failure *(41)*. However, because of the rapid loss of its diuretic effect and decreased potency compared with other classes of diuretics, thiazide and loop diuretics are replacing acetazolamide. Acetazolamide is frequently associated with decreased libido as a result of inhibition of central carbonic anhydrase; however, organic impotence has also been reported with the use of this drug for the treatment of glaucoma *(42,43)*.

Indapamide is an oral antihypertensive and diuretic in the newer indoline class. ED and libido decrease are rarely associated with this medication, and most published studies have indicated that sexual side effects are minimal or improved when patients switch from other antihypertensives to indapamide *(44,45)*. Compared with a generally more sexually favorable ACE inhibitor, sexual side effects appeared no higher than those from captopril *(44)*.

Spironolactone is a potassium-sparing anti-aldosterone agent that has been shown to improve overall survival and reduce hospitalization in patients with severe heart failure *(46)*. It has been reported to cause sexual problems in both male and female patients as a consequence of its similarity in structure to steroid compounds *(47,48)*. In men, competitive binding to androgen receptors leads to an increased conversion of testosterone to estradiol, causing gynecomastia, libido decrease, and impotence *(48)*. These side effects are dose-dependent and are easily reversible after discontinuation of the medication *(49,50)*. Dependable published data regarding other potassium-sparing diuretics, including amiloride and triamterene, are devoid of information on sexual effects; however, they appear to cause problems comparable to thiazides. A better alternative may be a new aldosterone receptor eplerenone, which differs from spironolactone by virtue of higher selectivity for the aldosterone receptor and is anticipated to cause a lower incidence of sexual dysfunction *(51)*. A recent randomized study comparing eplerenone and enalapril monotherapy demonstrated no increased incidence of sexual adverse events in the group receiving eplerenone, with equal blood pressure control efficacy *(52)*.

Management of diuretic-induced sexual dysfunction is often easily performed by either dose modification or alternative medication (various options exist). If medically acceptable, the first step is to decrease the dosage of the diuretic *(53)*. Hydrochlorothiazide should be started at the lower possible dose (sometimes <25 mg). If problems persist, then physicians should consider substituting for a different diuretic or class of antihypertensive that has a lower risk profile for sexual dysfunction, such as ACE inhibitors and calcium channel blockers. In circumstances in which a stronger diuretic effect is necessary, use of indapamide or a loop diuretic (such as furosemide, which has few sexual side effects despite widespread use) is recommended *(7)*. Because of their sexually toxic profiles, chlorthalidone and spironolactone should be avoided and replaced by another diuretic

or eplerenone. In combination treatments, the addition of a diuretic increases the impotence rate by about one-third and also increases the severity of any existing dysfunction when added to sexually benign single-drug therapy *(7,54)*. In sexually active hypertensive men, these side effects must be considered, and the ubiquitous use of diuretics should be reduced.

β-Blockers

β-blockers are an important and widely used class of drugs for the management of hypertension, chronic stable angina, and prevention of postmyocardial infarction *(55)*. This is highlighted by a prescribing survey of hypertensive patients that demonstrated that atenolol (a β-blocker) was the most commonly prescribed antihypertensive *(56)*. Generally, these drugs compete with adrenergic neurotransmitters for binding at sympathetic receptor sites and inhibiting stimulation mediated by β_1-adrenergic receptors in the heart and vascular smooth muscle. Similar to diuretics, β-blockers are notorious for causing sexual disorders, and sexual side effects arise from their action on diminishing β_2-vasodilation and creating unopposed α_1-vasoconstriction that alters normal cavernosal dynamics *(57)*. Additionally, β-blockers—especially those that are nonselective—have been found to reduce serum testosterone and, therefore, sexual drive *(57)*.

Atenolol is a competitive β_1-selective adrenergic antagonist with a longer half-life than metoprolol. In a randomized, double-blind study, atenolol significantly reduced sexual activity compared with both placebo and valsartan (4.2 vs 6.0 and 7.4 episodes/mo, respectively) as well as testosterone levels compared with baseline (18.2 vs 13.8 nmol/L; ref. *58*). Other studies have produced similar findings of testosterone decline and chronic worsening of sexual symptoms and activity with atenolol compared with ACE inhibitors and other classes of antihypertensives *(33,59)*. In the TAIM study, atenolol had an 11% incidence of adverse effects compared with a 3% incident in patients given placebo *(38)*. Bisoprolol, a similar once-a-day dosage β-blocker, was reported to have no detrimental effect on sexuality when initiated in newly diagnosed hypertensive men and improved sexuality, such as firmness of erection and satisfaction with functioning, when substituted for an antihypertensive *(60)*; this may provide a good alternative for patients suffering from significant sexual side effects. Metoprolol is another cardioselective adrenergic antagonist that has been reported to have minimal effects on sexual activity based on self-reported questionnaires *(61)*, and it can be administered as an extended-release form (Toprol XL) for once daily administration.

Propranolol and labetolol, both nonselective β-blockers, are the two agents in this class that are most commonly implicated in inducing sexual dysfunction. Both have an incidence rate of sexual dysfunction around 10 to 15%; however, whereas propranolol predominantly affects erection, labetalol often causes ejaculatory difficulties *(30,62–66)*. A multicenter, randomized, double-blind clinical trial found that scores for maintenance of erection and total sexual distress symptoms were significantly worse in patients treated with propranolol compared with those given placebo or methyldopa therapy *(15)*. Contributing to the sexual difficulties, propranolol has been shown to cause significantly more depression (thus requiring antidepressants) than other antihypertensives, with an incidence of about 5 to 15% *(67,68)*. Although labetolol does not generally cause as many CNS problems, it does have both α- and β-blocking properties and, therefore, tends to cause more ejaculatory dysfunction.

Although practically all β-blockers can cause sexual problems, the severity appears to increase with nonselective agents as well as with increasing dosages. Therefore, man-

agement of sexual side effects with men taking β-blockers consists of dosage reduction, substitution of nonselective for β_1-selective agents, or replacement for another class of antihypertensive agent. Physicians should also be cognizant that having knowledge of sexual dysfunction side effects resulting from β-blocker therapy can also influence and increase the incidence *(69)*.

α_1-Blockers

Systemic α-blockers (including doxazosin, terazosin, and prazosin) are used as oral agents in the management of hypertension and benign prostatic hypertrophy (BPH). Selective α_{1a}-subtype blockers, such as alfuzosin and tamsulosin, are used exclusively for BPH and bladder outlet obstruction, because they have minimal effects on blood pressure. Since the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) trial in 2000, which did not demonstrate that doxazosin decreases the risk of cardiovascular disease events in patients with high-risk hypertension, α-blockers have lost favor as monotherapy treatment for hypertension *(70)*. Blockade of α-receptors decreases adrenergic stimulation and induces peripheral vessel dilation, thereby reducing peripheral vascular resistance and blood pressure. Although this may increase cavernosal artery inflow and actually benefit erections, sexual side effects can arise from impaired signal transmission of the seminal vesicles, ejaculatory ducts, and bladder neck. Indirect sexual dysfunction via priapism, fatigue, and weakness can also occur. On the other hand, the sexual side effects profile of this class is generally the most benign of all antihypertensives.

Prazosin, doxazosin, and terazosin have consistently demonstrated little or no sexual side effects throughout their many years of use for treating either hypertension or BPH. The typical incidence rate of impotence for these medications was cited as 0.6% in a surveillance study of 934 men taking prazosin for hypertension *(71)*. The TOMHS study demonstrated a 2.8% rate of ED in patients taking doxazosin; this was less than the 4.9% rate for those patients taking placebo *(37)*. Conversely, the Veterans Administration Cooperative trial demonstrated considerable sexual dysfunction in patients taking a combination of prazosin and diuretic (27.7%), although distinguishing which drug primarily induced the dysfunction was impossible *(23)*. The primary adverse sexual effect noted for prazosin has been priapism, which is rare *(48,72,73)*. The mechanism for priapism presumably is the inhibition of adrenergic-induced vasoconstriction and consequent detumescence, leading to a painfully prolonged erection, risk of permanent tissue damage, and long-term ED. Multiple cases have been reported, and renal failure appears to be a risk factor *(72)*. Comparing doxazosin and terazosin, side effects are typically more frequent in the longer acting α-blockers, although studies directly comparing terazosin and prazosin have shown no differences *(7)*. The labeling notes report an incidence of impotence of 1 to 2% for terazosin and doxazosin compared with 1 to 1.9% for placebo.

Although the selective α_{1a}-adrenoreceptor antagonists are not used in the management of hypertension, they are widely used in men for treatment of BPH and lower urinary tract symptoms. Tamsulosin has been shown to induce ejaculatory dysfunction at a rate of 4 to 18%, increasing to 30% with long-term use *(74)*. Several placebo-controlled studies have confirmed this high rate, which appears to be dose-related *(75–78)*. Although direct comparative trials between alfuzosin and tamsulosin have demonstrated no significant differences in ejaculatory dysfunction between the two agents *(79)*, placebo-controlled alfuzosin studies, in contrast to tamsulosin, have shown no significant differences in the occurrence of ejaculatory disorders *(80)*. It is generally accepted that tamsulosin is unique

from other α-blockers in its profile because it negatively impacts ejaculation; a meta-analysis supporting the American Urological Association BPH guidelines has confirmed this finding *(81)*. Priapism also has been rarely reported following tamsulosin intake *(82)*. Other sexual side effects are low and are generally not encountered in men taking these α-blockers for treatment of BPH.

Calcium Channel Blockers

Generally, all calcium channel blockers are effective antihypertensives and anti-anginals. Agents of this class, including verapamil, diltiazem, felodipine, nifedipine, nicardipine, and amlodipine, block the influx of extracellular calcium across myocardial and vascular smooth muscle cell membranes, which, in turn, inhibits smooth muscle contractility, leading to coronary and peripheral vasodilation. Compared with other antihypertensives, calcium channel blcokers are considered to induce fewer sexual problems. However, side effects can arise via a combination of inhibition of dopamine activity (thus diminishing sexual drive), blockade of excitatory sensory peptides (thus leading to impotence), and decreasing bulbospongiosus and ischiocavernosus muscle contractility (thus causing erectile and ejaculatory disorders; ref. *7*).

Randomized, placebo-controlled studies have demonstrated amlodipine to have sexual function comparable to the ACE inhibitor enalapril and placebo *(23,83)*. In another study, nifedipine and diltiazem were noted to improve different markers of sexual function, whereas verapamil had a neutral effect *(84)*. Nicardipine was demonstrated to affect only cognitive and not sexual function in elderly patients when compared with a thiazide *(35)*. Given the findings of these clinical trials and general practice reports, calcium channel blockers are routinely recommended for their lack of negative sexual impact. However, the toxicity of calcium channel blockers may be understated. One placebo-controlled study demonstrated significant sexual dysfunction in the first 4 wk after the initiation of nifedipine *(33)*. Ejaculatory disorders occurred at almost twice the rate of those experienced with atenolol and trichloromethiazide, whereas incidence of ED with administration of nifedipine was comparable with that seen with those two agents. These problems may recover in the long term, as only patients taking atenolol experienced sexual dysfunction at 1 yr. Several reports have also shown calcium channel blockers to inhibit dopamine and increase prolactin, potentially leading to decreased libido, impotence, and gynecomastia *(85,86)*.

Despite a long history of these medications being used to treat high blood pressure, relatively little data from small studies exist in the literature, and no particular calcium channel blcoker has been consistently reported to be more or less toxic than others in the class. When sexual problems arise from administration of a calcium channel blocker, substitution for another class of antihypertensive with a more benign sexual profile—particularly ACE inhibitors or angiotensin receptor blockers—may yield the most promising result. However, the use of ACE inhibitors may necessitate a concurrent diuretic, which may eliminate the sexual advantage.

ACE Inhibitors

ACE inhibitors are important drugs in the treatment of hypertension and are first-line agents for the treatment of heart failure *(87,88)*. Among the more popular ACE inhibitors are captopril, lisinopril, enalapril, benazepril, fosinopril, and ramipril. These agents

interfere with the conversion of angiotensin I to angiotensin II by blocking ACE, thereby reducing aldosterone output and sodium re-absorption. This class of antihypertensive represents the best option for men who seek to avoid sexual dysfunction while still benefiting from effective blood pressure control. When sexual dysfunction is present, the presumed mechanism is likely from CNS effects such as fatigue, dizziness, and depression, which diminish sexual interest and activity.

Captopril was the first ACE inhibitor marketed in the United States. The Veterans Administration Cooperative trial reported a 0.8% impotence rate, which was less than the minimum placebo rate of 1% *(23)*. Based on self-reporting questionnaires, another study demonstrated that captopril did not cause sexual dysfunction in the short term (1–4 wk after initiation) or long term (1 yr; ref. *84*). Although adverse sexual side effects are rare, some patients do experience them; in a captopril quality-of-life study, five patients withdrew secondary to sexual symptoms *(89)*.

With the newer and more durable ACE inhibitors, including enalapril and lisinopril, negative sexual and psychological effects may appear more frequently *(90)*, although still at rates significantly lower than other antihypertensives. Enalapril may have more psychological side effects, including depression, fatigue, lassitude, and dizziness *(91)*. In the TOMHS study, patients who took enalapril monotherapy developed erectile difficulties at a rate only slightly higher than patients who took placebo (6.5 vs 4.9%; ref. *37*). Patients who suffer sexual dysfunction while taking an ACE inhibitor should be administered a reduced dose, if possible, or should be switched to another drug in this class.

Angiotensin Receptor Blockers

Angiotensin-II receptor blockers (ARBs) are specific and selective for the angiotensin II_1 receptor and inhibit the binding of angiotensin II to its endogenous receptor, causing a decrease in systemic vascular resistance without a marked change in heart rate *(92)*. Drugs in this class include losartan, valsartan, and irbesartan. Similar to the ACE inhibitors, the sexual side effect profile appears to be benign or even beneficial in men taking the drug.

Losartan was the first marketed ARB in the United States; it is indicated for treatment of essential hypertension, diabetic nephropathy, and proteinuria and remains an alternative therapy for patients intolerant to ACE inhibitors congestive heart failure *(92)*. In men with previous erectile problems, losartan improved both self-reported sexual activity (40.5 to 62.3%) and sexual satisfaction (7.3 to 58.5%; ref. *93*). The longevity of this beneficial effect is uncertain, because only 11.8% of the treated patients reported an improvement in sexual function. Overall perceived quality of life was improved in almost 75% of patients treated with losartan.

Valsartan has demonstrated a similarly favorable adverse sexual effects profile. In a randomized, placebo-controlled crossover study, sexual activity declined slightly during the first month (8.3 to 6.6 sexual intercourse episodes) but fully recovered and then improved with ongoing follow-up (10.2 episodes) in newly treated patients taking valsartan *(94)*. Only 1 of 120 patients (0.9%) reported impotence while taking valsartan, compared with 2.5% on placebo. In another population of patients with significant baseline ED, valsartan was noted to reduce this incidence by 20% and also increased sexual desire *(95)*. These favorable effects may be mediated by the principal ability of ARB to block angiotensin II, which has recently been identified as an important mediator of detumescence and, possibly, ED *(96)*. Although further research is necessary, ARBs appear to offer

an excellent therapeutic option for managing hypertensive patients suffering from sexual difficulties.

ANTIDEPRESSANTS

Historically, sexual disorders have been relatively common side effects of antidepressant pharmacology. The baseline incidence of ED and disorders of libido approach 70% in untreated depression *(97)*; when all forms of sexual dysfunction are included, the incidence of ED in men taking antidepressant medications may be up to 90% *(98)*. Like antihypertensive therapy, these side effects may compromise quality of life and result in noncompliance of the drug, which is detrimental to the patient's overall health *(99)*. Fortunately, the sexual toxicity of antidepressants has improved dramatically over the course of their development. Later generation agents, including bupropion, nefazodone, and mirtazapine, appear to be better tolerated in the sexual arena than earlier generation tricyclic antidepressants (TCAs), monamine oxidase inhibitors, and SSRIs. Antidepressants have been reported to cause disorder in all areas of sexual function, including erection, ejaculation, and libido.

Tricyclic Antidepressants

Since 1959, TCAs have been widely used to treat depression *(100)*. With the introduction of SSRIs in the late 1980s, the use of TCAs for depression has declined. These drugs cause an increased concentration of neurotransmitters—specifically norepinephrine and serotonin—by interfering with their re-uptake in neural synaptic clefts. Generally, tertiary amine tricyclics (amitriptyline, clomipramine, doxepin, imipramine, trimipramine) inhibit the re-uptake of serotonin more than secondary amines (desipramine, nortriptyline, protriptyline), which primarily inhibit norepinephrine. The latter group appears to have a less toxic sexual impact. Although depression can cause sexual dysfunction *(101)*, this problem can occur for the first time with TCA use. Impotence and decreased sexual drive are believed to arise primarily from the significant anticholinergic activity of several TCAs, and ejaculatory dysfunction has been proposed to be secondary to sympatholytic effects.

Clomipramine, amitriptyline, and doxepin appear to have the most negative impact on sexual function. Significant side effects are encountered at even the lowest doses for clomipramine, whereas side effects from amitriptyline and doxepin are strongly dose-related. From a multicenter comprehensive review of negative sexual side effects and the Food and Drug Administration (FDA)-approved drug labeling, clomipramine is reported to produce a 41 to 42% rate of ejaculation failure, an 18 to 20% change in libido, and 15 to 20% impotence rates *(7,102)*. Imipramine and protriptyline are considered to have moderately severe sexual toxicity, whereas desipramine and nortriptyline have the least sexual side effects *(7)*. In one study, imipramine produced a higher incidence of problems with orgasm and ejaculation, but there were no differences in sexual desire or frequency compared with placebo *(103)*. Another study reported a 55% sexual dysfunction rate—especially difficulty reaching orgasm—using detailed questionnaires in patients on imipramine therapy *(104)*. Although ejaculation disorders have been cited as the primary sexual side effect of TCAs *(105–108)*, several reports citing problems of erection and libido also exist *(105,109,110)*. It has been proposed that sexual dysfunction likely occurs at a higher frequency than reported in the literature because these problems were often attributed to the underlying depression rather than the drug treatment.

Despite a decline in the use of TCAs as antidepressants, they are still widely prescribed because of their effectiveness in treating many conditions, such as enuresis, social anxiety disorder, eating disorders, posttraumatic stress disorder, attention deficit-hyperactivity disorder, panic disorder, smoking cessation, migraine prophylaxis, and neuropathic pain syndromes *(100)*. Management of sexual side effects induced by these agents is best managed by substituting an alternative TCA, noting that desipramine and nortriptyline have the most benign sexual profile. In some situations, supplementing TCA therapy with cholinergic (bethanechol) or antiserotonin (cyproheptadine) drugs may help alleviate the dysfunction, but these drugs induce additional bothersome side effects that many patients cannot tolerate *(106,111,112)*. Reducing doses and switching to an alternative class of antidepressant—especially bupropion, trazodone, and nefazodone—may ultimately be required to remedy the problem.

Monoamine Oxidase Inhibitors

Like TCAs, monoamine oxidase inhibitors (MAOIs) were a first-generation class of antidepressants that were quickly superseded because of significant, intolerable, and dangerous side effects *(113)*. Current indications for MAOIs remain limited. MAOIs are used as alternative therapy for panic disorder, social phobia, and atypical depression and include phenelzine, isocarboxazid, tranylcypromine, clorgyline, and pargyline. These agents inhibit the MAO enzyme, which catalyzes the oxidation of serotonin, neuroepinephrine, and dopamine, raising their levels and thereby positively impacting mood. It is hypothesized that whereas TCAs impair sexual function via a predominantly anticholinergic effect, MAOIs primarily diminish sexual libido *(114)*.

The literature reports a 16 to 40% incidence of sexual disorder in this class of drugs *(103,115–117)*, but data regarding the nature and extent of these side effects have been paltry. Although several case reports of anorgasmia and ejaculatory dysfunction exist, they appear to be mostly anecdotal *(118,119)*. One of the few placebo-controlled studies demonstrated that when compared with placebo and imipramine (TCA), phenelzine caused significant differences in desire, enjoyment, and orgasm/ejaculation, as assessed by self-reported questionnaires *(103)*. An earlier systematic study of phenelzine use found a 22% incidence of sexual dysfunction consisting of anorgasmia, delayed ejaculation, and impotence but did not further break down this figure. On the other hand, tranylcypromine had a 2% anorgasmia/impotence rate. Dysfunction appeared to be dose-related and was more evident 4 to 12 wk after treatment. Priapism has also been reported with phenelzine use *(120)*.

Like TCA, dosage reduction, drug holidays, and substituting another drug or class of antidepressant are the main approaches for reducing MAOI-induced sexual dysfunction. Although tranylcypromine is less powerful than other agents in the class, it causes significantly less weight gain and sexual dysfunction and is much more well-tolerated for chronic use *(7)*. Bupropion is an excellent alternative for treatment of atypical depression because it appears to have a sexually beneficial profile. Finally, a newer type of "reversible" inhibitors of monoamine oxidase A, including moclobemide, befloxatone, and brofaromine, have been studied extensively in countries outside the United States *(113)*. In direct comparative, placebo-controlled studies, moclobemide has been found to maintain significantly better sexual function compared with phenelzine and doxepin, without compromising antidepressant efficacy *(121,122)*. Befloxatone and moclobemide are under investigation in the United States for the treatment of depression.

Selective Serotonin Re-Uptake Inhibitors

Since their introduction in 1988, SSRIs have quickly become first-line drugs in the medical treatment of depression *(123)*. Fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram are all considered members of this class. Although venlafaxine is not considered a true SSRI, its mechanism of action and side effects most resemble the drugs in the SSRI category. The most important clinical feature of these agents is their high specificity for blocking the re-uptake of serotonin compared with their effects on other known neurotransmitters, allowing for the selective potentiation of serotonin. The primary sexual disorders associated with SSRIs are ejaculatory delay/dysfunction and decreased libido. Several possible mechanisms for inducing sexual impairment have been postulated and include alterations of levels of sexually inhibiting serotonin and sexually stimulating dopamine, prolactin, and NO *(114)*.

Fluoxetine was the first SSRI approved in the United States, and it exhibits the longest half-life of all the SSRIs. Although the manufacturer cites a low 1.9% rate of sexual impairment from fluoxetine, the published literature has not been so kind, reporting an 8 to 75% rate of sexual side effects *(124–127)*. Anorgasmia and decreased sexual drive have been the primary complaints. In the most incriminating study, which reported a 75% incidence of ejaculatory dysfunction, the high numbers were likely secondary to specific questioning of ejaculatory changes. Lowering the dose improved ejaculatory problems in 50% of the men studied *(127)*. Penile anesthesia has also been reported in several case reports *(128,129)*.

Like fluoxetine, sertraline, paroxetine, and fluvoxamine share the same inhibitory effect on orgasm and ejaculation. Several of these drugs—particularly sertraline and paroxetine—are being evaluated and appear promising for the treatment of premature ejaculation. The incidence of sexual dysfunction in men using sertraline has ranged from 8 to 21% in placebo-controlled studies *(130–132)*. One randomized, double-blind, placebo-controlled study comparing sertraline with citalopram demonstrated decreased sexual desire, orgasmic dysfunction, and ejaculatory dysfunction in 25, 16.7, and 18.9% of men, respectively, with no difference between the two SSRIs *(133)*. Paroxetine has a similar reported incidence of ejaculatory and orgasm impairment (9–17%), but up to 50% of patients may be affected *(7,134–136)*.Unlike treatments that cause ejaculatory problems as a result of adrenergic blockade, ejaculation with paroxetine occurs normally, but orgasm is inhibited and there is decreased sensation at climax. Paroxetine is generally considered the most potent SSRI for delaying orgasm. Fluvaxamine has not been shown to cause as many sexual side effects; however, other side effects, such as severe nausea and nervousness, may diminish sexual drive and frequency *(137)*. Although sexual dysfunction is reported to range from 10 to 30%, the prevalence is clearly less than that observed with paroxetine *(7)*.

Venlafaxine is a combined serotonin and norepinephrine uptake inhibitor that was first marketed in the United States in 1994. Its drug labeling cites a 12% rate of retarded male orgasm and ejaculation. Although one study reported less sexual dysfunction self-reported by patients who were taking venlafaxine compared with patients taking other SSRIs *(138)*, a large-scale, nonrandomized study of 596 patients on various SSRIs reported that venlafaxine had the highest rate of sexual side effects (38%), with an overall incidence of 20% *(139)*. Only further clinical experience will show the true degree of venlafaxine's impact on sexual function.

Besides the typical approaches for managing antidepressant-induced sexual dysfunction (watchful waiting, dosage reduction, drug holidays, or substitution for another class

of antidepressant), several studies have investigated the use of sildenafil for SSRI-induced ED. In one study, 10 of 10 patients reported an improvement in erectile capability, and 7 of 10 reported a return of erectile function back to normal levels *(140)*. A larger prospective, randomized, double-blind, placebo-controlled trial reported lower but still favorable rates of "much or very much improved" sexual function in patients who took sildenafil compared with those who took placebo (54.4 vs 4.4%; ref. *141*). Men self-reported significantly improved erectile function, arousal, ejaculation, orgasm, and overall satisfaction with sildenafil compared with placebo. The use of sildenafil has been concluded to improve the compliance of men who suffer from sexual problems while undergoing effective antidepressant treatment.

The use of gingko biloba has also been recently investigated in the treatment of SSRI-induced sexual dysfunction. Although one study demonstrated this complementary drug extract to be 84% effective, with positive effects on all four phases of the sexual response cycle *(142)*, other studies have not been able to replicate these results *(143)*. Finally, the sexual benefits of switching men taking SSRIs to bupropion or nefazodone has been demonstrated in several studies that are described in later sections.

Although the side effects of ejaculatory and orgasm delay in men taking SSRI for the treatment of depression are a significant problem, in other men suffering from premature ejaculation, this manifestation can be of clinical benefit. Several prospective, double-blind studies have demonstrated the ability of paroxetine, sertraline, and fluoxetine to increase the time between vaginal penetration and orgasm, thus delaying early ejaculation *(144–146)*. In fact, a large-scale phase III clinical trial of dapoxetine, a "dual inhibitor" similar to venlafaxine that inhibits both serotonin and neuroepinephrine, was recently completed, and dapoxetine was submitted for FDA approval as a medical treatment for premature ejaculation.

Lithium

Lithium is the drug of choice for treatment of acute mania and recurrent bipolar affective disorder *(147)*. Although the mechanism of its antimanic and antidepressant action in the CNS is unknown, evidence suggests that the drug increases re-uptake and decreases synthesis, storage, and release of monoamine neurotransmitters—particularly central norepinephrine. Sexual side effects include decreased libido and erectile function, although few studies are available. The reported rate of sexual dysfunction is variable, and interpretation of results is difficult because other medication effects are often not controlled. One study demonstrated a 16.6% incidence of ED in men on chronic lithium; however, more than half of the men were on concurrent antidepressants, benzodiazepines, and neuroleptics *(148)*. In another study, only 1 of 36 patients reported sexual dysfunction on lithium alone, whereas those taking lithium in combination with benzodiazepines reported a 34% incidence of moderate-to-great decrease in desire and function *(149)*. Other authors have noted that male sexual dysfunction occurred when other psychotropic drugs were used concurrently with lithium. Although lithium-induced sexual toxicity does not appear to be an overly common problem—especially in the setting of the complex sexual behaviors of patients with bipolar disorder—alternate treatment with bupropion replacement or supplementation, if appropriate and effective, would be a sound approach to take when it occurs.

Trazadone and Nefazadone

Trazodone is an oral antidepressant that is unrelated to the previous classes of medications. It is used in the treatment of major depression, generalized anxiety disorder, and

insomnia *(150)*. Nefazodone is structurally similar to trazodone, but it carries less risk for the side effects of sedation and orthostatic hypotension *(151)*. Both drugs increase serotonin neurotransmission either by primarily inhibiting the re-uptake of serotonin at the presynaptic membrane (trazadone) or by antagonizing type 2 serotonin postsynaptic receptors (nefazosone), with minimal influence on the re-uptake of norepinephrine or dopamine within the CNS. With this predominantly serotonergic effect, sexual dysfunction typical of other serotonin potentiators might be expected; however, this does not appear to be the case.

The use of trazodone has been associated with side effects of prolonged nocturnal erections and priapism *(152,153)*. Therefore, trazodone has been investigated for the use of treating psychogenic and organic ED. Although some small studies have reported favorable results, with a 64 to 78% significant improvement in erectile capability *(154,155)*, a placebo-controlled, double-blind crossover study demonstrated no difference in erectile improvement from trazodone (19%) compared with placebo (24%; ref. *156*). From a general clinical experience perspective, trazodone has not proven to be a very effective drug treatment for impotence, and the risk of priapism remains real. Although the enhancement of erectile function and sexual drive are primarily anecdotal *(157)*, trazodone remains one of the more sexually benign agents in the pharmacological armamentarium to treat depression.

The sexual toxicity of nefazodone has been studied more extensively and rigorously than trazodone. It is typically grouped with bupropion as a sexually benign alternative to managing depression. In a large-scale observational study investigating sexual side effects of newer antidepressants, bupropion and nefazodone were noted to have the lowest incidence (25 and 28%, respectively; ref. *158*). Another multicenter, prospective study cited an 8% incidence of sexual dysfunction for nefazodone compared with a 55 to 78% incidence for different SSRIs *(159)*. Several studies have directly compared this agent to sertraline and have found a significant sexual advantage in the use of nefazodone *(160,161)*, emphasizing the importance of considering this drug in the management of antidepressant-induced sexual toxicity, particularly that produced by SSRIs.

Bupropion

Bupropion is indicated in the treatment of major depression and as an aide to smoking cessation *(162)*. It is unique to the aminoketone class and is unrelated to other known classes of antidepressants. Although bupropion's mechanism of action is not fully understood, it appears to selectively inhibit the neuronal re-uptake of dopamine with weaker effects at norephinephrine and serotonin receptors *(163)*. This dopamine potentiation should have generally positive effects on sexual desire and response, and several studies have reported findings consistent with this hypothesis.

In opposition to most clinical practice and literature findings, the *Physicians Desk Reference* misleadingly cites a 3% incidence of decreased libido and impotence with use of bupropion, exceeding incidence rates of fluoxetine. A 1991 study that compared bupropion to fluoxetine showed no sexual side effects from bupropion *(164)*. Generally, bupropion rarely decreases libido and often increases it *(7)*, as demonstrated by a placebo-controlled, double-blind crossover study investigating the treatment of mild-to-severe psychogenic sexual dysfunction with bupropion *(165)*. Patients treated with bupropion had a 63% "much improved" rating of sexual function compared with only a 3% incidence in patients taking placebo. Several studies have also demonstrated the ability of bupropion to successfully manage antidepressant-induced sexual dysfunction when

these patients are switched over. A recent study demonstrated a 94% rate of partially or completely resolving orgasm problems and an 81% rate of improved libido that had been diminished because of fluoxetine *(166)*. Despite this finding, bupropion can cause nervousness and hypersensitivity in patients as a result of its stimulant actions, which can negatively impact sexual function. At low doses, the positive sexual effects of bupropion may not be present, whereas the stimulating side effects are encountered. This was likely the case in a randomized, placebo-controlled study that showed a 16.7 and 26.7% incidence of decreased libido and ED, respectively, and no difference compared with placebo in men taking a low-dose (150 mg), sustained-release bupropion for SSRI-induced sexual dysfunction *(167)*. Because doses of 300 to 450 mg/d of bupropion are typically well-tolerated in men, this agent should generally benefit men who suffer from drug-induced sexual dysfunction and should be considered in the management of this problem, when clinically appropriate.

Mirtazapine

Mirtazapine is a member of a new class of antidepressants, the noradrenergic and specific serotonergic antidepressants, and is not chemically related to any of the agents previously described *(168)*. It is characterized by a unique receptor-specific pharmacological profile of presynaptic α_2-adrenoreceptor and postsynaptic 5-HT_2 and 5-HT_3 receptors blockade, which produce a profile of benign side effects, including decreased insomnia, agitation, and sexual dysfunction *(169)*. Mirtazapine has been reported to successfully reverse SSRI-induced sexual dysfunction in 69 to 100% of those treated and even improves baseline levels in a certain proportion of patients (11%; refs. *170–172*). All areas of sexual function, including libido, erection, and ejaculation/orgasm, appear to benefit in some way *(173)*. The results of large-scale observational studies are more modest, demonstrating lower sexual toxicity (24–36%) compared with SSRIs (43–73%); however, the sexual toxicity of mirtazapine is not as favorable as that of bupropion or nefazodone (8–28%; refs. *158* and *159*). Although still clinically new, this agent appears promising as an effective strategy for treating SSRI-related sexual dysfunction without compromising any therapeutic antidepressant response.

ANTIPSYCHOTICS

Similar to antidepressants, antipsychotic medications, or neuroleptics, have been well-recognized to cause significant negative sexual side effects. Unfortunately, unlike antidepressants, the alternatives for treating certain psychiatric conditions are limited and often clinically inferior, and development of newer drugs with more benign sexual profiles has been slow *(7)*. The incidence of sexual dysfunction in psychiatric patients is significant (as high as 82% in one cohort of male schizophrenia patients), and sorting out whether the disease or treatment is the etiology has proven difficult *(174,175)*. Traditionally, most practitioners have disregarded or underestimated this issue and considered the loss of sexual function a small sacrifice for the gain of sanity *(176)*. However, patient noncompliance, which can be as high as 50% in the psychiatric population, argues strongly against this philosophy, because sexual dysfunction is considered one of the most significantly distressing side effects of treatment with psychiatric drugs *(177–179)*.

Antipsychotics are typically differentiated based on their classification as a conventional or atypical agent *(180)*. Conventional agents include chlorpromazine, thioridazine, haloperidol, and fluphenazine, and atypical antipsychotics include clozapine, olanzapine,

risperidone, ziprasidone, and quetiapine. Although the psychoses-stabilizing effect of antipsychotics derives from the blockade of dopamine receptors in the CNS, there is a wide difference in specific dopamine receptor (D_1–D_4), α-adrenoceptor, and acetylcholine receptor selectivity that dictates the profile of side effects. Conventional antipsychotics typically antagonize D_1 and D_2 receptors. In the nigostriatal and tuberoinfundibular tracts, nonspecific D_2 inhibition can cause extrapyramidal symptoms and hyperprolactinemia, respectively. In this subclass of antipsychotics and risperidone, hyperprolactinemia has been demonstrated to occur in 40 to 60% of patients and likely accounts for a significant portion of sexual dysfunction encountered *(178)*. Decreased sexual libido is the predominant toxicity, occurring in as many as one of three patients, along with other symptoms, such as gynecomastia, ED, hypogonadism, and infertility *(178,181,182)*. Conventional antipsychotics also tend to have significant anticholinergic and α-blocking effects, leading to sedation and ejaculatory problems, respectively, which have various implications on sexual functioning. Thioridazine is one the worst offenders, with an incidence of sexual dysfunction approaching 60% (compared with 25% in other conventional antipsychotics; ref. *183*). Studies have shown that phenothiazine causes significant sedation, the greatest decrease of libido of all the neuroleptics, ejaculatory problems in up to 50% of men, and primary testosterone inhibition *(183–185)*. Chlorpromazine has also been demonstrated to cause ejaculatory dysfunction *(48)*. Most of these problems are apparent within the first 24 h of drug initiation and are reversible once treatment is discontinued *(186)*.

Atypical antipsychotics have greater specificity for D_4 receptors and less affinity for D_2 receptors. These neuroleptics also have serotonin 5-HT_2 receptor antagonism, which would theoretically enhance sexual ability over conventional agents; clinical reports have generally confirmed this *(175)*. Because these drugs have minimal D_2 receptor affinity in the tuberoinfundibular tracts, atypical antipsychotics tend to be "prolactin-sparing" and, therefore, libido-sparing. These atypicals include clozapine, olanzapine, quetiapine, and ziprasidone and are capable of normalizing prolactin levels and improving self-reported sexual function in patients with antipsychotic-induced sexual dysfunction *(187–189)*. Compared with conventional antipsychotics and risperidone, clozapine (the prototypical atypical antipsychotic) consistently demonstrated better functioning in all sexual areas, including desire, ejaculation, and erection *(190,191)*. Risperidone is the only atypical antipsychotic that regularly causes hyperprolactinemia and its attendant toxicities. Furthermore, risperidone can cause impairment via potent α_1-adrenergic antagonism, and ejaculatory problems have often been reported *(192,193)*.

Ironically, priapism has been reported to occur repeatedly with antipsychotics *(194)*. This is believed to arise from α-adrenergic sympathetic blockade, which prevents detumescence. Of the conventional neuroleptics, chlorpromazine and thioridazine have the greatest affinity for α-adrenoreceptors and are most associated with this urological emergency. Of the atypicals, risperidone is the most well-recognized, although three of the five FDA-approved atypicals have been reported to cause priapsim *(195)*.

Several treatment strategies for antipsychotic-induced sexual dysfunction have been investigated. Dose reduction is often the first approach; however, reduction may be severely limited by suboptimal therapeutic effects. As reported earlier, switching from a conventional antipsychotic or risperidone to a prolactin-sparing atypical antipsychotic has proved to be successful in a proportion of patients. Finally, initiation of additional medication is a third option. Amantadine is often prescribed to manage the extrapyramidal Parkinsonian-like symptoms that may arise from use of neuroleptics. One study demonstrated that co-administration of amantadine improved patient scores in three of the four

areas of sexual function (i.e., desire, erection, and satisfaction from sexual performance; ref. *196*). However, the use of PDE-5 inhibitors in this population may be even more promising. In small pilot studies, sildenafil has been shown to be 70 to 75% successful in treating sexual dysfunction caused by olanzapine and risperidone, and the use of this class of drugs can likely be broadened for administration with other antipsychotics *(197–199)*.

BENZODIAZEPINES

Benzodiazepines, a class of drugs including chlordiazepoxide, diazepam, oxazepam, alprazolam, clonazepam, and lorazepam, are commonly used as sedatives/hypnotics and anti-anxiety medications. Benzodiazepines are the drugs of choice for treating symptoms associated with acute anxiety disorders, anxiety associated with depression, agitation and anxiety in the setting of dementia, and for management of symptoms associated with acute ethanol withdrawal *(200)*. Traditionally, this class of medications was not commonly associated with sexual dysfunction *(201)*, but more recent studies have raised this idea for contention. Benzodiazepines in combination with lithium were associated with sexual problems in 49% of patients, compared with 14% using lithium alone and 17% using lithium with other drugs *(149)*. Apparently, serum lithium and prolactin levels did not differ among the groups. Another study found that clonazepam induced a high incidence of sexual dysfunction (42.9%), whereas diazepam, alprazolam, and lorazepam were free of sexually related complaints. Unfortunately, no prospective studies have been performed to further investigate this issue. The remaining published literature primarily consists of case reports citing problems of decreased libido, impotence, and ejaculation, and almost all drugs of this class have been implicated *(202–205)*.

Although direct drug actions mediated through central serotonergic activity have been implicated *(206)*, the primary mechanism of sexual impairment with benzodiazepines likely is a function of its sedation, disruption of normal sleep patterns, and muscle relaxation *(7)*. Combined with the underlying anxiety state of the patient, this creates a setting that makes sexual interest and functioning difficult. In other settings, however, these drugs can be both dangerous and a sort of sexual weapon. Benzodiazepines—particularly flunitrazepam—have been used on unsuspecting victims and are frequently associated with date or acquaintance rape *(207,208)*. Victims lose their ability to ward off attackers, develop amnesia, and are unreliable witnesses. Low-dose or chronic benzodiazepines have also been observed to cause states of disinhibition that promote sexual activity; unfortunately, this often occurs in a negative setting of impropriety or hostility *(7,186,209)*.

Treatment for benzodiazepine-induced sexual problems primarily consists of watchful waiting, dose reduction, or switching to another benzodiazepine or sedative/hypnotic drug to produce possible decreased side effects. Zolpidem, a nonbenzodiazepine sedative/hypnotic, is a potential alternative because it has not been shown to have any adverse sexual effects, although its mechanism of action suggests that it could lead to decreased libido and response *(7)*.

H_2-BLOCKERS

H_2-blockers are widely prescribed in the treatment of gastrointestinal disorders, including peptic ulcer disease. These drugs block the effects of histamine at the receptor located on the basolateral membrane of the parietal cell and include cimetidine, ranitidine, famotidine, and nizatidine. Within this group, cimetidine appears to have several adverse sexual toxicities, whereas the other three do not *(186)*. Unlike the other three drugs, cimetidine

is known to have anti-androgenic and hyperprolactinemic effects in humans, leading to symptoms of gynecomastia, impotence, decreased libido, and decreased sperm count *(210–212)*. The anti-androgenic properties are believed to arise from interference with testosterone metabolism and androgen receptor binding *(7,213)*.

Elevated estrogens have also been demonstrated with cimetidine use secondary to inhibition of estradiol 2-hydroxylation, which further exacerbates sex drive and response in men *(214)*. Despite this finding, gynecomastia occurs infrequently (0.2–0.8% incidence; ref. *215*). Sexual dysfunction appears to be dose-related, and the incidence can be as high as 41% in men treated for gastric hypersecretory states, requiring more than 5000 mg per day *(216)*. Several studies have investigated cimetidine and lowered sperm count, and conflicting data exist *(217–219)*. Although sperm count may be affected and reduced by as much as 43%, it appears to be consistently reversible with discontinuation of the agent to a degree of reduction that would not impact fertility in men with normal sperm counts *(217)*. Because no study has been performed on men with low or borderline sperm counts who may be at greater risk for having drug-induced infertility, it appears prudent to avoid the use of cimetidine in this population of men.

Although there are few randomized and even fewer prospective studies comparing the different sexual side effects of H_2-blockers, reports that associate ranitidine, famotidine, and nizatidine with adverse sexual effects are far less frequent than those involving cimetidine. The incidence of sexual dysfunction with these H_2-blockers appears similar to the incidence of these events in the normal male population *(220)*. Reversal of sexual problems by switching to one of these H_2-blockers has been frequently reported, and this appears to be the simplest remedy for H_2-blocker-induced sexual toxicity. Alternatively, because of their low incidence of sexual side effects, proton pump inhibitors, which can commonly treat similar gastrointestinal disorders, can be used in place of these agents *(221)*.

DIGOXIN

Digoxin is a cardiac glycoside indicated for the treatment of congestive heart failure and for control of ventricular rates in patients with atrial fibrillation *(222)*. Administration has been declining because ACE inhibitors and calcium channel blockers have slowly replaced digoxin in the treatment of both of these disease states, respectively. Because of its extended period of clinical use, this agent has long been associated with sexual dysfunction. Since the inception of digoxin in the 1950s, gynecomastia and hyperplasia of breast tissue have been reported in both men and women after long-term use *(223, 224)*. Comparing rheumatic heart disease cohorts with and without the administration of digoxin, one study found a significant self-reported decrease in sexual drive, erectile ability, and the frequency of sexual activity *(225)*. The incidence of sexual side effects in patients who were administered digoxin was 35.7% compared with 0% for controls. This study, as well as earlier studies, demonstrated a 50% decrease in testosterone and luteinizing hormone (LH) and a twofold increase in estrogen with chronic digitialis administration, which explains these side effects *(225–227)*. The mechanism of these hormonal alterations stems from the steroidal structure of digoxin, which allows it to compete with sex steroids for receptor sites; however, this proposed mechanism was disputed by findings from a study that did not demonstrate a significant alteration in these hormones. These findings suggest that ED is caused by inhibition of corporeal smooth muscle sodium pump activity, which promotes contraction and impedes NO-induced relaxation *(228)*. Although the mechanism is not entirely clear, treatment of digoxin-

induced sexual dysfunction is obvious and should include discontinuation and substitution with another medication. As mentioned previously, calcium channel blockers and ACE inhibitors are two classes of sexually benign drugs that may be clinically appropriate.

ANTILIPEMICS

Antilipemics encompass a large family of drug classes used to treat hypercholesterolemia, including fibric acid derivatives (clofibrate, gemfibrozil, fenofibrate), bile acid sequestrants (cholestyramine, colestipol), 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin), and miscellaneous agents (niacin or nicotinic acid, probucol; ref. *229*). Because these agents are commonly taken in conjunction with antihypertenive medications in patents with atherosclerotic vascular disease, determining the exact etiology of any existing sexual dysfunction is often challenging. Generally, lipid-lowering drugs can decrease levels of sex hormones by limiting the availability of cholesterol *(230)*. The earliest experience of sexual dysfunction from antilipemics followed the use of clofibrate and gemfibrozil. Both demonstrated ED that resolved with discontinuation and then recurred with rechallenge of the drug *(231–234)*. Clofibrate has been reported to have a 14.1% incidence of ED and is hypothesized to increase metabolism of androgens by competing for protein-binding sites *(235)*.

Statins inhibit the HMG-CoA reductase enzyme (the rate-limiting step of cholesterol synthesis) and, therefore, may block the synthesis of steroid hormones derived from cholesterol, including testosterone. The first case of ED caused by statins was reported in 1996, and subsequent case reports have followed *(236–238)*. A case–control study showed a 12% incidence of impotence in men taking antilipemics vs a 5.6% incidence in controls, and statins demonstrated as much risk for sexual difficulties as fibrates *(230)*. There is some degree of discrepancy between conclusions drawn from case reports and smaller studies and those drawn from large-scale controlled studies. Randomized, double-blind controlled studies investigating these agents have not reported significant rates of impotence *(239–241)*, but this may be secondary to failure to recognize and ask patients about this potential side effect, because patients generally underreport sexual dysfunction unless they are specifically prompted about it. Studies have provided evidence that simvastatin can lead to minor changes in serum androgen levels in asymptomatic men *(242,243)*, whereas pravastatin does not appear to have the same effect *(244,245)*.

Antilipemic-induced sexual toxicity can be treated by discontinuing the offending drug and substituting it for another drug. Although ED caused by HMG-CoA reductase inhibitors may be a class effect, attempting to switch from one statin to another may be beneficial *(246)*. Currently, uncertainty exists regarding whether certain statins are superior to others in terms of decreased sexual toxicity, and randomized controlled studies targeting adverse sexual effects are needed.

ANTICONVULSANTS

Since 1912, anticonvulsants have been used in the United States for the management of seizures. Anticonvulsants are believed to mediate the actions of seizures by limiting the spread of discharge from a focus and/or by elevating the seizure threshold through various biochemical mechanisms *(247)*. Although patients with seizure disorders often have baseline sexual abnormalities, anticonvulsant medications have also been regularly associated with sexual dysfunction. The self-reported incidence of decreased sexual

drive and behavior in patients with epiplepsy ranges from 14 to 66% *(248)*. Modulation of hormone release from the hypothalamic–pituitary–gonadal axis by these drugs is believed to have direct inhibitory effects on sexual behavior.

Valproic Acid

Valproic acid is indicated for the treatment of generalized tonic–clonic, complex partial seizures, and myoclonic seizures *(249)*. Although the exact mechanism of action is unclear, it is believed that valproic acid increases brain concentrations of γ-aminobutyric acid, an inhibitory neurotransmitter in the CNS. Although valproate is associated with several reproductive endocrine disorders in women, it is considered a sexually benign drug in men. It has been found to result in desirable hormonal effects compared with other anticonvulsants, including increased levels of serum androgen and dihydroepiandrosterone (DHEA) and its sulfated form (DHEAS; refs. *250* and *251*), with no increase in prolactin or sex hormone-binding globulin (SHBG; ref. *252*). This difference between valproate and other anticonvulsants apparently results from its absence of liver enzyme induction. Therefore, decreased sexual drive and response occurs minimally, and this anti-epileptic has been recommended for treatment of patients suffering from anticonvulsant-induced sexual dysfunction *(253)*.

Carbamazepine

Carbamazepine is used in the treatment of partial seizures, both simple and complex, and for tonic–clonic seizures. Carbamazepine blocks use-dependent sodium channels, inhibiting sustained repetitive firing. Conversely to valproic acid, carbamazepine causes several hormonal abnormalities as a result of of its potent liver-enzyme-inducing effects. Generally, androgenic DHEAS and free testosterone levels diminish, whereas prolactin and SHBG increase *(250,251,253,254)*. The decrease in free testosterone likely is a function of increased SHBG production by the liver rather than a result of increased steroid catabolism. Nevertheless, these alterations can severely impact libido and erectile ability. Oxcarbazepine, a close structural analog to carbamazepine, appears to have minimal involvement with the hepatic cytochrome P-450-dependent enzymes and bioactivity of androgens *(250,251,255)*. Therefore, when patients have switched from carbamazepine to oxcarbazepine, hormonal imbalances have been reported to normalize *(254)*, making oxcarbazepine a potentially effective alternative for patients with severe hyposexuality side effects.

Phenytoin

Because phenytoin is also a potent inducer of hepatic enzymes, it affects hormones similarly to carbamazepine, with decreased free testosterone and DHEAS and increased prolactin and SHBG *(256)*. One study demonstrated an increase in total and free estradiol levels in men taking chronic phenytoin, suggesting that free testosterone levels may be decreased not only by increased binding to greater SHBG levels but also through conversion by aromatase *(257)*. Increased estradiol leads to negative feedback on the pituitary as well as suppression of LH levels and can ultimately lead to hypogonadotropic hypogonadism and testicular failure. Therefore, sexual side effects with phenytoin are both dose- and time-related. Associated side effects of sedation and neurological disturbances can also contribute significantly to poor sexual function *(7)*. Treatment consists of dose reduction and switching to another anti-epileptic, if clinically appropriate.

Phenobarbital and Primidone

Phenobarbital and primidone are structurally related barbiturates effective in all seizure disorders, with the exception of absence (petit mal; refs. *258* and *259*). These agents inhibit the spread of seizure activity in the cortex, thalamus, and limbic systems and increase the threshold for electrical stimulation of the motor cortex. As two of the earliest anticonvulsants available, phenobarbital and primidone have been associated with decreased libido and ED more frequently than other antivulsants *(260)*. With chronic treatment, adverse sexual effects have been noted to progress, unlike other side effects that typically decrease over the first 6 mo of use *(261)*. Sedation is also a significant side effect of barbiturates that affect sexual function.

Because newer anticonvulsants can control seizures as effectively as phenobarbital and primidone, switching to another anticonvulsant should benefit patients in terms of improved sexual quality of life. Lamotrigine, one of the newest anticonvulsants, has been reported to be useful in treating anti-epileptic-induced sexual dysfunction arising from phenobarbital, carbamazepine, and gabapentin *(262)*. Further studies are needed to verify and clarify this benefit.

HORMONAL AGENTS

By definition and mechanism of action, sexual side effects are to be expected from this class of medication in men. Common drugs used by male patients include gonadotropin-releasing hormone (GnRH) agonists, anti-androgens, 5-α-reductase inhibitors, and anabolic steroids.

Drugs commonly used in the treatment of metastatic prostate cancer include GnRH agonists (such as goserelin and leuprolide) with or without nonsteroidal anti-androgens (including flutamide, bicalutamide, and nilutamide). Medical castration from GnRH agonists results from the continuous nature of its administration, conversely to the normal pulsatile release of the hormone characteristic of the hypothalamus. This leads to down-regulation of the GnRH receptor on the pituitary gland, decreased production of follicle-stimulating hormone and LH, and a drop in serum levels of testosterone into the range normally seen in surgically castrated men approx 2 to 4 wk after initiation of therapy *(263)*. Therefore, accessory sex organ regresses, and sexual desire, interest, frequency of intercourse, and quality of life suffer. Nocturnal erections have also been noted to suffer significant decline in frequency, magnitude, duration, and rigidity *(264)*. Because of these sexual effects, GnRH agonists have been studied for the treatment of paraphilias (e.g., sadism or pedophilia; ref. *265*). The use of intermittent androgen ablation is one approach under investigation for the treatment of advanced prostate cancer; studies have been promising with regards to oncological control and improved quality of life and sexual function during the off-therapy periods *(266,267)*.

Nonsteroidal anti-androgens are used with GnRH agonists to achieve maximal androgen blockade in the treatment of metastatic prostate cancer. These agents competitively inhibit the action of androgens by binding to cytoplasmic androgen receptors, primarily in the prostate *(268)*. Compared with steroidal anti-androgens such as cyproterone acetate, bicalutamide and its analogs should have fewer effects on sexual potency. Several large, randomized studies of bicalutamide administered alone for the treatment of localized or locally advanced prostate cancer have demonstrated survival benefits similar to castration in addition to improved quality of life, fewer EDs, and preserved sexual libido

(269–271). Gynecomastia and breast pain were the most frequently reported side effects, and these can be prophylactically managed by radiation or surgery.

Finasteride is used in conjunction with α-blockers to treat symptomatic BPH. It acts as a competitive, specific inhibitor of type II 5-α-reductase, an intracellular enzyme that converts testosterone to the potent androgen 5-α-DHT, which is found primarily found in the prostate, seminal vesicles, epididymis, and hair follicles. DHT is the primary androgen that stimulates prostatic tissue growth. Studies have reported a low-to-moderate incidence of sexual toxicity that appears to be most predominant during the early periods of administration. In the Prostate Cancer Prevention Trial, men who took finasteride reported significantly increased frequencies of decreased ejaculate volume, impotence, loss of libido, and gynecomastia compared with men on placebo *(272)*. The Proscar Long-Term Efficacy and Safety Study demonstrated a 15 and 7% incidence of sexual adverse events in patients treated with finasteride and placebo, respectively, which equalized to 7% for both groups during years 2 to 4 *(273)*. Another large, randomized, placebo-controlled trial reported a low incidence of drug-related sexual adverse events during the first year, with rates of 3.8, 3.1, and 4.8% in libido, ejaculation, and erection dysfunction, respectively, and even fewer occurrences during the 5-yr open extension (all <0.7% at year 6; ref. *274*). In men who have sexual side effects from finasteride, it seems appropriate to follow a watchful waiting approach to determine whether side effects resolve with time, if the patient can tolerate this approach.

Testosterone is the primary androgen found in the body and is synthesized by cells in the testis, ovary, and adrenal cortex. Clinically, testosterone is used in the management of hypogonadism, either congenital or acquired *(268)*. Anabolic steroids, which are derivatives of testosterone, have been used illegally and are now controlled substances. Their use has skyrocketed in the recent years as athletes, both professional and amateur, have strived to gain a physical advantage in competitive sports. The use of anabolic steroids is well-documented to have serious consequences on fertility and sexual function. Steroid administration disturbs the regular endogenous production of gonadotrophins by the hypothalamus and pituitary gland. Consequent suppression of testosterone production by the Leydig cells results in a deficient spermatogenesis and sterility *(275)*. In fact, the use of testosterone has been investigated as a male contraceptive. These hormonal changes appear to be reversible but often require several months to a year for recovery *(276)*. Other untoward effects of steroid abuse that male athletes often self-report include an increase in sexual drive, the occurrence of acne vulgaris, increased body hair, and increments of aggressive behavior, which may promote negative sexual tendencies and actions *(277)*. Treatment includes counseling and behavioral modifications for cessation of steroid abuse.

RECREATIONAL DRUGS

Like prescription drugs, several recreational drugs have been associated with sexual impairment. In a contemporary epidemiological survey of substance use and sexual dysfunction, there were prevalence rates of 11% for delayed orgasm, 13% for painful sex, 5% for decreased sexual excitement, 7% for inhibited sexual desire, and 26% for any of these sexual dysfunctions *(278)*. Alcohol, narcotics, nicotine, caffeine, marijuana, and cocaine are widely used—legally or not—by the general population and deserve specific mention.

Alcohol

Alcohol consumption is a popular social practice in the United States and worldwide. It has been reported to have both favorable and unfavorable effects on sexual function. In low quantities, alcohol can cause relaxation and disinhibition, consequently improving sociability and sexual libido. These psychological factors have been shown to facilitate psychogenic erections *(279)*. Conversely, the sedative effects of alcohol can override any interest, causing premature cessation of sexual activities. With continued chronic consumption, men typically experience a dose-dependent deterioration of erectile and ejaculatory abilities. Studies of chronic alcoholics have demonstrated incidences of erectile and ejaculatory dysfunction as high as 54 and 25%, respectively *(280–282)*. Decreased libido may also occur in more than half of men who are dependent on alcohol *(283,284)*. Endocrine response to alcohol has been found to be variable and susceptible to situational and individual differences, and testosterone suppression does not appear to account for the associated sexual problems, as the literature has reported both decreased *(285–288)* and no change *(283,289,290)* in testosterone levels in alcoholics. Other biological changes reported that may contribute to sexual dysfunction include increases in prolactin *(283)*, aromatase *(291)*, SHBG *(292)*, and estrogen and decreases in 5-α-reductase *(293)* and DHEAS *(294)*. However, localized gonadal tissue damage in conjunction with CNS injury appears to be most responsible for these effects *(7)*. Additionally, other diseases caused or aggravated by alcohol abuse, such as diabetes, heart and liver disease, and peripheral polyneuropathy, can exacerbate the situation; however, impotence can occur in male alcoholics free of these comorbidities.

Some degree of infertility resulting from testicular atrophy and loss of germ cells is commonly seen in up to 70% of male alcoholics *(295)*. Atrophy has been linked to deficiencies in nutritients, such as zinc *(296)*, and direct toxic effects from the oxidative metabolism of alcohol; liver dysfunction from alcohol abuse is not required for this effect to occur *(297)*. Sperm changes include decreased total numbers in 30% and low motility in 23% of male alcoholics *(298)*. Finally, the negative effects of alcohol on sexuality extend to the social and behavioral levels. With the tendency of alcohol to disinhibit aggressive and belligerent behaviors, it has been strongly associated with sexual crimes, such as child sexual abuse, incest, and rape.

Nicotine

Nicotine is one of the most widely abused drugs in the world, as smoking has become a global health concern. In 2002, the World Health Organization estimated that about 10 million cigarettes are sold every minute. Besides the numerous other negative health sequelae from nicotine, it is also one of the most recognized recreational drugs that contributes to sexual dysfunction, because it has potent vasoconstricting and atherosclerosis-inducing properties. Diminished blood flow to the penis via local vasoconstriction of the internal pudendal artery and increased penile venous outflow are among the physiological effects caused by nicotine, thereby setting the stage for ED *(63)*. This has been reflected in epidemiological studies showing that the rate of impotence in smokers may be almost twice that of age-matched nonsmokers *(299)*; there is also an overrepresentation of heavy smokers (58–78%) among impotent men compared with a 30 to 40% prevalence in the general male population *(300)*.

Cigarette smoking was identified as an independent risk factor for impotence in several epidemiological studies, even confounding factors (including vascular disease and

marital status) were controllied for *(10,301,302)*. Specific toxicity to the penile arterial vasculature *(302a)*, nerves *(303)* and cavernosal tissue *(304)* with smoking have all been reported in the literature. Although nicotine does not appear to have a significant consistent effect on testosterone *(305–307)*, it appears to increase DHEAS levels *(307a)*. Regarding CNS effects, it is postulated that chronic nicotine intake increases dopamine and decreases serotonin release in the brain *(7)*. Although the hormonal and neurotransmitter alterations typically favor sexual drive and response in men, these mechanisms are generally not potent enough to override the significant peripheral toxicities, and erectile difficulties are encountered more commonly than benefits.

Finally, in several small reports, smoking has been shown to negatively affect sperm parameters, including total count, normal forms, and motility *(308–310)*. Although proper epidemiological studies are lacking to confirm or deny this finding, men with potential infertility issues would best be served by avoiding smoking and nicotine exposure.

Caffeine

Caffeine is seldom viewed in the public eye as a drug because of its ubiquitous consumption in the United States. In 2000, according to the National Coffee Association, more than three-quarters of the adult US population experienced exposure to caffeine through coffee, with 54 and 25% reporting daily and occasional intake, repsectively *(311)*. Caffeine is a mild CNS stimulant and diuretic and is believed to inhibit adenosine receptors to promote neurotransmitter release *(312)*. Consequently, coffee may positively affect sexual function by stimulating cortical and reticular formation arousal pathways, thereby increasing alertness and wakefulness; however, its role as an aphrodisiac is minimal, at best *(7,313)*. Most sexual associations with caffeine are negative, and epidemiological studies have found caffeine consumption to be an independent risk factor for ED *(314,315)*.

In terms of vascular effects, caffeine has been shown to cause vasoconstriction of cerebral vessels, thus decreasing blood flow to the brain *(316)*; a similar effect may occur with other vessels, including those involved in penile arterial flow *(317)*. Furthermore, adenosine has been shown to be pro-erectile because it causes profound relaxation of smooth muscle when injected directly into cavernosal tissue *(318)*. By inhibiting adenosine-induced vasodilation, caffeine can lead to a decreased penile resting tone and erectile tumescence rigidity.

Finally, because of the diuretic effects of caffeine, it can cause or worsen urinary incontinence, leading to decreased sexual activity through urogenital sensitivity and insecurity *(7)*. These effects are likely dose-dependent and may be avoided by not exceeding a recommended "moderate" amount of caffeine (about 200–300 mg, which is equivalent to 3 cups of instant coffee per day).

Narcotics

Narcotic drugs originate from the opium poppy plant and are widely used in the clinical setting for pain control. Abuse of these drugs can lead to physical dependence and illicit use of narcotics (including codeine, meperidine, morphine, hydromorphone, hydrocodone, methadone, and especially heroin) is common. The primary mechanism of action is via antagonism of opioid receptors μ, κ, and δ, which are distributed throughout the CNS. There is very little argument that opiates can cause dose-dependent sexual dysfunction, including decreased libido, diminished sensual responsiveness, and delayed orgasm and ejaculation *(7,319,320)*. The most noticeable initial effect is the inhibition of orgasm and

ejaculation, and this has been cited as a motivating factor for young heroin users to prolong their sexual prowess. This effect apparently derives from blockade of presynaptic opioid receptors involved in the ejaculatory circuit that are critical for movement of semen into the posterior urethra *(29,321)*. However, any initial enhancement in sexual function is quickly lost and replaced by diminished orgasm/ejaculation and libido resulting from chronic use *(322)*. Often the "high" or rush of the narcotic becomes preferred and replaces the pleasure obtained from sex *(323)*. During drug withdrawal, spontaneous erection and ejaculation are frequently encountered as a result of extended inhibition during prior opiate use. Considered far from sexually beneficial, this phenomenon is often bothersome and inconvenient to the individual.

One of the primary ways that opiates impair sexual function is by disrupting the hypothalamus–pituitary–gonadal axis: inhibition of luteinizing hormone-releasing hormone by the hypothalamus suppresses LH secretion by the pituitary gland, which ultimately decreases testosterone levels *(324)*. The opioid receptor agonists naloxone and naltrexone have been shown capable of reversing these changes *(325)*. Although men may achieve tolerance to testosterone inhibition with continued use of narcotics, sexual dysfunction or disinterest progresses with chronic administration beyond 6 to 12 mo *(7)*. Other purported mechanisms of opiate-induced sexual dysfunction include an increase in prolactin levels *(326)* and diversion of blood away from the penile organ as a result of selective vasoconstrictive effects on cutaneous arteriolar circulation *(327,328)*.

Marijuana

Also known as *Cannabis sativa,* hash, grass, joints, reefers, and Mary Jane, the active ingredient of marijuana is Δ-9-tetrahydrocannabinal. For centuries, marijuana has carried a reputation as an aphrodisiac and has even been referred to as the "foreplay drug" *(7)*. Increased libido, heightened sexual sensation, decreased aggressive and inhibitive tendencies, and altered time and tactile perceptions have been the sexual benefits reported from use of marijuana *(114)*. Therefore, a majority of users describe more subjective benefits such as greater enjoyment and satisfaction rather than objective benefits such as improved performance capabilities *(329)*; however, there are reports of enhanced sexual function when marijuana has been taken in the acute setting *(281)*. In one study, only a minority of males (12–27%) reported that marijuana increased sexual performance, including duration of intercourse, number of orgasms, or ability to repeat intercourse. However, with high-dose use or "getting stoned," most enhancements of the sexual experience are lost because cannabis intoxication causes sedation and mental impairment, which interfere with sexual attention and performance *(330)*. Several studies from the 1970s that reported reduced testosterone in men who smoked marijuana spurred debate regarding whether marijuana could cause sexual problems, especially with chronic use. Subsequent studies have negated these findings, showing that other than occasional fluctuations noted in various sexual hormones, no clinically significant changes were found in testosterone, LH, and FSH *(331–333)*. Furthermore, a cohort study demonstrated no difference in sexual hormone levels between regular marijuana users and nonuser controls *(334)*. In conclusion, marijuana appears to have sexually beneficial effects when taken in moderation.

Cocaine

Cocaine is a naturally occurring alkaloid present in the leaves of *Erythroxylon coca* *(335)*. Despite being an excellent local anesthetic, the risk of abuse and the potent local

vasoconstriction it causes prevent cocaine from being more widely used in the clinical setting. Its sexual effects are mixed. Recreationally, cocaine induces significant euphoria, caused by the potentiation of catecholamines, including an acute dopamine release and inhibition of dopamine re-uptake in the synapse. Theoretically, prolactin levels are predicted to decrease, accounting for the aphrodisiac and sex-promoting quality reported with acute intake of this drug *(7,186)*. Conversely, published reports have not infrequently reported sexual dysfunction in cocaine users. One study reported a 62% incidence in males who abused both cocaine and alcohol *(336)*, and another study reported that 7 of 10 chronic abusers developed hyperprolactinemia and decreased libido *(337)*. This reversal of fortunes likely is a function of progressive dopamine depletion in the brain resulting from regular use. Furthermore, tremors, agitation, and vomiting, which may be stimulated by increased doses of cocaine, contribute to decreased sexual interest and response. Ejaculation may also be affected and delayed, likely secondary to peripheral α-adrenergic inhibition; for men, this may be viewed as increasing sexual endurance and, therefore, as a benefit, whereas in women, this is typically not considered pleasureable. Finally, priapism has been well-recognized as a result of cocaine use in the urological literature, thus increasing the risk for permanent ED *(338,339)*.

CONCLUSION

Erection is a complex event that incorporates psychic, neural, vascular, and hormonal factors. Many currently used pharmaceutical agents can interfere in the coordinated sequence that leads to the initiation and maintenance of erection. Health care practioners should be knowledgable about the possible adverse sexual effects of the medications they use and should be prepared to modify a therapeutic regimen to minimize the potential for ED. Therefore, quality of life for both patient and partner can be maintained.

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9 Neurogenic Sexual Dysfunction in Men and Women

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SUMMARY

The penis is innervated by parasympathetic nerves arising from the second to fourth sacral cord segments (pelvic nerves) that ultimately become the cavernosal nerves. Sympathetic innervation, via the hypogastric nerve and pelvic plexus, causes detumescence but may also serve as an alternate erectile pathway. Somatic (sensory and motor) nerves reach the penis via the pudendal nerve. In the female, the genital organs have a complex innervation that is not well understood. The pelvic nerves appear to subserve sensation from the vagina while the pudendal nerve subserves sensation from the labia and clitoris. In the male central nervous system, the medial dorsal nucleus of the thalamus and the medial pre-optic area are important centers that control penile erection and sexual drive. Serotonin tends to inhibit penile erection at both spinal and supraspinal sites while dopamine and dopamine agonists such as apomorphine tend to induce penile erection. Oxytocin appears to be an important facilitator of erection at the spinal and supraspinal levels. Nitric oxide (NO) has recently been added to the list of compounds that act in the central nervous system to facilitate penile erection. Peripheral control of erection is mediated through NO, which modulates cavernosal smooth muscle relaxation and vasodilation. Norepinephrine is the primary adrenergic transmitter in the penis and controls penile detumescence by inducing penile smooth muscle contraction. Acetylcholine has a variety of effects that tend to promote erection including co-release of NO and perhaps vasoactive intestinal polypeptide from cholinergic nerve terminals, release of NO from the vascular endothelium, and suppression of norepinephrine release. The mechanism of vaginal engorgement during sexual arousal involves vasodilation and significant changes in vaginal tone, including relaxation and lengthening. The clitoral and penile smooth muscle appears to share a similar neuroregulatory mechanisms.

Key Words: Penile erection; female sexual response; nitric oxide; acetylcholine; norepinephrine.

INTRODUCTION

Sexual disorders affect both men and women and are mediated by organic, psychological, or combined mechanisms. Organic male and female sexual disorders may involve various vascular, neuronal, or neurovascular factors that produce problems with libido,

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lubrication, erection, ejaculation, and/or orgasm. Knowledge regarding female sexual physiology is much less developed than that pertaining to male sexual function. Currently, female sexual dysfunction (FSD) is a largely undeveloped field in medicine, and organic causes of FSD have not been established. However, the hemodynamic and neurogenic mechanisms of female sexual response are beginning to receive research attention in both animal models *(1–6)* and in human studies *(7–15)*. This chapter focuses on the neurophysiology of sexual function and neurological causes of sexual dysfunction in men and women.

NEUROANATOMY OF THE PENIS

At the T9 to L4 levels of the spinal cord, the intermediolateral column of gray matter gives rise to the sympathetic preganglionic fibers. The intermediolateral column gives rise to parasympathetic nerve fibers at the S2 through S4 levels. These nerve fibers continue to form the pelvic and hypogastric plexus. The penis is innervated by autonomic (parasympathetic and sympathetic) and somatic (sensory and motor) nerves *(16,17)*.

The parasympathetic nerves to the penis arise from neurons in the intermediolateral cell columns of the second, third, and fourth sacral spinal cord segments (pelvic nerves). The preganglionic nerves enter the pelvic plexus, where they are joined by sympathetic nerves from the hypogastric plexus. Branches of this plexus innervate the rectum, bladder, prostate, and urinary sphincters. Branches of the pelvic plexus that innervate the corpora cavernosa of the penis are called cavernosal nerves *(17)*. The cavernosal nerves are also preganglionic nerves that synapse with nitregric nerves within or near the tunica albuginea. Stimulation of the pelvic or the cavernosal nerves causes penile erection in both animals *(18–20)* and humans *(21)*. However, it remains unclear whether the cavernous nerve is a purely parasympathetic nerve. Some sympathetic fibers emanating from the lumbosacral sympathetic chain have been shown to exist in the pelvic nerve of the male rat *(22)*. The precise function of the sympathetic component of the cavernous nerve is unknown.

The cavernosal nerves pass posterolateral to the apex of the prostate and then proceed lateral to the membranous urethra and anterior to the bulbous urethra, where they enter the hilum of the penis *(17)*. This nerve is closely applied to the apex of the prostate and membranous urethra; it may be easily injured during radical pelvic surgery as well as during transurethral prostatectomy, external sphincterotomy, or any procedure using electrocautery in that region *(23–25)*.

The sympathetic nerves to the penis originate from the 10th to 12th thoracic spinal segments and descend through the inferior mesenteric plexus, the hypogastric plexus, and the perivesical plexus. The hypogastric nerve is a discrete branch from these plexuses that enters the perivesical plexus, where it may communicate with parasympathetic nerve fibers. Stimulation of the hypogastric nerve or the sympathetic trunk causes no change in intracavernosal pressure, but stimulation during an established erection causes penile detumescence *(26)*. As mentioned earlier, some sympathetic fibers travel to the penis via the cavernous nerves in the rat. Stimulation of the cut distal end of the pudendal nerve during erection also causes deturmescence *(25,26)*. Therefore, it appears that some sympathetic fibers also travel via the pudendal nerve—especially the sensory branch. At the same time, stimulation of the sympathetic nerves can also induce erection *(25,26)*. The mechanism of sympathetic pro-erectile activity is unclear. Sympathetic fibers may interact with nitregic nerves in the corpus cavernosum to release nitric oxide (NO), or they may cause pelvic vasoconstriction and shunting of blood toward the penis. In patients with lesions of the parasympathetic pathway, this may represent an alternative pathway that allows psychogenic erections to occur.

The sensory nerves of the penis begin as free and specialized receptors primarily in the penile skin and glans *(27,28)*. In the glans, the most numerous nerve terminals are free nerve endings (FNEs) present in almost every dermal papilla. Genital end bulbs are present throughout the glans, especially in the corona and near the frenulum. The ratio of FNEs to corpuscular receptors is approx 10:1 *(28)*. At an ultrastructural level, the genital end bulbs unique to the glans penis consist of axon terminals that resemble a tangled web of FNEs *(28)*. Simple, Pacinian, and Ruffini corpuscles are occasionally identified (predominantly in the corona of the glans). There are also sensory nerves in the urethra and corpora cavernosa that relay pain and pressure sensation.

Temperature and nociceptive (pain) signals from FNEs travel via small-diameter, thinly myelinated, or unmyelinated nerve fibers, whereas vibration, touch, and pressure utilize large-diameter, myelinated fibers *(28)*. All these nerve fibers converge to form the dorsal nerve of the penis *(29)*, which joins other perineal nerves to become the internal pudendal nerve and ascends to the dorsal roots of the second to fourth sacral nerves. The dorsal nerve appears to separately innervate the glans and the urethra, suggesting that it provides afferent impulses for sexual stimulation and ejaculation *(28)*. Ascending pathways within the spinal cord include the spinothalamic tract to the thalamus and to the sensory cortex.

The somatic motor nerves to the penis originate from the ventral roots of sacral segments 2 through 4 and coalesce to form the pudendal nerves. These nerves pass into the perineum as the perineal nerve and innervate the bulbocavernous and ischiocavernous muscles *(29)*. The major role of these muscles in penile erection is to provide temporary increases in intracavernosal pressure *(30)*. As mentioned earlier, perineal muscle contraction can also cause increased intraspongiosal pressure. Voluntary perineal muscle contraction during erection can produce intracavernosal pressures of several hundred millimeters of mercury—albeit only for brief periods. These brief surges in intracavernosal pressure, with its resulting increased penile rigidity, aid in successful vaginal penetration. However, perineal muscle contraction is not essential to penile erection, because patients with paralysis of the pelvic floor can still be potent *(29,30)*.

Immunohistochemical staining shows that human corpus cavernosum and spongiosum are richly innervated by cholinergic nerves *(31)*. These same nerves appear to contain neuronal NO synthase (NOS) and vasoactive intestinal polypeptide *(31)*. Calcitonin-gene-related peptide (CGRP), a vasorelaxant, has also been localized within cavernosal nerves, but its colocalization and role in penile erection remain unclear *(32)*. Adrenergic nerves have been demonstrated to be abundant in human cavernosal tissue, particularly around the helicine arteries *(33)*. Such nerves have been shown to contain not only norepinephrine but also neuropeptide Y, another vasoconstrictor agent *(34,35)*.

NEUROANATOMY OF THE FEMALE GENITALS

The autonomic nervous system innervates most of the pelvic vescera. The somatic sensory and motor system innervates the skin and muscles of the perineum. The external genitalia parasympathetic and sympathetic system originate from the same sources that innervate other pelvic organs. The parasympathetic system relaxes the smooth muscle of the vessels and erectile tissue of the clitoris and the bulb and causes contraction of the bulbocavernosus and ischiocavernosus muscles. The pudendal and ilioinguinal nerves provide somatic sensory branches to the skin of the perineum and parts of the external genitalia as well as motor branches to the muscle of the perineum.

The vagina has a complex innervation that is not well understood. The pelvic nerves appear to subserve sensation from the vagina, whereas the pudendal nerve subserves sen-

sation from the labia and clitoris *(36)*. Afferent nerves in the vagina appear to contain substance P in both animal and human tissue samples, although nerves that contain substance P appear to be sparse in the human vagina *(36–38)*. Nerves containing NOS have been demonstrated in animal *(39)* and human vagina *(40)*. Nerves containing CGRP, neuro-peptide Y, vasoactive intestinal polypeptide (VIP), and peptide histidine-methionine have also been found in human vagina *(40,41)*.

The glans of the clitoris forms a cap that sits on the ends of the corporal bodies and is richly innervated by sensory nerve endings *(42)*. The deep dorsal nerves perforate the glans on the dorsal aspect of its junction with the corporal bodies. Recent studies have confirmed that the dorsal nerve of the clitoris is relatively large (>2 mm in diameter; ref. *43*). The cavernous nerve runs along the cavernous artery as it enters the bodies of the clitoris. Nerves containing neuronal NOS (nNOS) have been detected in both the body and the glans of the human clitoris *(44)*, suggesting that NO is involved in the control of clitoral smooth muscle tone. Nerve fibers containing VIP, CGRP, and substance P have also been described in human clitoral tissue *(41,45,46)*.

NEUROPHYSIOLOGY OF SEXUAL RESPONSE IN MEN

Both the central and peripheral nervous systems are involved in the neurophysiology of sexual function in men. Male sexual response is a complex, multilevel, biological process that involves central regulation of libido and arousability as well as local regulation of penile erection, rigidity, orgasm, and ejaculation. Physiological sexual function depends on the integrity of both central and peripheral neuronal mechanisms. The following sections discuss the central, spinal, parasympathetic, sympathetic, and sensory neuronal components that regulate male sexual response.

Central Mechanisms

Compared to the peripheral nervous system, knowledge of central mechanisms is much less complete. Much of it is derived from animal experiments and from observations in human patients with spinal cord injury. The initiation of sexual response in men depends on cerebrocortical function. The precise areas of the cerebral cortex involved in regulating libido and sexual fantasy remain unknown. Studies of individuals who have had injuries to the temporal and frontal lobes suggest that these centers may play a crucial role in regulating sexual interest and behavior.

In the male central nervous system (CNS), the erection centers include the septal portion of the hippocampus, the anterior cingulate gyrus, the anterior thalamic nuclei, the mammillothalamic tract, and the mammillary bodies. The medial dorsal nucleus of the thalamus and, particularly, the medial pre-optic area appear to be important centers that control penile erection and sexual drive *(47,48)*. These centers send descending pathways via the medial forebrain bundle *(47)* and then enter the dorsolateral columns of the spinal cord.

Central Neurotransmitters

Substances acting as neurotransmitters in the CNS and controlling penile erection include serotonin (5-hydroxytryptamine), dopamine, norepinephrine, NO, and many others.

Serotonin tends to inhibit penile erection at both spinal *(49)* and supraspinal sites *(50)*. Other known central inhibitors of sexual activity include γ-aminobutyric acid *(51)*, prolactin *(52)*, and endogenous opioid peptides *(53)*. Serotoninergic nerves appear to be respon-

sible for supraspinal inhibition of segmental penile erection reflexes *(48)*. Trazodone, a serotonin antagonist, has long been recognized as an agent that induces priapism, although the precise mechanism of action of trazadone in producing priapism is unclear *(54)*.

When administered systemically, dopamine and dopamine agonists, such as apomorphine, induced penile erection in experimental animals *(55)*. These effects are blocked by centrally acting dopamine receptor blockers (haloperidol) but not by peripherally acting dopamine blockers (domperidol), indicating that dopamine effects occur within the CNS *(56)*. It is likely that dopamine induces penile erection by acting on oxytocin-containing neurons in the paraventricular nucleus of the hypothalamus *(56)*. Apomorphine has been reported to cause penile erection in humans, but these erections are usually only partial, are not associated with sexual desire, and are often accompanied by nausea *(57,58)*.

Norepinephrine has various effects on sexual function in the CNS. Central inhibition of α_2-adrenoceptors facilitates sexual function, whereas stimulation of these receptors inhibits sexual function *(59,60)*. Clonidine, a central α_2-receptor agonist used as an antihypertensive agent, is associated with erectile dysfunction (ED). Yohimbine, a central α_2-receptor blocker, can enhance sexual motivation *(61)*.

Oxytocin appears to be an important facilitator of erection at the spinal and supraspinal levels. Ascending sensory stimuli from the dorsal penile nerve appear to preferentially stimulate oxytocin-containing cells in the supraoptic nucleus. Electrical and tactile stimulation of the rat dorsal penile nerve stimulated 60% of the oxytocin cells in the contralateral supra-optic nucleus *(62)*. Oxytocin has been localized in descending pathways from hypothalamus to brain stem and autonomic centers in the spinal cord *(63)*. As mentioned earlier, that the effects of dopamine on penile erection likely are mediated by oxytocin-containing neurons in the hypothalamus *(56)*. In the rat, spinal autonomic neurons controlling penile erection appear to receive oxytocinergic innervation from the paraventricular nucleus of the hypothalamus that facilitates erection *(64)*.

NO has recently been added to the list of compounds that act in the CNS to facilitate penile erection *(65)*. The paraventricular nucleus of the hypothalamus is one of the richest areas of NOS in the brain and is also where dopamine and oxytocin act to induce penile erection. The ability of NOS inhibitors injected in the lateral ventricles or in the paraventricular nucleus of the hypothalamus to prevent penile erection induced by dopamine agonists and oxytocin suggests a role for NO. The inhibitory effect of NOS inhibitors was not observed when these compounds were injected concomitantly with L-arginine, the precursor of NO. NO likely acts as an intracellular, rather than an intercellular, modulator *(66)*.

Opioids have long been recognized to interfere with erection. Recent work has shown that morphine blocks erection by interfering with increased NO production *(67)*. It also blocks the actions of dopamine and oxytocin in producing erection *(68)*.

Adrenocorticotropin and related peptides (melanocortin) have been observed to induce spontaneous penile erections and ejaculation in many animal species *(69)*. Intracerebral injection of an NOS inhibitor appears to block erections because of these peptides *(67)*. A synthetic analog of α-melanocyte-stimulating hormone has been shown to be effective in treating ED *(69)*.

Spinal Mechanisms

Spinal reflexes constitute a crucial component of erectile physiology. The spinal cord, paraspinal sympathetic ganglia, and parasympathetic nerves play a direct role in regulating functional changes of the male genitals. In the spinal cord, the intermediolateral column of gray matter gives rise to sympathetic nerve fibers at the level of T9 to L4. The parasym-

pathetic nerve fibers originate from intermediolateral column at the levels of S2 to S4. These nerve fibers continue to form the pelvic and hypogastric plexus. The cavernosal nerve branches from the pelvic plexus and travels through the pelvic facia and crosses the prostate at its posterolateral aspect. The parasympathetic nerves exit the spinal cord through the ventral roots and constitute the pelvic nerves.

In physiological terms, penile erection is a spinal reflex initiated by recruitment of penile stimulation traveling through the dorsal penile nerve as well as by visual, olfactory, and imaginary stimuli. The reflex involves both autonomic and somatic efferent pathways. The dorsal nerve of the penis provides afferent input, and the pelvic nerves provide the motor pathway. Local segmental reflexes in the lumbosacral cord subserve penile erection in both normal humans and those with spinal cord injury *(70–72)*. In the intact individual, these reflexes are under net tonic inhibitory control by higher centers *(73)*. Especially in humans, segmental reflexes are heavily modulated by supraspinal influences.

Peripheral Mechanisms

Peripheral control of erection has received greater research and clinical attention than the central and spinal mechanisms. Extensive and detailed investigation of the mechanism of penile smooth muscle contractility has been performed in the last two decades, ultimately leading to the development of oral medications for treatment of ED. Penile smooth muscle tone determines tumescence and detumescence and is regulated by a complicated neuronal mechanism involving the adrenergic, cholinergic, and nonadrenergic noncholinergic (NANC) pathways. Studies with experimental models have shown that electrical stimulation of the pelvic plexus and the cavernous nerve leads to erection, whereas stimulation of the hypogastric nerve or the sympathetic trunk induces detumescence. This clearly suggests that tumescence is regulated by the sacral parasympathetic input and that detumescence is mediated by the thoracolumbar sympathetic input. Stimuli related to initiating and maintaining erection arise primarily in the glans and travel via the dorsal nerve of the penis *(27,28)*. Peripheral motor control of penile erection is established through control of smooth muscle tone in the sinusoidal trabeculae and arterioles in the corpora cavernosa. Smooth muscle tone in the corpora cavernosa is controlled through impulses from both the sympathetic and parasympathetic nervous systems as well as from endothelial-mediated mechanisms. The tone of the arterioles controls the amount of blood entering the cavernosal sinusoids, and the tone of the trabeculae controls the amount of blood leaving the corpora.

Adrenergic Neurotransmission

Norepinephrine is the primary adrenergic transmitter in the penis and controls penile detumescence by inducing penile smooth muscle contraction. However, the regulation of adrenergic neurotransmission in the penis is complex and involves interaction with the cholinergic and NANC neurons. For example, cholinergic nerves prejunctionally inhibit norepinephrine release from adrenergic nerves *(74)*. The presence of α- and β-adrenergic receptors in penile blood vessels and cavernous smooth muscle has been demonstrated *(33,75)*. In the corporal smooth muscle, the α_1-receptor is the primary adrenergic receptor, wheread both α_1- and α_2-receptors are present in cavernous artery *(76,77)*. α_2-receptors are found on both prejunctional sites of the adrenergic nerves and corporal smooth muscle cells.

On prejunctional sites, α_2-receptors mediate the feedback inhibition of norepinephrine neurotransmitter release from the adrenergic nerve *(73)*. Norepinephrine release from the

adrenergic nerves binds to the prejunctional α_2-adrenoceptor on the adrenergic nerves and inhibits norepinephrine release. Therefore, blockade of this reaction by selective α_2-receptor antagonists (e.g., yohimbine) enhances release of norepinephrine and inhibits erection. Meanwhile, norepinephrine release from the adrenergic nerves binds to the prejunctional α_2-adrenoceptor on the NANC nerves and inhibits NO synthesis and release. Blockade of this reaction by selective α_2-receptor antagonists (e.g., yohimbine) enhances NO release and facilitates erection. The α_2-receptors on the smooth muscle cell also appear to be involved in the mediation of smooth muscle cell contraction. Specifically, α_2-agonists cause trabecular smooth muscle contraction. Blockade of these smooth muscle α_2-receptors by yohimbine or rauwolscine induces trabecular smooth muscle relaxation, facilitating erection *(78,79)*. The net effect of an agent such as yohimbine appears to be to facilitate erection, although most of its action may be on central, rather than peripheral, sites.

Cholinergic Neurotransmission

Immunohistochemical studies have demonstrated that the corpus cavernosum and the corpus spongiosum have a rich cholinergic innervation *(31)*.These cholinergic nerves also stain positive for NOS and VIP, suggesting that NO and VIP are released along with acetylcholine (ACh) from cholinergic nerves *(31,80)*. Under most conditions, all of these agents are vasodilators and smooth muscle relaxants.

ACh, whether released from cholinergic nerves or applied directly to tissue, has various effects. Intra-arterial *(81,82)* and intracavernosal *(83)* injection of ACh can produce penile erection. These effects are only partially blocked by atropine but are abolished by removal of the endothelium *(84,85)*. Although ACh has no effect on flaccid cavernosal tissue, it causes concentration-dependent relaxation of cavernosal tissue that has been precontracted with norepinephrine *(86,87)*. The relaxant effect of ACh is markedly attenuated by removal of the epithelium, indicating the release of an endothelial-derived relaxing factor from the epithelium under the influence of ACh *(86)*. Acetylcholine may also act on adrenergic nerve terminals to suppress the release of norepinephrine *(84,86)*. Therefore, there are at least three mechanisms by which ACh may induce cavernosal smooth muscle relaxation: (a) corelease of NO, and perhaps VIP, from cholinergic nerve terminals; (b) release of NO from the vascular endothelium; and (c) suppression of norepinephrine release.

Nonadrenergic, Noncholinergic Neurotransmission

NO is a key NANC neurotransmitter in the penis that modulates cavernosal smooth muscle relaxation and vasodilation as well as the resulting erection *(85,88)*. Released by cavernous nerves and endothelium, NO activates guanylate cyclase and catalyzes the formation of cyclic guanosine monophosphate (cGMP) from guanosine-triphosphate. The increased levels of cGMP initiate a cascade of intracellular events, leading to reduction of cytosolic free calcium and smooth muscle relaxation *(85,88)*. Relaxation of the trabecular smooth muscle is blocked by methylene blue that inhibits cGMP synthesis *(85)*. NO is derived from L-arginine and molecular oxygen, a reaction that is catalyzed by NOS. NOS exists in Ca^{2+}-dependent constitutive nNOS and endothelial (eNOS) forms as well as Ca^{2+}-independent inducible NOS (iNOS) form. Basal production of NO is regulated by constitutive NOS and contributes to the physiology of cardiac and pulmonary perfusion, heart rate, myocardial contractility, vasodilation, and penile erection *(89)*. However, NO generated by iNOS is shown to be involved in pathophysiological states, such as oxidative stress and myocardial dysfunction *(90)*.

Other Factors in Erection

Neuropeptides have been identified in nerves supplying the penis, including VIP, substance P, neuropeptide Y, somatostatin, peptide histidine-isoleucine, enkephalins, and CGRPs *(33–42)*. The exact role of these substances is not well-understood. As mentioned earlier, VIP appears to serve as a cotransmitter; NO is released from cholinergic nerves, whereas neuropeptide Y, a vasoconstrictor, is released from adrenergic nerves *(91)*.

Paracrine factors such as endothelin *(92)*, angiotensin *(93)*, prostaglandin F2 α *(94)*, thromboxane *(95)*, and histamine *(96)* all have some vasoconstrictive actions. It is unclear whether these agents have a primary role or are modulators of vascular smooth muscle tone.

Endothelin is localized in the endothelial cell and, to a lesser degree, in the trabecular smooth muscle. Endothelins are potent constrictors that cause longlasting contractions of corporal smooth muscle strips. Endothelin appears to have three isoforms, ET-1, ET-2, and ET-3, as well as two different receptors, ET_A and ET_B *(92)*. The ET_A receptor is located on vascular smooth muscle and mediates contraction and proliferation, and the ET_B receptor is located on the endothelial cell and generally mediates vasodilation, perhaps through release of NO.

Angiotensin II is produced and secreted in physiologically relevant amounts in human cavernosal tissue *(97)*. Angiotensin II, a potent vasoconstrictor, is formed from angioten-sin I by angiotensin-converting enzyme. Two subtypes of angiotensin II receptors (AT1 and AT2) have been characterized. It appears that male rabbit cavernosal tissue contains the AT1 receptor *(98)* and that angiotensin II causes a dose-dependent contraction of canine cavernosal smooth muscle that is inhibited by giving angiotensin II receptor antagonist *(99)*.

Prostaglandins probably act as modulators of cavernosal smooth muscle tone by activating cyclic adenosine monophosphate *(100,101)*. Prostaglandin F_{2a} (PGF_{2a}), prostacyclin2, and, especially, thromboxane A_2 act as potent vasoconstrictors of cavernosal tissue, whereas prostaglandin E $(PGE)_1$ and PGE_2 have vasorelaxant effects *(102)*. In addition to direct vascular smooth muscle relaxation, PGE_1 may also act to inhibit release of neuronal norepinephrine *(103)*. There are various factors that appear important in controlling the actions of prostaglandins. For example, the local production of prostanoids appears to be inhibited under hypoxic conditions *(104)*. Binding of PGE_1 to cavernosal tissue appears to vary widely among species and is suppressed by estrogens *(105)*. Furthermore, cavernosal relaxation in response to PGE_1 is markedly diminished after castration, indicating that androgens are a prerequisite for their action *(106)*.

Bradykinin has relaxant effects on human corpus cavernosum that are mediated through cyclic adenosine monophosphate and cGMP *(93)*. Bradykinin appears to act on cavernosal BK2 receptors, leading to release of endothelial nitric oxide *(107)*.

Histamine appears to induce an endothelium-independent relaxation of vascular tissue *(96,108)*. The vasodilation induced by histamine appears to be mediated mainly by histamine receptors located on vascular smooth muscle, without the intervention of NO or relaxant prostanoids *(108)*.

Role of Hormones

Circulating levels of hormones appear to have a marked impact on the neurophysiology of penile erection. Peripherally, androgens appear to influence the peripheral nervous system, the reactivity of cavernosal smooth muscle, and the perineal striated muscles. Testosterone has been shown to affect peripheral parasympathetic ganglia *(109)*, the dorsal

penile nerve *(110)*, and NOS-containing nerves in the corpus cavernosum *(111)*. In the rabbit, castration has been shown to reduce intracavernosal pressure and to cause reduction of cavernosal smooth muscle content, effects that could be reversed by testosterone replacement *(112)*. Castration also produced failure of the veno-occlusive mechanism in rats by interfering with NO release in the corpora *(113)*. Finally, androgens appear to be effective in maintaining the function of the ischiocavernosus and bulbocavernosus muscles. Within 2 wk of castration, there was a significant decrease in the weight of ischiocavernosus muscles and the size of their spinal motoneurons *(114)*. In humans, testosterone has been shown to increase the rigidity, but not the frequency, of nocturnal erections *(115)*.

Androgens are essential in supporting male sexual development. However, the precise role of androgens in the postpubertal male is complex *(116)*. Castration may not always cause ED in animals or in humans. Castration in rats prevents erections following injection of apomorphine *(117)* and oxytocin *(118)*; the efficacy of both agents is restored after exogenous testosterone. Testosterone *(118)* appears to be important in maintaining certain central dopaminergic pathways related to sexual arousal. In men, nocturnal erections appear to be androgen-dependent, whereas visually stimulated erections appear not to be androgen-dependent *(119)*. There may be a phylogenetically older system of sexual arousal that is androgen-dependent as well as another androgen-independent system activated through the cerebral cortex.

NEUROPHYSIOLOGY OF SEXUAL RESPONSE IN WOMEN

Central Mechanisms

Little is known regarding the central control of female sexual arousal. Sexual stimulation activates specific areas of the CNS, such as the medial pre-optic region, the anterior hypothalamic region, and the related limbic hippocampal structures. This stimulates transmission of signals via the parasympathetic and sympathetic pathways. The medial amygdala appears to be an important center that uses vasopressin as a central neurotransmitter *(120)*. Oxytocin is also clearly involved; in one study, oxytocin serum levels measured before and after sexual stimulation in 12 healthy women were significantly elevated *(121)*. Although intravenous apomorphine, a centrally acting dopaminergic agent, has been shown to cause increased peak clitoral and vaginal wall blood flow *(122)*, the role of dopamine in female sexual behavior has not been established.

Spinal Mechanisms

The mechanism of genital arousal and orgasm during sexual stimulation involve spinal cord reflexes mediated by genital afferents originating from the pudendal nerve. Interneurons mediating these reflexes are known to be in a column in the central portion of the spinal gray matter. The efferent arm of the spinal reflexes involves sympathetic, parasympathetic, and somatic activity *(123)*. Studies using a rabbit model showed that electrical stimulation of the vaginal branch of the pelvic nerve increased clitoral intracavernosal pressure and blood flow, vaginal wall pressure, and blood flow and vaginal length. Afferent signaling during sexual stimulation enters the spinal cord in the sacral segments, which is then transmitted to supraspinal sites via the spinothalamic and spinoreticular systems *(123)*. The spinothalamic pathway contains myelinated fibers that end in the posterolateral nucleus of the thalamus, from which the signals are relayed to the medial thalamus. The precise reflex mechanisms of clitoral erection and vaginal engorgement have yet to be studied.

Peripheral Mechanisms

The mechanism of vaginal engorgement during sexual arousal involves vasodilation and significant changes in vaginal tone. The vaginal tissue responds to sexual arousal by relaxing and lengthening *(2)*. Atropine abolished pelvic nerve stimulated increased vaginal tone, whereas vercuronium bromide (a striated muscle relaxant) prevented the subsequent fall in vaginal tension *(4)*. These results suggest that vaginal contraction may be under cholinergic control, whereas vaginal lengthening or enlargement may result from striated muscle contraction. The mechanism by which striated muscle contraction produces a decrease in vaginal pressure is unclear. Studies in humans have shown that the distal part of the vagina contains more nerve fibers compared to proximal part, and the anterior vaginal wall is more densely innervated than the posterior wall *(124)*. Embryological origins of proximal and distal vagina have also been suggested to be different. The distal two-thirds of the vagina is suggested to be a derivative of urogenital sinus, whereas the proximal part is believed to originate from the uterovaginal primordium *(125)*.

In the rabbit, stimulation of the vaginal branch of the pelvic nerve results in lengthening and dilation of the vagina, which further leads to a lowering of vaginal luminal pressure and an increase in intravaginal wall pressure *(2)*. In rats, stimulation of the pelvic nerve causes a biphasic response in vaginal wall tension. There is a rapid, short-lived increase in vaginal wall tension followed by a fall in tension to below baseline value, which is indicative of vaginal wall relaxation *(2,4)*.

Organ bath studies with the rabbit vaginal tissue have shown that at baseline tension, electrical field stimulation (EFS) causes a biphasic contraction and relaxation response *(126)*. The α_2-adrenoceptor blocker yohimbine and the β-blocker propranolol were found to have little effect on vaginal tissue contraction in response to EFS and norepinephrine. Prazosin appeared to be significantly effective in inhibiting these contractile responses, suggesting that vaginal tissue contraction may be primarily mediated by the α_1-adrenoceptor *(126)*. Relaxation of the vaginal tissue appears to involve a NANC mechanism. The nature of the vaginal NANC neurotransmission remains controversial. The rabbit vaginal tissue relaxes after exposure to ACh, VIP, papaverine, and the NO donor nitroprusside in a concentration-dependent manner *(126)*. VIP was found to be more effective in relaxing the vaginal tissue than the clitoral tissue. The NO precursor L-arginine and the NOS inhibitor nomega-nitro-L-arginine (NNA) appeared to have little effect on vaginal tissue relaxation. However, another study found that NNA significantly inhibited the electrically stimulated relaxation of rabbit vaginal tissue *(127)*. The authors performed immunohistochemical staining, which revealed marked eNOS and nNOS in the rabbit vagina. Additionally, estrogen treatment was found to downregulate eNOS and nNOS expression in the rabbit vagina.

The VIP receptor antagonist (VIP fragment 6-28 and [D-P-Cl-ph^6,Leu^{17}]-VIP) has been shown to significantly increase the relaxation response to VIP but has little effect on EFS-induced relaxation of the vaginal tissue *(126)*. Additionally, nerve fibers in the vagina that run subepithelium and near the vascular bed are rich in VIP-immunoreactivity *(128)*. Human vaginal nerve fibers contain not only VIP and NOS but neuropeptide Y, cGMP, CGRP, and substance P *(129)*. Immunohistochemical staining has revealed the expression of five functional domains of the VIP precursor throughout the female human genital tract in neuronal elements closely related to the epithelial lining, perivascular tissue, and nonvascular smooth muscle *(130)*.

The clitoral and penile smooth muscle appears to share a similar neuroregulatory mechanism. Similar to the human penis, immunohistochemical staining of human clitoral

cavernosal tissue revealed NOS subtype expression, suggesting the involvement of NO in the regulation of clitoral smooth muscle contractility and the development of clitoral engorgement *(127)*. Organ bath studies with the rabbit clitoral cavernosal tissue have shown that contraction of the clitoral tissue is primarily mediated by α_1-adrenoceptor *(126)*. Like the penile tissue, ACh, VIP, papaverine, and the NO donor nitroprusside produce concentration-dependent relaxation in clitoral tissue. L-arginine significantly increases and NNA inhibits the clitoral relaxation to EFS and ACh, suggesting that NO may mediate endothelium-dependent and neurogenic relaxation of clitoral tissue. Another study showed that clitoral smooth muscle relaxation is enhanced by sildenafil, suggesting involvement of cGMP *(131)*. Angiotensin II has been shown to be a potent constrictor of rabbit clitoral smooth muscle in the organ bath *(132)*. The clitoris has been shown to have angiotensin II receptors of the AT_1 variety.

Sexual Arousal Response in Women

Female sexual arousal is a complex neurovascular phenomenon involving several hemodynamic phases affecting the clitoris, vestibular bulbs, labia minora, and the vagina. In the resting phase, the vagina is a sheath containing a potential space with minimal blood flow and very low oxygen tension in the wall *(10,12)*. Based on studies with experimental models, the earliest detectable sign of sexual arousal is a significant increase in vaginal wall and clitoral blood flow *(2)*. There is also a significant increase in clitoral cavernosal pressure. With the onset of increased vaginal blood flow, production of vaginal transudate ensues *(133,134)*. A significant rise in tissue oxygen tension follows about 20 s later, indicating increased inflow of arterial blood. In humans, vaginal and labial oxygen tension increases from four to eight times the baseline during sexual stimulation *(10,11)*, and vaginal wall blood flow increases about threefold *(12–15)*. Additionally, clitoral blood flow has been estimated to increase from 4 to 11 times the baseline *(135)*. The increased blood flow reaches a plateau phase during which vaginal fluid transudate production continues. The final or resolution phase is characterized by slow return of blood flow to baseline values. In women, up to 20 to 30 min is required for vaginal oxygen tension to return to baseline *(10)*.

Increased clitoral intracavernosal and vaginal wall blood flow are believed to partly result from a decrease in vascular resistance caused by relaxation of clitoral cavernosal and vaginal wall tissues. The precise identity of the neurotransmitter(s) that control vaginal blood flow is unknown. Atropine does not affect the pelvic-nerve-stimulated rise in vaginal blood flow in animals *(2,5)* or the rise in vaginal blood flow seen in human females *(136)*. This evidence suggests that muscarinic neurotransmission is probably not involved. The ability of sildenafil to relax clitoral tissue and enhance nerve-stimulated vaginal blood flow has been reported *(51,131)*. This obviously suggests the involvement of the NO–cGMP pathway *(131,137)*.

Meanwhile, administration of VIP has been reported to increase vaginal blood flow and induce vaginal fluid production, either intravenously or by injection in the vaginal wall *(11,133)*. Peptide histidine methionine has effects similar to VIP but at a lower potency *(138)*. Intravaginal PGE_1 can also increase vaginal blood flow *(139)*. Although some authors have stated that VIP is the primary neurotransmitter in the vaginal circulation *(12,13)*, much more research is required. A study with the rabbit model showed that systemic administration of apomorphine had no effect on basal clitoral intracavernosal and vaginal wall blood flow but significantly increased blood inflow in these organs during nerve-stimulated vaginal and clitoral engorgement *(122)*. The precise mecha-

nism by which apomorphine enhances nerve-stimulated blood flow but not basal clitoral intracavernosal and vaginal blood flow remains unknown. Apomorphine at concentrations of 0.1 and 0.2 mg/kg was shown to be most effective in increasing nerve-stimulated clitoral intracavernosal and vaginal wall blood flows in the rabbit. This may suggest the involvement of dopaminergic receptors in regulating the hemodynamic mechanism of clitoral and vaginal engorgement. Vaginal blood flow appears to undergo phasic shifts in conjunction with rapid eye movement sleep *(140)*.

NEUROLOGICAL CAUSES OF SEXUAL DYSFUNCTION

Neurogenic ED

Male sexual disorders have been investigated to a greater extent than FSDs. The etiology of male sexual disorders includes psychological and organic problems. Epidemiological studies have revealed that organic problems are the leading cause of sexual dysfunction in men. Sexual disorders in men may cover a range of areas involving ED, orgasmic disorders, and premature ejaculation. Impotence is defined as inability to perform sexually in the broadest sense. It is too broad a term to be useful in diagnosis. Libido is a term derived from psychoanalytical theory that describes sexual desire, drive, or interest in both sexes. Lack of libido in men may underlie many instances of impotence. ED is defined as the consistent inability to obtain or maintain an erection of sufficient rigidity to enable satisfactory sexual intercourse. Disorders of semen delivery include lack of emission (deposition of seminal fluid in the prostatic urethra), anejaculation (lack of ejaculation), and retrograde ejaculation (ejaculation through an incompetent bladder neck into the bladder). Anorgasmia is the persistent inability to achieve orgasm despite adequate sexual arousal.

ED may result from psychogenic and/or organic causes. In most cases, however, the etiology of ED involves an organic problem. It is estimated that about 80% of cases of ED result solely or predominantly from organic causes *(141)*. Organic ED is the persistent inability to achieve or maintain satisfactory erection primarily as a result of organic or physical factors. In contrast to psychogenic ED, there is often a gradual deterioration of sexual function over months or years. Typically, the patient first notes a mild decrease in penile rigidity, then a decrease in the frequency of erections, followed by sporadic failure of erection with fatigue. Nocturnal erections gradually disappear, as do early morning erections on awakening. In organic impotence, full erection may be achieved, but it frequently subsides quickly. Finally, many patients complain of a partial erection that is insufficient for vaginal penetration. Typically, libido and ejaculatory function are unaffected in organic ED, at least in the early stages.

A large number of diseases and conditions may lead to organic ED, including peripheral and central neurological lesions, hypogonadism and other hormonal disturbances, hypercholesterolemia and pelvic atherosclerotic disease, microvascular disease, diabetes, hypertension, veno-occlusive dysfunction, Peyronie's disease, and drug therapies (especially antihypertensive agents; refs. *142–145*).

Neurogenic ED can be defined as inability to obtain or maintain penile erection as a result of neurological lesion or impairment. There are a vast number of neurological diseases that may impact erectile ability, and this chapter attempts to discuss them only as examples of broad pathphysiological mechanisms rather than as individual entities. Neurologic disorders may act through blocking or disorganizing central control, affecting penile sensation, or interfering with the motor input to the penile vasculature.

Central Factors in ED

Penile erection is largely dependent on CNS control. The crucial roles in sexual function of central dopamine, oxytocin, NO, norepinephrine, and serotonin were reviewed earlier *(50–69)*. Clinical experience with spinal cord injury clearly demonstrates that with appropriate afferent stimulation, the isolated spinal cord is fully capable of subserving penile erection. Inhibition of spinal sexual responses is mediated by the neurotransmitter serotonin. At the same time, the central dopaminergic system acts to promote penile erection. Dopamine can likely trigger penile erection by acting on oxytocinergic neurons located in the paraventricular nucleus of the hypothalamus and, perhaps, on the sacral parasympathetic nucleus within the spinal cord *(57)*.

Parkinson's disease is a disorder of the basal ganglia characterized by tremor, akinesia, and rigidity. Although it is associated with degeneration of the dopamine-containing cells in the sustantia nigra, the cause remains unknown *(146)*. The incidence of decreased erectile ability in Parkinson's disease has been reported at about 80% *(147)*. Dopaminergic agents, such as apomorphine, have been reported to produce penile erction in patients with Parkinson's disease *(148)*. Based on animal studies, this agent produces erection by stimulating central D_2 dopamine receptors, leading to release of oxytocin from the paraventricular nucleus of the hypothalamus. This is one of clearest examples of ED resulting from a specific central neurotransmitter deficit and of its reversal by pharmacological replacement.

Epilepsy, especially of the temporal lobe variety, confers an approximately fivefold increase in risk of ED *(149)*. Loss of libido is also common in patients with epilepsy. These problems may result from a combination of the epilepsy itself, anti-epileptic drugs, and social constraints. The prevalence of ED among men with temporal lobe epilepsy is about 50% *(150)*. Abnormal nocturnal tumescence characterized primarily by decreased rigidity has been reported in most men with temporal lobe epilepsy and ED *(149)*.

Various endocrine abnormalities have also been found in epileptic patients with ED—most commonly hypogonadotropic hypogonadism *(150)*. Hyperprolactinemia and hypergonadotropic hypogonadism have also been described. Estradiol levels significantly increase, resulting in decreased androgen/estrogen ratios, and luteinizing hormone-releasing hormone infusion is less effective in releasing luteinizing hormone *(151)*. Interestingly, some anti-epileptic agents such as valproate have been shown to increase androgen levels in men with epilepsy *(152)*. Lamotrigine, a newer anticonvulsant, has been reported to improve ED in men with epilepsy *(153)*. Temporal lobe epilepsy appears to be an interesting example of a neurological condition that impacts sexual function primarily through an endocrine mechanism.

Antipsychotic agents are commonly associated with ED *(154)* as well as Parkinsonian-like side effects *(155)*. The dopamine hypothesis of schizophrenia implicates an enhanced dopaminergic function in the pathophysiology of the disorder *(156)*. Because dopamine acts as an inhibiting factor in the release of prolactin, any dopamine-blocking agent is likely to induce hyperprolactinemia. It is not surprising that many antipsychotic agents block or deplete dopamine and also cause hyperprolactinemia *(156)*. Therefore, dopamine and its effects on prolactin release serve as a fundamental connection between Parkinson's disease, anti-Parkinsonian drugs, schizophrenia, antipsychotic agents, epilepsy, and ED. The first generation of antipsychotic agents was typically associated with hyperprolactinemia. However, there is a newer class of antipsychotics that are not associated with significant prolactin increase, such as clozapine, olanzapine, quetiapine, sertindole, and ziprasid-

one *(157)*. The new antipsychotics appear to spare dopamine blockade and have a much lower incidence of sexual side effects.

Spinal Causes of ED

Spinal mechanisms play a crucial role in penile neurophysiology. Spinal cord lesions may profoundly affect sexual function by interrupting or impairing neuronal traffic between the higher centers and the periphery. Lesions may be congenital, such as spinal dysraphism, or acquired, such as spinal cord trauma and multiple sclerosis *(158–160)*.

Spinal dysraphism is a developmental anomaly caused by impaired closure of the neural tube that includes spina bifida and myelomeningocele *(160)*. Occasionally, one finds tethered cord syndrome manifested by a thickened fium terminal and a low positioned conus medullaris *(159)*. The patients generally present with sensory and/or motor deficits of the lower extremities, combined with incontinence. The pathophysiology of this condition appears to be congenital deficits in spinal nerve roots combined with variable degrees of suprasacral dysfunction resulting from tethering of the spinal cord *(160,161)*. Spinal cord tethering appears to cause ischemia/hypoxia of the lower spinal cord, leading to a form of intermittent vascular myelopathy *(161)*.

Because these patients now have a markedly increased life expectancy, ED has become a recognized problem. Estimation of the prevalence of ED in spinal dysraphism from the literature is difficult. In cases of tethered cord syndrome, surgical untethering appears to have little effect—either positive or negative—on sexual dysfunction *(161)*. Oral sildenafil (50 mg) appears to produce improvement in 80% of cases of spinal dysraphism with ED *(160)*. This suggests that erectile tissue function is preserved in these patients. The efficacy of sildenafil in low doses may suggest some element of lower motor neuron deficit in patients with spinal dysraphism.

Spinal Cord Trauma

The patient with spinal cord injury allows one to determine the role of various parts of the spinal cord in male sexual function. Generally, penile erection is viewed as a segmental reflex located in the sacral spinal cord that is controlled by higher CNS centers. However, Chapelle and colleagues *(162)* observed different types of reflex erection following complete spinal transection at different levels. In patients with lesions above the T10 to T12 segments, reflex erection involves both corpus cavernosum and corpus spongiosum. If the lesion is below T12, the erection involves only the corpus cavernosum. This suggests that the thoracolumbar sympathetic outflow is essential for control of the corpus spongiosum and glans penis.

Patients with lesions below T12 may have psychogenic erections; they may respond to visual stimuli or sexual fantasy. Conversely, men with complete lesions above T12 require penile stimulation to achieve erection and do not respond to visual stimuli. This suggests that there are two neural pathways innervating the genitals. The primary pathway is the sacral parasympathetic outflow, and a second pathway exists through the thoracolumbar sympathetic outflow. In theory, the second thoracic–lumbar pathway can compensate for the loss of the sacral pathway in cases of low spinal lesions. An animal study showed that 85% of paraplegic rats with lesions below the thoracolumbar outflow had erection following hypothalamic stimulation *(164)*. In male paraplegics, it has been shown that preservation of the sympathetic skin response correlates with preservation of psychogenic erection *(164)*.

Sildenafil (50 mg) is effective in improving erectile function in patients with spinal cord injury *(166)*. However, the efficacy of sildenafil depends on sparing of either sacral (S2–S4) or thoracolumbar (T10–L2) spinal segments *(165)*. As mentioned earlier, the thoracolumbar or sympathetic outflow is important in mediating psychogenic erections in male patients with spinal cord injury and must be intact for sildenafil to be effective. The thoracolumbar outflow can be shown to be intact clinically by preservation of testicular sensation. The efficacy of sildenafil in the low paraplegic and its dependence on the thoracolumbar outflow suggests that some sympathetic fibers may stimulate NO production or release in the penis.

Multiple Sclerosis and ED

ED is common problem among patients with multiple sclerosis (MS). MS is a demyelinating disease of the CNS and often produces abnormalities in sexual function and urinary control *(166,167)*. Although auto-immunity is believed to play a role, the cause of the demyelination is basically unknown. Cortical and subcortical gray matter plaques occur commonly in MS and have been related to disease duration, clinical course, and the level of neurological disability *(168)*. These plaques occur primarily in the thalamus, basal ganglia, and rolandic cortex. Cortical atrophy is also a common finding. Spinal cord MS plaques are characteristically located in the periphery of the spinal cord, occupy less than two vertebral segments in length, and occupy less than half the cross-sectional area of the cord *(169)*. Approximately 75% of men with MS complain of ED *(169)*. Ejaculatory dysfunction and reduced libido are also more common among male patients with MS *(167)*. Generally, there appears to be an increase in symptoms of sexual disability over time and a strong correlation with bladder symptoms and bladder hyperreflexia *(166,170)*.

Penile arterial inflow and venous outflow were found to be normal in male patients with MS who suffered from ED *(171)*. Abnormal pudendal evoked potential was found in 90% of patients with MS and ED but was normal in patients with MS who did not suffer from ED *(171)*. Erectile failure was invariably associated with pyramidal signs in the lower limbs *(172)*. These findings suggest that ED in MS results from spinal lesions situated in the suprasacral spinal cord. Additional sexual disability may result from cortical atrophy and depression, both of which are common in MS. Like other neurological conditions, intracorporeal injections of papaverine produced satisfactory erections in the majority of patients with MS and ED *(172)*.

Peripheral Autonomic Motor Deficits

Peripheral autonomic motor deficits may result from lesions of the cauda equina *(173)*, the anterior nerve root *(174)*, or the peripheral nerves subserving erection *(175)*. However, it is important to remember that no direct test of penile autonomic motor neuropathy exists.

Cauda equina syndrome is characterized by lower extremity paralysis and pain (sciatica); erectile failure may not be noticed. However, midline compression of the cauda may affect only the perineal innervation without lower extremity signs. The most common causes of such a picture are midline prolapse of a disc and tumor *(173)*. The sudden onset of bladder areflexia, sphincter incompetence, and erectile failure combined with saddle anesthesia should be viewed as highly suspicious for midline cauda eqina compression. In 50% of cases, the L5–S1 disc is prolapsed, and recovery of sexual function after laminectomy may be slow.

Nerve root compression most commonly results from a herniated intervertebral disc but may be secondary to other causes such as tumor. Chronic nerve compression is believed to result in local ischemia and inflammatory changes, with resultant decreased nerve conduction velocity *(176)*. ED has been reported in association with herniated disc, but the literature is sparse. Although reversal of ED has been reported after surgery *(174)*, in many cases, the ED is psychogenic in origin or related to chronic pain.

Polyneuropathy is often accompanied by autonomic dysfunction and may cause voiding abnormalities as well as ED *(177)*. Polyneuropathy was found in about 20% of 341 patients complaining of impotence *(175)*. Some autonomic neuropathies are of acute onset, but most are chronic and of gradual onset. Conditions that primarily affect small nerve fibers or cause acute demyelination of small myelinated fibers are most likely to cause autonomic neuropathy. Examples include acute dysautonomia, familial and primary amyloidosis, Guillain–Barre syndrome, diabetes mellitus, porphyria, and Chagas' disease.

Aging-Related Neuropathy

ED is an age-dependent problem. Aging-related neuropathy may play a leading role in the development of ED in the elderly. However, there is relatively little information on aging *per se* as a factor in neurogenic ED. In a rat model, the number of NOS-containing nerve fibers was significantly less in the elderly rats than in young and middle-aged rats *(178)*. The number of apomorphine-induced erections and the response to intracavernous papaverine was also significantly less in the older rats than in the young rats *(178)*. Conversely, VIP levels and distribution in the rat penis were not noted to deteriorate with age *(179)*. Muscle weakness of the perineal floor may also be a factor in aging-associated ED *(180)*.

Diabetic Neuropathy

ED is a common problem among patients with diabetes. Although neuropathy is not the only cause of ED in diabetic patients, it is clearly a major component *(181)*. Diabetic neuropathies include both focal neuropathies and diffuse polyneuropathy, which is the most common form. Despite intensive investigation, the pathophysiology of diabetic polyneuropathy remains unclear *(182)*. Microvascular disease appears to lead to autonomic fiber loss. There is impairment in the elaboration of trophic factors that are critical for peripheral nerves and their ganglia. Additionally, diabetic nerves fail to regenerate as effectively as nondiabetics *(182)*. As mentioned previously, glycosylated hemoglobin is more prevalent in erectile tissue from diabetic than from control animals and causes impaired neuronal-NO-mediated relaxation *(183)*. Aminoguanidine, an agent that prevents formation of glycation products, was shown to reverse impaired cavernosal relaxation of diabetic penile tissue *(183)*.

For any etiology, the presence of neuropathy reduces erectile response to visual stimulation in diabetics, regardless of whether they are insulin-dependent or not *(182)*. Neurogenic relaxation of cavernosal smooth muscle from diabetic men is significantly reduced *(184)*. ACh synthesis and release were significantly reduced in the cavernosal tissue from diabetic patients compared to that from nondiabetic patients *(185)*. The impairment in ACh synthesis worsened with the duration of diabetes. No differences were found in the parameters measured between insulin-dependent and non-insulin-dependent diabetic patients. A marked reduction was observed in VIP-like immunoreactivity in nerves associated with the cavernous smooth muscle, whereas acetylcholinesterase-positive staining was reduced in patients with diabetes *(186)*. The noradrenaline content of the

corpus cavernosum from diabetic patients was significantly lower than that of a non-neuropathic group *(186)*. These results indicate a marked effect on neuronal function in the penile tissues of diabetic patients.

Iatrogenic Nerve Trauma

Neural injury generally resulting from surgery constitutes an important cause of neurogenic ED. Trauma to the cavernous nerves may occur in radical prostatectomy *(187)*, radical cystoprostatectomy *(188)*, proctectomy *(189)*, and transurethral prostatectomy (TURP) *(190)*. The incidence of ED in men undergoing TURP has been estimated as 8% *(190)*, but incidence up to 50% has been reported *(191)*. The risk of ED following TURP is increased for prostate resection of less than 10 g *(190)* as well as perforation of the capsule near the neurovascular bundle *(192)*. In one study, the risk of ED was 28% if the capsule was perforated and 10% if it was not *(193)*. It seems likely that ED following TURP is related to heat transferred outside the prostatic capsule that can damage the neurovascular bundle.

In 1974, the nerve-sparing prostatectomy was developed to preserve the neurovascular bundles near the prostate, thus preserving potency *(187)*. The technique has also led to reduced urinary incontinence *(187)*. However, the assumption that postradical prostatectomy ED results primarily from nerve trauma must be questioned. Most studies do not provide objective evidence of erectile function before surgery. In one recent study where pre-operative studies were performed *(189)*, only 17% of patients were found to have normal erectile function before surgery. After nerve-sparing radical retropubic prostatectomy, 63% of these patients had preserved erectile function. In those who became impotent, neurogenic factors contributed to ED in 60% and vascular factors contributed to ED in 40%. Cavernosal artery insufficiency following radical prostatectomy has been reported in approx 40% of patients *(194)*. New onset of veno-occlusive dysfunction after radical prostatectomy has also been reported *(195)*. Therefore, improved potency rates after "nerve-sparing" radical prostatectomy may be result from vascular sparing as well as nerve sparing accomplished by the technique.

Importantly, the autonomic nerves lateral to the prostate are preganglionic nerves. They synapse with ganglia that lie close to the corpora cavernosa, and these postganglionic nerves release NO and other neurotransmitters *(196)*. Therefore, cutting the preganglionic fibers does not necessarily completely denervate the cavernosal smooth muscle. This may explain why bilateral cavernosal neurotomy in rats resulted in a moderate-to-severe deficit in erectile function but some animals were still able to obtain erection *(197)*. Bilateral cavernosal nerve section produced a marked decrease in electrical activity of cavernosal smooth muscle *(198)*. After bilateral cavernosal neurotomy in rats, NOS-positive nerve fibers were significantly decreased at 3 wk and had not recovered at 6 mo *(199)*. No erectile response could be elicited by pelvic nerve stimulation. After unilateral neurotomy, the NOS-positive nerve fibers were similarly decreased on the side of the neurotomy at 3 wk, but by 6 mo, the number had increased significantly and approximated the level on the contralateral side *(199)*. Therefore, unilateral nerve sparing appears to be sufficient to preserve erectile function.

Because several authors have found that stimulation of the hypogastric nerve can produce erection *(25,200,201)*, one might wonder about the effect of sympathectomy or cutting the hypogastric nerve on erection. Section of the hypogastric nerve in animals appears to have no effect on erection *(197)*, and sympathectomy in humans seems to have no significant effect on potency *(202)*. However, when erection is induced by hypothalamic stimulation in animals, surgical or chemical sympathectomy appears to block

these erections *(26)*. Therefore, there is some experimental evidence that centrally mediated erections use sympathetic nerve pathways. However, because of alternative parasympathetic pathways, sympathectomy alone is insufficient to reduce potency.

Sensory Nerve Deficits

The dorsal nerve of the penis is critical for sexual function *(28)*. It innervates the shaft of the penis and the glans penis, which provides most of the sensory input for reflex erection *(203)*. Decreased sensation in the penis may be the primary etiology for ED *(204)*.

Somatic innervation of the penis may be tested by biothesiometry (vibration; ref. *205*), electrical stimulation *(206)*, sympathetic skin response *(207)*, and thermal sensitivity testing *(208)*. Electrical stimulation of the dorsal nerve may be used to determine nerve conduction velocity, bulbocavernosus reflex latency, or somatosensory latency. These various testing methods tend to correlate poorly because they stimulate differing receptors and axonal populations *(209,210)*. In a direct comparison of thermal sensitivity to electrophysiological testing, thermal sensitivity was found to correlate much better with clinical assessment of ED *(211)*. This may result from the fact that thermal testing stimulates the smaller unmyelinated sensory nerve fibers of the penis, whereas electrophysiological testing stimulates the larger myelinated fibers.

Penile threshold to electrical and vibratory stimulation increases with age *(212–214)*. This is a phenomenon also observed in other parts of the sensory nervous system with age *(215)*. In the penis, there is a curvilinear rather than a linear relationship between penile threshold and aging. As age increases, sensory threshold rises with increasing slope *(212)*. Mean sensory thresholds occur at about age 45 and reaches two standard deviations higher at about age 68.

Sensory thresholds in men with ED are consistently higher than in age-matched controls *(216,217)*. Interestingly, men suffering from premature ejaculation as an isolated complaint were not found to have an abnormal penile sensory threshold *(217)*.

There is a significant elevation in threshold after intracavernous papaverine-induced erection and this elevation is particularly pronounced in men with ED *(216)*. Therefore, a paradoxical decrease exists in penile sensitivity in all individuals during penile erection. Because elevation of skin temperature has been shown to decrease sensitivity to vibration *(218)*, this may be a possible mechanism for this phenomenon.

Untreated hypogonadal men were found to have a lower vibrotactile threshold and were slightly more sensitive to touch than men with higher levels of androgen *(219)*. Testosterone replacement appeared to normalize the threshold values.

Diabetes mellitus tends to affect small-diameter myelinated and unmyelinated sensory nerve fibers that are best assessed with thermal testing *(211,220)*. Sexually dysfunctional diabetic men have a higher threshold to vibration in the penis than potent men with diabetes *(161,214)*. In a study comparing 35 diabetic patients with ED and 25 normal male subjects, cold threshold and warm threshold were much more sensitive parameters than vibration or standard electrophysiological tests *(211)*.

Ischemic Neuropathy

Peripheral nerves are supplied by a rich anastomotic system of blood vessels. Vascular proliferation and increased vascular density is a well-known phenomenon associated with repair of the nervous tissue. A crucial role of vasculopathy in diabetic neuropathy has been described in experimental models. The microvasculature in the early stages of retinopathy has been characterized by supersensitivity and progressive arterial luminal

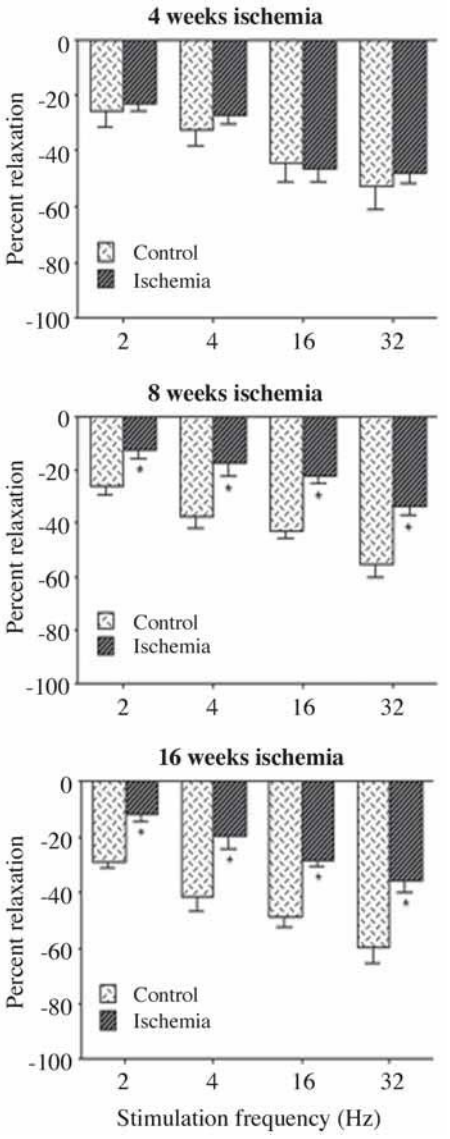

Fig. 1. Impairment of electrical field stimulation-induced neurogenic relaxation in rabbit ischemic erectile tissue. * indicates significant differences in the ischemic tissues in comparison to age-matched controls in a specific time point. (From ref. *223*.)

occlusion *(221)*. Underarterial occlusive disease and ischemia angiogenic factors were found to be predominantly upregulated in the ganglion cell layer of the diabetic rats.

Laboratory and clinical research data have revealed that the degree of vasculogenic ED cannot be predicted exclusively by the arterial hemodynamic integrity. Cavernosal arterial insufficiency also appears to adversely affect other components of erectile tissue, including the cavernosal nerves, smooth muscle, and endothelium, thereby impeding corporal smooth muscle relaxation and altering erection quality. Chronic ischemia alters nerve-mediated contractility of rabbit erectile tissue. Atherosclerosis-induced cavernosal ischemia in the rabbit induces functional alterations in EFS-induced neurogenic cavernosal smooth muscle relaxation (Fig. 1; ref. *222*). These functional changes are asso-

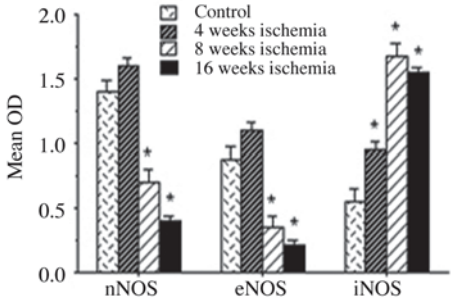

Fig. 2. Densitometric analysis NOS isoforms protein levels in the ischemic and control rabbit erectile tissues. *Indicates significant changes in the ischemic tissues in comparison with the control tissues. (From ref. *223*.)

ciated with impaired NOS activity *(222)*. Treatment with L-arginine was found to have no significant effect on smooth muscle relaxation in the ischemic cavernosal tissue, suggesting impairment of NO production by cavernosal nerves and endothelium.

Immunohistochemical staining of chronically ischemic cavernosal tissues has shown dramatic changes in NOS-containing nerves. nNOS expression was unchanged at the early stages of ischemia but dramatically decreased after 8 and 16 wk of ischemia. eNOS expression also decreased with prolonged ischemia. Unlike nNOS and eNOS, iNOS expression progressively increased between 4 and 16 wk of ischemia *(223)*. Semi-quantitative real-time-polymerase chain reaction showed that nNOS gene expression initially increased in the early stages of ischemia, reaching a 1.8-fold increase over control levels 6 wk after the induction of ischemia *(224)*. The nNOS levels then significantly decreased to approx 50% of the controls after 8 wk of ischemia. The nNOS levels further decreased after 16 wk of ischemia. Western blotting of chronically ischemic cavernosal tissues showed that cavernosal nNOS and eNOS protein levels were unaffected after 4 wk of ischemia but significantly decreased at weeks 8 and 16 following the induction of ischemia (Fig. 2; refs. *223* and *224*). iNOS protein gradually increased over the course of ischemia (Fig. 2). Excessive iNOS production in the ischemic tissue is believed to play a role in neurotoxicity and structural damage.

Chronic ischemia increases the contractile response of erectile tissue to EFS but has no effect on contraction to norepinephrine *(94)*. Tissue treatment with NG-monomethyl-L-arginine was found to increase contraction of control tissues but had little effect on the contraction of ischemic tissues. The precise mechanism of increased contraction of ischemic erectile tissue remains to be determined. It may involve increased output of sympathetic neurotransmitters, lack of the inhibitory influence of NO, or both.

Neurogenic Female Sexual Dysfunction

FSDs have been categorized into problems with desire, arousal, orgasm, and pain *(225–228)*. Sexual desire disorders are subclassified into hypoactive sexual desire disorders and sexual aversion disorders. Hypoactive sexual desire disorder is defined as persistent or recurrent lack of or absence of sexual fantasies and thoughts or desire for sexual activity. Sexual aversion disorder is a persistent or recurring fear, aversion to, and avoidance of sexual contact with a partner. Sexual arousal disorder is defined as the persistent or recurrent inability to achieve or maintain sexual excitement. This may be expressed as lack of excitement, lack of lubrication, lack of vaginal and clitoral engorgement, or lack

of expression of other somatic responses. Orgasmic disorder is defined as the persistent or recurrent inability to achieve orgasm with sexual stimulation and arousal.

Sexual pain disorders are subclassified into dyspareunia, vaginismus, and other sexual pain disorders. Dyspareunia is defined as recurrent or persistent genital pain during sexual intercourse. Vaginismus is the recurrent or persistent involuntary spasm of outer vaginal musculature, which makes vaginal penetration difficult. Other sexual pain disorders include noncoital sexual pain, which is defined as recurrent or persistent genital pain caused by noncoital sexual stimulation.

All types of sexual desire disorders are likely to lead to personal distress. Each category of FSD is divided to subtypes as chronic vs acquired, generalized vs situational, and organic vs psychogenic.

Conversely to the male, the pathophysiology of FSD is not easily categorized as vasculogenic, neurological, or hormonal. Rather, it appears to involve multidimensional biological, psychological, and interpersonal aspects. The prevalence of FSD is difficult to estimate because relatively few studies have been performed in community settings. Sexual dysfunction in women correlates with age and educational level *(229)*. The frequency of these sexual problems increases as menopause approaches and reaches a peak in the postmenopausal years *(229,230)*.

Neurological disorders are known to be associated with sexual dysfunction in both women and men. However, the role of neurological factors in FSD remains generally unexplored and may be undiagnosed. Many neurological disorders, including autonomic and peripheral neuropathy, spinal cord injury, diabetic neuropathy, MS, and lumbar radiculopathy, are likely to interfere with the neurophysiology of the female genital organs and lead to their dysfunction. It is believed that any neural lesion, central or peripheral, can interfere with the sensory and somatic component of the female genitals, leading to dysfunction. Dysfunction of the sensory fibers may interfere with the afferent signaling and sensory modalities that are quite important in female sexual response. The following sections discuss the neurological factors that interfere with female sexual response and lead to dysfunction.

Central Factors in Female Sexual Dysfunction

Central regulation of female sexual response has been explored to some extent. Central lesions are likely to interfere with female sexual physiology and lead to dysfunction. The precise mechanism by which central lesions affect female sexual function remains to be determined. Generally, researchers believe that any central lesion alters the efferent and afferent pathways of female sexual response, leading to dysfunction.

Spinal Causes of Female Sexual Dysfunction

The relationship between spinal cord lesions and FSD has frequently been reported. In women, spinal cord injury may be associated with orgasmic and/or lubrication failure *(231)*. Arousal may be secondary to audiovisual stimuli, fantasy, or genital stimulation. In women with complete suprasacral spinal cord injury above T6, audiovisual stimuli fail to cause any change in vaginal pulse amplitude *(232)*. However, in women with preservation of sensory function in T11–L2 dermatomes, psychogenically mediated genital vasocongestion is possible *(233)*. This suggests that similarly to the male, the sympathetic outflow is an important pathway for psychogenic genital response in the female.

Women with complete or incomplete suprasacral injury can achieve reflex genital response by manual stimulation but not when there is involvement of the sacral segments

(234). Orgasm is less likely in women with spinal cord injury and correlates poorly with the type of injury *(233)*.

Diabetic Neuropathy

Diabetes affects sexual function in both women and men. Diabetes mellitus, which is known to cause ED in men, may interfere with sexual function in women *(235–238)*. However, this issue has been poorly investigated, and it is unclear how diabetes leads to sexual disorders in women *(239)*. FSD can be regarded as a silent complication of diabetes mellitus. Jensen *(238)* studied the sexual function of 80 diabetic women and 40 nondiabetic women. A significantly larger number of women with diabetes (11%) complained of lack of orgasm than nondiabetic women (7.5%). A much greater number of women with diabetes (24%) reported difficulty in achieving vaginal lubrication compared with nondiabetic women (8%). Within the diabetic group, the incidence of sexual dysfunction was much greater in women with diabetes-related peripheral neuropathy (44%) compared with diabetic women without neuropathy.

Another study showed that peripheral neuropathy closely correlates with sexual dysfunction in women with diabetes *(240)*. Other studies of diabetic women have reported increased problems with vaginal lubrication *(237,241)*. Using vaginal photoplethysmographical measures of capillary engorgement, diabetic women have been demonstrated to have significantly less physiological arousal to erotic stimuli than controls, although their subjective responses were comparable *(242)*. Biothesiometric examination revealed that the sensation of introitus vagina, labium minora, and clitoris were markedly deteriorated in diabetic women compared with nondiabetic women *(243)*.

Studies with a rat model of streptozotocin-induced diabetes have shown that diabetes impairs the relaxation responses of the vaginal tissue to EFS, to NO donors, and to CGRP *(4)*. Studies have also shown that diabetes impairs the contractile response of vaginal tissue to norepinephrine and EFS. In the latter study, both the NO donors and CGRP inhibited EFS-induced contractions in diabetic and nondiabetic strips, but the inhibition was found to be significantly lower in the diabetic group *(4)*.

Peripheral Factors

Peripheral neurological disorders are known to be associated with sexual dysfunction in both women and men. Peripheral neuropathy is a common cause of ED, but there is little relevant literature regarding females. Clitoral neuropathy has been observed to cause sexual dysfunction *(244)*. In a test of female genital pressure and touch sensation, 32 neurologically intact women and 5 neurologically impaired women were tested *(245)*. A clear association was determined between reduced vulvar sensitivity to pressure/touch and estrogen deficiency, sexual dysfunction, and neurological impairment. Postmenopausal and hypoestrogenic women had significantly reduced sensitivity to pressure/touch compared with premenopausal and normoestrogenic women, respectively.

Pudendal neuropathy as a complication of orthopedic surgery involving traction has been shown to induce sexual dysfunction *(246)*. This condition was associated with signs of pudendal neurodegeneration and abnormal somatosensory-evoked potentials of the pudendal nerve. Stretch neuropathy of the internal pudendal nerve and perineal nerve motor latency have been reported because of stretch injury of the pelvic musculature when the pelvic floor diaphragm is weak *(247)*. Perineal stretch neuropathy was found to closely correlate with the incidence of sexual dysfunction in women *(247)*.

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10 Female Sexual Dysfunction

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SUMMARY

The focus of this book is men and their sexual function and dysfunction, however, many women will also develop some degree of sexual health problems concerned with sexual desire, arousal, orgasm, and/or pain. The goal is to make relevant evidence-based clinical information to help identify and treat specific biologically based pathophysiologies available to the motivated health care professional. The prevalence of sexual problems among adult women is estimated to be 43%. A basic physiological principle is that the structure–function of a woman's genitalia is highly dependent on the sex steroid hormonal milieu. As a woman ages, her supply of sex steroid hormones diminishes significantly. Biologically focused management of women's desire, arousal, and orgasm sexual health concerns operates under the premise that physiological processes can be altered by pathology, for example, hormonal deficiency. From the perspective of biology-focused clinicians, the essential principle guiding their medical decision making is identification of the underlying pathophysiology of the sexual dysfunction. If the biological basis of the desire, arousal, and orgasm dysfunction can be diagnosed, management outcome may be successfully directed to the source pathophysiology using various evidence-based available treatment options.

Key Words: Sexual desire; sexual arousal; sexual orgasm; sexual pain; sex steroid hormones; estradiol; testosterone; dehydroepiandrosterone; vasodilators; phosphodiestersase type.

INTRODUCTION

Why have a chapter concerning female sexual dysfunction in a textbook entitled *Male Sexual Function*? The fact is that men frequently share sexual activity with a partner. For men who have sexual activity with a female partner, it is entirely relevant for them and their health care provider to better understand the sexual functions of both members of the couple—the man and the woman.

Although the focus of this text has been on men and their sexual function and/or dysfunction, it is not surprising that many women also develop some degree of sexual health problem concerned with sexual desire, arousal, orgasm, and/or pain *(1–9)*. This may occur for many reasons, including as a result of psychological and/or biological causes such

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as a partner's sexual dysfunction, her own psychological/medical conditions, postoperative hysterectomy and bilateral salpingooophorectomy, use of medications (e.g., oral contraceptive pills or antidepressants), transition to menopause, pregnancy-related issues and the postpartum period, infertility treatments, and numerous other biologically related pathophysiologies *(1)*.

When a man develops sexual problems, there are numerous health care providers trained to provide him with sexual health care delivery (as evidenced by all the outstanding contributions in this textbook on male sexual dysfunction management). Conversely, there are limited numbers of health care professionals offering comprehensive psychological and biological sexual health care for women.

Several explanations exist for this lack of options. First, physicians who provide health care delivery to women face a challenge in finding the time and opportunity to discuss their female patients' sexual health concerns, especially with the increasing and growing demands for other health care issues, including the significant financial pressures of providing "managed care." Additionally, many physicians have limited training in the diagnosis and treatment of women with sexual health concerns. Many medical schools devote only limited time in the curriculum to sexual medicine issues. Currently, the majority of American medical schools devote less than 10 h to sexual medicine education *(10)*. Patients also are often unwilling or too uncomfortable to inform the physician or to initiate a discussion regarding their sexual problems *(11)*. Sexual medicine issues are complex, and it is often difficult to separate psychological issues from interpersonal relationship concerns and/or biological disorders. Finally, there are only limited evidence-based data available for management.

SEXUAL HEALTH CARE DELIVERY TO WOMEN WILL INCREASE IN THE FUTURE

The current climate in which women's sexual health care delivery is virtually ignored will change. Many forces will fuel the transformation. First, multiple population-based studies have revealed a high prevalence of sexual health concerns in women of all ages *(1–9)*. In approx 25% of women with sexual health concerns, sexual problems can cause significant personal distress, including a diminution of self-worth and self-esteem, a reduction in life satisfaction, and a decline in the quality of relationships with partners *(1–9)*. Second, sexual health, similarly to general health, is a fundamental human right *(12)*. Sexual health, referring to a state of physical, emotional, mental, and social well-being related to sexuality, must also be a basic human right. All women have the right to safe, pleasurable sexual experiences that are a source of physical, psychological, intellectual, and spiritual satisfaction and that are free from coercion, discrimination, and violence *(12)*. Third, many investigations have shown that a satisfying sex life is important to most women throughout most of their lives *(13)*. Fourth, as life expectancy increases, there are increasing numbers of aging women. Sexual health concerns are more common among aging women than in younger women *(1–9)*. In 2000, there were 569 million postmenopausal women worldwide; that number is projected to grow to 967 million by 2020 and to 1.2 billion by 2030 *(14)*. Finally, the controversy concerning hormone therapy that followed the release of the Women's Health Initiative *(15)* resulted in millions of menopausal women altering and or discontinuing hormone therapy practices, thereby directly influencing many women's subsequent vaginal physiology and sexual interest *(16)*. As the decline in estrogen production begins in aging women during transition and

menopause, sexual dysfunction is common and often interferes with a woman's interest in, and satisfaction with, sexual activity.

It is important to note the existence of the International Society for the Study of Women's Sexual Health (ISSWSH), an international, multidisciplinary, academic, clinical, and scientific organization. The purposes of ISSWSH are to provide opportunities for communication among scholars, researchers, and practitioners about women's sexual health; to support the highest standards of ethics and professionalism in research, education, and clinical practice relative to women's sexual health; and to provide the public with accurate information about women's sexual health. For more information, interested health care professionals should visit the organization's website (http://www.isswsh.org). If the reader wishes more detailed information about ISSWSH or the management of women's sexual health concerns, refer to the multidisciplinary text written primarily by ISSWSH members, entitled *Women's Sexual Function and Dysfunction: Study, Diagnosis and Treatment (17)*.

This chapter aims to provide the interested health care professional relevant evidence-based clinical information to help identify and treat specific biologically based pathophysiologies *(1,16)*. It is not logical or rational to continue to focus primarily on sexual health care for males only.

It is not within the realm of this chapter to thoroughly discuss psychological management of women's sexual health issues. Although health care professionals need to be holistic in managing women (and men) with sexual dysfunction, the goal is to educate the biologically focused health care professional about how to identify the biological pathology or pathologies associated with the sexual health concern and to provide evidence-based safe and effective biological management strategies *(18)*.

This chapter discusses current data on epidemiology and classification; hormonal physiology and pathophysiology; the contribution of the male partner in women's sexual health; and, finally, the biologically focused management strategies for women with health concerns regarding desire, arousal, orgasm, and sexual pain. The resultant clinical biologically based paradigm is founded on results derived from emerging basic science and evidence-based data derived from clinical research.

EPIDEMIOLOGY AND CLASSIFICATION

There are limited population-based epidemiological studies in women with sexual health concerns *(1–9)*. Based on current published information, the following is the most contemporary, internationally consented classification system *(18–20)*.

1. Women's sexual interest/desire disorder: "Absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies and a lack of responsive desire. Motivations (here defined as reasons/incentives) for attempting to become sexually aroused are scarce or absent. The lack of interest is considered to be beyond a normative lessening with life cycle and relationship duration."
2. Subjective sexual arousal disorder: "Absence of or markedly diminished feelings of sexual arousal, (sexual excitement and sexual pleasure), from any type of sexual stimulation. Vaginal lubrication or other signs of physical response still occur."
3. Genital sexual arousal disorder: "Complaints of absent or impaired genital sexual arousal. Self-reports may include minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. Subjective sexual excitement still occurs from nongenital sexual stimuli."

4. Combined genital and subjective arousal disorder: "Absence of, or markedly diminished feelings of, sexual arousal (sexual excitement and sexual pleasure) from any type of sexual stimulation as well as complaints of absent or impaired genital sexual arousal (vulval swelling, lubrication)."
5. Persistent sexual arousal disorder: "Spontaneous, intrusive and unwanted genital arousal (e.g. tingling, throbbing, pulsating) in the absence of sexual interest and desire. Any awareness of subjective arousal is typically but not invariably unpleasant. The arousal is unrelieved by one or more orgasms and the feelings of arousal persist for hours or days."
6. Women's orgasmic disorder: Despite the self-report of high sexual arousal/excitement, there is either lack of orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm from any kind of stimulation.
7. Dyspareunia: "Persistent or recurrent pain with attempted or complete vaginal entry and/or penile vaginal intercourse."
8. Vaginismus: "Persistent difficulties to allow vaginal entry of a penis, a finger, and/or any object, despite the woman's expressed wish to do so. There is variable involuntary pelvic muscle contraction, (phobic) avoidance and anticipation/fear/experience of pain. Structural or other physical abnormalities must be ruled out/addressed."
9. Sexual aversion disorder: "Extreme anxiety and/or disgust at the anticipation of/or attempt to have any sexual activity."

In a US population-based study of more than 1700 women, Laumann et al. *(2,3)* observed that an excess of 40% of women studied reported sexual health concern. In that investigation, the most common sexual health concern was lack of sexual desire, followed by inability to achieve orgasm, lack of pleasure from sex, and pain during sex. Poor health, emotional problems or stress, decline in social status, and having ever been sexually coerced were among the factors associated with low desire, arousal disorder, and sexual pain. A worldwide survey of more than 27,000 men and women aged 40 to 80 assessed the relevance of sex and the prevalence of sexual dysfunction *(21)*. In that survey, women's sexual health concerns were classified into five subcategories: lack of interest in sex, inability to achieve orgasm, lubrication difficulties (dryness), sex not pleasurable, and pain during sexual intercourse (dyspareunia). The percentage of women who reported having at least one sexual health concern on a frequent or persistent basis was 39%. The percentage of women who reported having only one of the five sexual health concerns ranged from 10% for "dyspareunia" to 21% for "lack of interest in sex" *(7,21)*.

Contemporary international prevalence data concerning women's sexual health problems are represented. Seven percent of women reported a current prevalence of problems with sexual desire or interest, whereas 31% reported lifetime prevalence in the same area. In the category of women who experienced problems with excitement or pleasure, estimates for 1-yr prevalence were 23%, whereas an estimated 20% of women reported experiencing lifetime prevalence. In the category of lubrication difficulties or vaginal dryness, estimates were 20% for 1-yr prevalence and ranged from 19 to 23% for lifetime prevalence. In women who reported having infrequent orgasm or difficulties in reaching orgasm, lifetime prevalence estimates ranged from 4 to 41%. For those women who experienced an inability to experience orgasm for several months, one population-based study estimated the prevalence to be 16% of women, whereas another study reported that 18% of women had problems with orgasm for 2 mo or more, and 25% had trouble reaching orgasm more than 50% of the time. In the category of pain during or after sex, prevalence estimates ranged from 3 to 48%; lifetime estimates from population-based studies ranged

from 17 to 19%, whereas clinical-based studies reported prevalence estimates of 10 to 20%. In the category of women who experienced a problem with desire, arousal, orgasm, or pain, two population-based surveys using similar instruments estimated a prevalence of 33 and 35%, respectively. In the category of women who experienced a current sexual problem, one national study estimated a 1-mo prevalence of 45%. Finally, in the category of adult women who reported any sexual problems, the prevalence was estimated at 43%.

PHYSIOLOGY AND PATHOPHYSIOLOGY: EFFECT OF THE MALE PARTNER WHO HAS ERECTILE DYSFUNCTION

Until recently, although substantial investigations had occurred regarding the effects of selective phosphodiesterase (PDE)-5 inhibitors in men with erectile dysfunction (ED), little attention had been given to the sexual responses of their female partners. A typical inclusion criterion in the selective PDE-5 inhibitor trial of such couples was the existence of a stable heterosexual relationship. Participation of the woman was voluntary and was limited to assessments of treatment satisfaction. The women who were sexually involved with men suffering from ED were believed to unconditionally support their partners' sexual treatment. The issues relating to perspective of the woman and her well-being, quality of life, sexual function, and sexual satisfaction, either in relation to existing or successfully treated ED were not considered.

Couples share sexual dysfunction. Women with men who suffer from ED may have their adversely affected sexual function. What are the scientific data available concerning changes in the woman's sexual function among women whose partners have ED? Blumel et al. *(22)* examined a sample of 534 otherwise healthy women who had ceased sexual activity with their male partners. It was noted that among the cohort under age 45, ED was the most frequently cited reason for cessation of the woman's sexual activity.

However, initial studies were obtained with data from the man's perspective. Past research in this area involved inquiries of the man with ED regarding the effect his sexual problem had on his female partner(s). One study showed that significant improvement in the marital interaction score was noted when men with ED used a selective PDE-5 inhibitor *(23)*.

Contemporary research has finally begun to address the issue from the woman's perspective. Data from several investigations are derived from the woman, as her own study subject. Cayan et al. *(24)* reported on a prospective study assessing the sexual function of women with men who had ED. The study involved 38 women whose male partners had ED and 49 women whose male partners did not have ED. Women's sexual function results (including sexual arousal, lubrication, orgasm, satisfaction, pain, and total score) were significantly diminished among women with men who had ED compared with results from women in the control group. Among those women whose male partners received treatment (e.g., penile prosthesis insertion, oral PDE-5 inhibitor treatment) for ED, significant improvement in sexual arousal, lubrication, orgasm, satisfaction, and pain was identified.

Montorsi et al. *(25)* investigated thoughts and views and intercourse satisfaction in 930 women whose male partners were taking a selective PDE-5 inhibitor to manage ED. Women with men using a selective PDE-5 inhibitor had significantly higher intercourse satisfaction compared with women whose male partners were given a placebo.

Chevret et al. *(26)* developed and validated the Index of Sexual Life to measure women's sexual function in relationships with men suffering from ED. Women partnered with men with ED were found to have significantly diminished sexual drive and sexual satisfaction compared with women whose male partners did not have ED.

Oberg et al. *(27)* examined data from a Swedish nationally representative cross-sectional population investigation of sexual life, attitudes, and behavior. A total of 926 women aged 18 to 65 were sexually active in a heterosexual steady partner relationship during the 12 mo before the investigation. Data from women who claimed personally distressing sexual dysfunctions quite often, nearly all of the time, and all of the time were compared with data from women who had no sexually dysfunctional distress. Women reporting distress at low sexual interest or orgasmic dysfunction were very likely to have a partner with ED (odds ratio [OR]: 47.6 and 20.0, respectively).

In the Female Experience of Men's Attitudes to Life Events and Sexuality Study, data were analyzed from 283 women in 8 countries whose male partners had ED *(28)*. Women with men who had ED were asked multiple questions comparing their sexual activity, sexual function, and beliefs about sexuality before and since their partners experienced difficulties with erections. Data from the women were stratified by the man's self-reported degree (mild, moderate, or severe) of ED. Women whose partners had ED reported a lower frequency of sexual activity currently compared with before their partner developed erectile difficulties. Significantly fewer women reported that they experienced current sexual desire, sexual arousal, orgasm, or sexual satisfaction ("almost always" or "most times") compared with before their partners developed erectile difficulties. There was a significant correlation between the reduction in frequency of the woman's orgasm, the reduction in her sexual satisfaction, and the degree of her partner's self-reported ED (mild, moderate, severe). Women had the lowest frequency of orgasm and the lowest satisfaction with the sexual experience when their partners experienced severe ED.

Scientific data have been obtained from a double-blind, multicenter, 3-mo randomized trial involving men with ED in heterosexual couples who were in a stable relationship for at least 6 mo *(29,30)*. In this trial, women whose male partners had ED were asked to complete the validated Female Sexual Function Inventory at the initial screening. Significant improvement of the woman's sexual function and sexual satisfaction were observed.

WOMEN WITH MEN WHO SUFFER FROM PREMATURE EJACULATION

Because premature ejaculation is the most common male sexual dysfunction (affecting approx 25% of men), it is likely that at some point, many women will experience a sexual relationship with a man with premature ejaculation *(31)*. Premature ejaculation is objectively determined using a stopwatch to record intravaginal ejaculatory latency time, defined as the time between vaginal intromission and intravaginal ejaculation. It has been suggested that an intravaginal ejaculatory latency time of 2 min or less may serve as a criterion for defining premature ejaculation *(32)*.

Women with men who suffer from premature ejaculation may experience significant distress, interpersonal difficulties, and dissatisfaction with sexual intercourse *(33)*. The woman's distress is a common reason for the man to consult a clinician about premature ejaculation.

Byers et al. *(34)* investigated the effect of premature ejaculation on the sexual function of 152 couples. Concerning the couple's perceptions regarding whether the premature

ejaculation was a problem, reports of women and men were only moderately correlated. The results of both the women and the men showed that couples who reported more characteristics of premature ejaculation also reported lower sexual satisfaction. The results suggest that for most couples, the premature or early timing of ejaculation adversely affects sexual satisfaction.

Patrick et al. *(33)* carefully selected patients with and without premature ejaculation based on stopwatch testing. In the 207 men suffering from premature ejaculation, the mean intravaginal ejaculatory latency time was 1.8 min. This was significantly lower than the time for the 1380 men without premature ejaculation (7.3 min). Women whose partners suffered from premature ejaculation were found to significantly differ from women whose partners did not suffer from premature ejaculation in terms of decreased satisfaction with sexual intercourse and increased interpersonal difficulty and distress ($p < 0.0001$). More women partners of men with premature ejaculation claimed "poor" or "very poor" for satisfaction with sexual intercourse compared with women whose partners did not have premature ejaculation (28 vs 2%, respectively) and gave worse ratings ("quite a bit" or "extremely") for personal distress, couple relationship (44 vs 3%, respectively) and interpersonal difficulty (25 vs 2%, respectively; $p < 0.0001$).

PHYSIOLOGY AND PATHOPHYSIOLOGY: CHANGES IN THE FEMALE GENITALIA WITH AGING

The structure and function of a woman's genitalia largely depend on the sex steroid hormonal milieu *(1,16,35–39)*. As a woman ages or as a young woman is exposed to medicines that interfere with the hormonal milieu (e.g., oral contraceptives, tamoxifene), her supply of sex steroid hormones (estradiol, testosterone, and progesterone) significantly diminishes *(1)*.

Importantly, not all women have absent estradiol synthesis during menopause. During menopause, ovarian estradiol production ceases in all women. However, estrogen continues to be synthesized in the periphery (e.g., skin, adipose tissue, bone, muscle) in postmenopausal women through conversion of androstenedione to estrone and testosterone to estradiol, but the amount of estradiol synthesized partly depends on the enzymatic activity of aromatase.

Estrogens and androgens are required for genital tissue structure and function *(16)*. These hormones act on estrogen and androgen receptors, respectively, which exist in high numbers in genital tissues, including the epithelial/endothelial cells and smooth muscle cells of the vagina, vulva, vestibule, labia, and urethra. Diminished estrogen production for natural or iatrogenic reasons renders women's genital tissues highly susceptible to atrophy. Physical examination *(40,41)* of the postmenopausal woman's genitalia shows clitoral atrophy, phimosis, and nearly absent labia minora. The appearance of a woman's labia minora mirrors her level of estradiol, because these labia are exquisitely sensitive to estradiol. The urogenital area termed the vestibule is extremely important in female sexual function because it contains organs that are sensitive to both estrogen and androgen. For example, the clitoral tissues and prepuce are androgen-sensitive. The minor vestibular glands (located in the labial–hymenal junction) are embryologically derived from the glands of Littre, which are also androgen-dependent. The glands of Littre are located on the anterior surface of the urethra.

A host of structural changes and cellular dysfunctions occur in women's genital tissues as a result of estrogen deficiency *(40–45)*. For example, estrogen deficiency specifically

in the vagina leads to vaginal atrophy. One consequence is an alteration in the normally acidic vaginal pH that discourages the growth of pathogenic bacteria. The change to an alkaline pH value in the atrophic vagina leads to a shift in the vaginal flora, increasing the likelihood of discharge and odor. In an estrogen-rich environment, glycogen from sloughed epithelial cells is hydrolyzed into glucose and then metabolized to lactic acid by normal vaginal flora. In postmenopausal women, however, epithelial thinning reduces the available glycogen.

In addition to vaginal atrophy and a reduction in organ size, other signs of a decline in sex hormones in women include vaginal dryness, no secretions or lubrication, pale or inflamed tissue, petechiae, epithelial/mucosal thinning, organ prolapse, changes in external genitalia, decreased tissue elasticity, and loss of smooth muscle. When taking a history in a menopausal woman, a clinician may discover the following symptoms of women's sexual health concerns: dyspareunia, vaginismus, coital anorgasmia, vaginal and/or urinary tract infections (pH imbalance), or overactive bladder/incontinence *(40–45)*.

PHYSIOLOGY AND PATHOPHYSIOLOGY: EFFECTS OF SEX STEROID HORMONES ON THE VAGINA

The human vagina consists of three layers of tissue: the epithelium (composed of squamous cells), the lamina propria, and the muscularis (inner circular and outer longitudinal smooth muscle). The epithelium undergoes mild changes during the menstrual cycle. The lamina propria is replete with tiny blood vessels that become engorged with blood during sexual arousal, leading to lubrication. The smooth muscle of the muscularis enables the vagina to dilate and lengthen during penile penetration; relaxation of that muscle leads to arousal. These three layers of tissue may function in an interrelated way. The blood vessels in the lamina propria that allow for lubrication are hypothesized to depend on growth factors, and growth factors are hypothesized to derive from the muscularis. Postmenopausal atrophy of vaginal tissues may result from decreased synthesis of these growth factors, resulting in diminished number of critical blood vessels in the lamina propria.

Controlled studies employing a rat model of vaginal atrophy demonstrated the effects of different dosages of estrogen, progestin, testosterone, and various combinations of these hormones on various physiological and anatomical outcome parameters *(46)*. These measures included organ wet weight, vaginal blood flow, epithelial height, muscularis thickness, and vaginal innervation. In each study, the effects of different dosages of the hormone being tested on the vagina were compared between rats that had undergone sham ovariectomies and rats that had actually had both ovaries removed. The hormones (or saline) were delivered through a pump inserted into the back of the neck of each animal. A Doppler probe inserted into the vagina was used to record blood flow following electrical stimulation of a nerve next to the vagina. All animals were then euthanized, and vaginal tissue was removed for biochemical or histological studies. In those animal studies, removal of the ovaries reduced the wet weight of the uterus, which rose with administration of estrogen, because the uterus is a very estrogen-sensitive organ—much more so than the vagina.

Increased vaginal blood flow is an indicator of sexual arousal. Genital swelling and lubrication are responses to increased clitoral and vaginal perfusion; increased length and diameter of the vaginal canal and clitoral corpora cavernosa; engorgement of the vagina wall, clitoris, and labia major and minora; and transudation of lubricating fluid from the

vaginal epithelium. In the aforementioned animal studies, blood flow to the vagina was greatly reduced in the oophorectomized rats compared to the intact rats. Contrary to expectations, in oophorectomized rats, subphysiological doses of estradiol increased vaginal blood flow more than either physiological or supraphysiological doses *(46)*. Ovariectomy deprived the rats of estradiol, causing the vaginal epithelium to thin to a single layer. Subphysiological doses of estradiol showed the greatest increase of the thickness of the vaginal epithelium because the oophorectomized rats had more estrogen-α receptors in the epithelium than the intact animals. A small amount of estradiol delivered to tissue with many estrogen-α receptors produced a huge response. Therefore, estradiol regulates estrogen receptors through a negative feedback system. The more estradiol that is available, the fewer estrogen receptors there are. The muscularis, the muscle that enables the vagina to lengthen and widen during sexual arousal, also atrophies without estrogen. In postmenopausal women who do not receive hormone therapy, the vaginal epithelium, lamina propria blood vessels, and muscularis all decrease. Similarly to the epithelium, the muscularis responds to estradiol by increasing in thickness *(46)*.

DIAGNOSIS OF WOMEN WITH SEXUAL HEALTH CONCERNS

History

There are limited consensed management paradigms for the diagnosis of women with sexual health complaints. The cornerstone of the physical-based diagnosis of women with sexual dysfunction is a history and physical examination performed by the biologically focused health care professional. Specifically, obtaining a careful history is crucial because this aspect of the diagnosis establishes impressions and forms the basis of emphasis on a physical exam *(40,41)*.

The history of a woman with sexual health concerns includes sexual, medical, and psychosocial aspects to characterize the many physical and psychological factors that often contribute to the sexual health difficulty. It is advised that women with sexual health concerns undergo a separate and concomitant psychological interview by a psychologically focused health care professional to broaden the psychosocial information derived during the interview process *(40,41)*.

To begin the *sexual history*, the patient should describe the sexual problem. The following questions may help obtain maximal descriptive information: "What is the sexual problem? When did the sexual problem manifest? How long have you had the sexual problem? Does the sexual problem happen all the time? Does the sexual problem occur during partner-related sexual activity? Does the sexual problem occur during self-stimulation? In which situations is the sexual problem minimized? In which situations is the sexual problem maximized? Did you ever experience full capabilities for sexual interest, sexual arousal, and sexual orgasm? How many years were you at peak sexual function? What is your current sexual functioning in terms of interest, arousal and orgasm compared to when you were at peak sexual function? Is the sexual problem associated with any degree of discomfort, tenderness, soreness, or pain? If so, can you localize the site of the pain on a schematic diagram of a woman's genitalia? What tests have you already to evaluate your sexual health concern? What treatments have you already received and what are the outcomes of the various treatments? How does the sexual problem affect you? How is your partner affected by the sexual problem? Does the sexual problem cause you to withdraw from partner-related sexual activity, from self-stimulated sexual activity, or from the relationship? How would you feel if the sexual problem were cured?"

It is relevant to inquire about the sexual health of the partner. For women with male partners, male sexual dysfunctions such as ED, early ejaculation, or an anatomical concern, such as Peyronie's disease, may be present.

Data regarding the importance of the male partner to the sexual function of the woman are expanding exponentially. Current knowledge indicates that in a committed heterosexual relationship, the male partner's sexual performance is linked to his female partner's sexual function and sexual satisfaction. Therefore, if the male partner has some form of sexual dysfunction, such as ED, the woman's desire, arousal, ease of achieving orgasm, and satisfaction are reduced. It is imperative that clinicians obtain this information while taking a patient's history.

The use of validated, reliable, standardized self-rated questionnaires *(47–50)* is a very useful clinical starting point to assist in identification of the presence or absence of a sexual problem as well as in identification of the disorders of desire, arousal, orgasm, and/or sexual pain subtypes of women's sexual dysfunction that are involved. Such self-report measures are valuable screening tools that are easy to administer and score and that have normative values for populations of women with and without sexual dysfunction. Common self-rated questionnaires include the Female Sexual Function and the Sexual Function Questionnaire. As in all areas of clinical medicine, the use of screening tools for clinical diagnosis has recognized limitations. The determination of particular psychological contributors or confounds, contextual conditions, and other features and characteristics that cause individual women their unique sexual concerns requires more traditional assessment through structured history and physical examination.

The *medical history* should include focused questions on any accompanying medical/surgical illnesses and/or the use of medications. Topics of importance in the medical history may include the following: (a) chronic/medical illnesses such as diabetes, anemia, or renal failure; (b) neurological illnesses such as spinal cord injury, multiple sclerosis, or lumbosacral disc disease; (c) endocrinological illnesses such as hypogonadism, hyperprolactinemia, or thyroid disorders; (d) atherosclerotic vascular risk factor exposure such as hypercholesterolemia, hypertension, diabetes, smoking, or family history; (e) nonhormonal medication/recreational drug use, including use of antihypertensives, selective serotonin re-uptake inhibitors antidepressants, over-the-counter drugs, street drugs, alcohol, or cocaine; (f) use of hormonal medications such as combined oral contraceptives, infertility drugs, or leuprolide acetate; (g) pelvic/perineal/genital trauma such as pelvic fracture or bicycling injury; (h) gynecological history such as childbirth, abortions, episiotomy, abnormal PAP smears, sexually transmitted diseases, pelvic inflammatory disorder, endometriosis, fibroids, hysterectomy with or without oophorectomy, or menopause; (i) urological history such as incontinence, frequent urinary tract infections, interstitial cystitis, or pelvic surgeries; (j) surgical history such as laminectomy, colon/anal surgery, or vascular bypass surgery; and (k) psychiatric history such as depression, panic, or anxiety.

Because sex steroid hormones are critical for genital structure and function, the medical history should routinely probe and evaluate for symptoms of estrogen deficiency such as vaginal dryness, vaginal bleeding with minimal sexual contact, pain and soreness after sexual activity, hot flashes, and night sweats. Symptoms of androgen deficiency include fatigue, lack of energy, diminished skeletal muscle strength, depressed mood, falling asleep after meals, decreased athletic performance, or lack of interest in sexual activity.

The *psychosocial history* should assess such issues as social factors, past sexual beliefs, past sexual abuse and trauma, emotional concerns, and interpersonal relationship issues. Any history of mood or psychiatric disorders should be identified.

There are multiple caveats to taking histories from women with sexual health concerns. One is that the health care professional should consider history-taking as more than just the first diagnostic step toward resolution of the sexual problem. History-taking may be viewed as the actual beginning of treatment for the woman with sexual health concerns. A woman often feels empowered following a detailed discussion about her sexual health, because she has now taken the first step in overcoming her past failures to take action in this area. It is not uncommon for the discussion with the health care provider to become a model of what is possible about sexual health conversation. Many patients then initiate sexual health conversations with partners, close friends, or family members.

The second caveat is that the health care professional should be cognizant that although the woman may have a specific complaint (i.e., lack of interest), there may be additional and more complex mind, body, and relationship issues in the overall pathophysiology. For example, a woman may experience sexual pain during intercourse. She may be so psychologically distracted by the discomfort, throbbing, stinging, aching, soreness, burning, and/or tenderness that physiological desire, arousal, and orgasm responses during sexual stimulation cannot manifest. This woman may present with a primary sexual complaint such as lack of interest or orgasm, but more detailed history and physical examination may yield the concomitant longstanding genital sexual pain problem.

Physical Examination

The physical examination for a woman with sexual health concerns should be tailored to the sexual medicine complaint obtained during the history interview. For example, if the history uncovers that genital itching is a major sexual health problem, a careful assessment should follow for the presence of a genital dermatitis condition. If a woman with sexual health problems is under age 50 and experiences sexual pain, a careful physical examination should evaluate for the presence or absence of vulvar vestibulitis syndrome/vestibular adenitis. Similar complaints of sexual pain in a woman over age 50 should assess for the presence of vaginal atrophy with dryness, loss of rugae, mucosal thinning, pale hue, and lack of shiny vaginal secretions. Ideally, the physical examination should be performed without menses and without intercourse or douching for 24 h before the exam. If dysfunction occurs at a specific time, such as midcycle dyspareunia, the physical examination should be scheduled at the time of the sexual problem. Such scheduling may require two visits: one for history-taking and one for the physical examination *(40,41)*.

The genital-focused examination should be considered routine in the diagnosis of women's sexual health problems, but its personal character demands that a rational explanation exist for its inclusion in the diagnostic process. A focused peripheral genital examination is recommended in women with sexual dysfunction for complaints of dyspareunia, vaginismus, genital arousal disorder and combined arousal disorder, orgasmic disorder, pelvic trauma history, and any disease that affects genital health (such as herpes or lichen sclerosis). For women with suspected neurological disorders, the examiner may also assess for anal and vaginal tone, voluntary tightening of anus, and bulbocavernosal reflexes.

It is particularly important that the patient with sexual dysfunction has full communication with the health care provider as well as final authority during the physical examination to terminate at any time, to ask questions, to have control over who may attend, and to understand the extent of the assessment. It is vital that the patient is aware of the purpose. Inclusion of the sexual partner, with permission of the patient, is advantageous and provides necessary patient support. Allowing the patient (and the partner) to observe any pathology via mirrors or digital photography is often therapeutic, allowing (for the first

time in many cases) an illustration and connection of a detected physical abnormality with the sexual health problem. If a genital sexual pain history exists, the patient should point with her finger to the locations of the discomfort during the physical examination.

Independent of the gender of the examining health care provider, it is strongly recommended that a female chaperone health care provider is present during the examination. The following equipment should be available: examination table, hospital gown, bed sheet, disposable absorbing chucks, patient covering sheet, surgical loupes or magnifying glass, examination light source, examination gloves, gauze, lubricant, Q-tip, speculum, pH paper, glass slide, saline, and microscope. The patient should wear a hospital gown, and a sheet should cover her lower torso. The patient should be placed in the lithotomy position, and the examining health care provider should sit comfortably, using magnified vision and a carefully focused light source.

The first part of the examination involves inspection. If appropriate, lubricant should be placed on the vulva. Gauze can be grasped between thumb and index finger and can be used to retract the labia majora for a full inspection of the vestibular contents. Two gloved fingers are placed on either side of the clitoral shaft, and using an upward force in the cephalic direction, the prepuce is retracted to gain full exposure of the glans clitoris, corona, and right and left frenulum emanating at 5 o'clock and 7 o'clock from the posterior portion of the glans clitoris. Using gauze to retract the labia minora, the labial–hymenal junction is identified. A Q-tip cotton swab test is performed by gently applying pressure on the minor vestibular glands to document the quality of the discomfort or pain. The Q-tip cotton swab may also be placed at multiple locations in the vulva and vestibule. Palpation is then performed using a single-digit examination. This procedure occurs before both insertion of the speculum and bimanual searches for vaginismus. Single-digit palpation is achieved by gently placing a finger into the vaginal opening and depressing the bulbocavernosus muscle. If hypertonicity and pain are present, the test is positive.

The goals of the physical examination for a woman with sexual health concerns are to confirm normal architecture, to detect any existing pathology or abnormalities, to educate the woman about normal anatomy and physiology, and, if pain is a feature, to reproduce and localize the pain to potential tender areas of the vulva, vagina, or pelvis or hypertonicity of the pelvic floor.

If indicated, a bimanual examination and evaluation of pelvic floor may be subsequently performed. Two fingers are placed against the lateral walls, and the levators and underlying obturator are assessed for tenderness or taut bands. Additionally, a bimanual examination can evaluate the integrity of the fornices, bladder, and urethral bases and pelvic organs. A rectovaginal examination and speculum examination can be performed, if indicated. A warm, lubricated speculum should be used for the speculum examination. The vaginal wall is examined for estrogen milieu integrity, inflammation of the walls, and any vaginal lesions. The health care physician should also perform a complete physical, such as examining for a thyroid goiter, to rule out other comorbid conditions that might cause sexual dysfunction. A general physical exam is highly recommended in women with chronic illnesses and as part of good medical care; this examination should include evaluation of blood pressure, heart rate, and a detailed breast exam *(40,41)*.

Laboratory Testing

There are no consensed recommended routine laboratory tests for the evaluation of women with sexual health concerns involving desire, arousal, and orgasm. Blood testing should be dictated by clinical suspicion, especially using the results of the history and

physical examination. If appropriate, the health care clinician may assess multiple androgen and estrogen values, such as dehydroepiandrosterone sulfate, androstenedione, total testosterone, free testosterone, sex hormone-binding globulin (SHBG), dihydrotestosterone, estradiol, and estrone. Pituitary function may be measured by obtaining luteinizing hormone, follicle-stimulating hormone, and prolactin. Thyroid-stimulating hormone should be measured to exclude subclinical thyroid disease *(51–54)*.

There are multiple problems with the determination of serum hormone levels. Additionally, the normal ranges of testosterone concentration values for women of different age groups without sexual dysfunction are not well-defined. Testosterone levels reach a nadir during the early follicular phase, with small but less significant variation across the rest of the cycle. Testosterone assays are not uniformly sensitive or reliable enough to accurately measure testosterone at the low serum concentrations that are typically found in women. Free testosterone is clinically more important than total testosterone in sexual function, because the vast majority of testosterone is bound to SHBG, and only a small amount of total testosterone is biologically available. Measuring SHBG is not controversial and is relatively simple, with good reproducibility. Equilibrium dialysis is a highly sensitive assay for free testosterone; however, this method is not feasible for clinical practice. Measuring free testosterone by analog assays is unreliable. Free androgen may also be calculated using the free androgen index, defined as total testosterone (nmol/L) divided by SHBG (nmol/L). Calculated free testosterone may be determined and accounts for total testosterone, SHBG, and albumin. A calculator for this free testosterone is available online at http://www.issam.ch/freetesto.htm *(51–54)*.

Dehydroepiandrosterone sulfate is commonly measured because the half-life is much longer than dehydroepiandrosterone, resulting in more stable levels. The immunoassay for dehydroepiandrosterone sulfate is relatively robust and simple to perform. Dehydroepiandrosterone sulfate does not vary in concentration within the various phases of the menstrual cycle. Multiple investigators have shown consistent decline curves for dehydroepiandrosterone sulfate with aging.

Although there is a lack of clinical consensus regarding the value, specificity, and sensitivity of individual hormone blood tests, there are evidence-based, placebo-controlled, double-blind data to support the efficacy of exogenous sex steroid hormone treatment in women with sexual health concerns. Therefore, the prudent physician may wish to discuss with the patient the strategy of serial blood test surveillance testing to address safety concerns during such treatment.

A common and controversial question concerns the "normal range" for sex steroid blood test values in women with sexual health problems. Guay et al. *(51–54)* examined androgen values in women "without sexual dysfunction" (as determined by a validated Sexual Function Questionnaire). Androgen concentrations were highest in the women ages 20 to 29, decreased at approximately age 30, and remained relatively constant thereafter. The free androgen index in women "without sexual dysfunction" was approx 3.7 for women ages 20 to 29 yr old and 2.0 for women between the ages of 30 and 39 yr old *(51–54)*.

Serum levels of sex steroids can measure only deficiency or excess. Sex steroid hormone actions are quite complex and involve critical enzymes and critical hormone receptors that also determine tissue exposure, tissue sensitivity, and tissue responsiveness. For example, in individuals, there are variations in the amount and activity of critical enzymes such as 5 α-reductase and aromatase. Additionally, individuals have variations in individual sex steroid hormone receptor sequencing. Therefore, independent of the values of sex steroid hormones, the unique individual variations in critical enzymes and sex steroid

hormone receptors result in individual differences in tissue exposure, tissue sensitivity, and tissue responsiveness. More research is needed in the blood testing of sex steroid hormones in women with sexual health concerns.

TREATMENT

This goal of this section is to discuss the biologically focused management of women who have sexual health issues—especially relating to desire, arousal, and orgasm. The ideal management of all women with sexual health concerns is holistic, engaging psychological and biological strategies. The inclusion of health care professionals with expertise in physical therapy is especially relevant for sexual pain issues but may also be helpful with orgasmic issues.

Hormonal

Sex steroid hormones are critical for sexual structure and function *(16,38,51–54)*. Numerous studies have demonstrated that hormone therapy using systemic or local preparations improves sexual desire, arousal, orgasm, and frequency of sexual activity. There is no one hormonal intervention that is effective in all women with sexual health concerns involving desire, arousal, and/or orgasm that are secondary, in part, to sex steroid hormone deficiency states.

Studies have consistently reported that androgen sex steroid hormone values decline gradually and estradiol values decline abruptly in menopausal women. Hormone insufficiency states may also be caused by several clinical conditions and medications, including the use of oral contraceptive therapy.

The use of systemic testosterone, systemic estrogen, and/or local estrogen with or without systemic progesterone must be individualized to each patient's desires, wishes, requirements, and expectations *(41)*. Systemic hormone therapy can successfully improve hot flashes, night sweats, and sleep disturbances that can otherwise markedly diminish the body image and mood of women suffering from them. Local hormone therapy can successfully improve vaginal lubrication dryness and dyspareunia. Alleviation of hormone deficiency-induced symptoms by systemic and/or localized sex steroid hormones can increase quality of life, desire, arousal, and orgasmic function. Although not yet specifically approved for clinical use in women with sexual health concerns, sex steroid hormones may eventually provide a safe and effective treatment option. However, more research is necessary.

The following sections represent a clinical paradigm currently used in our outpatient sexual health clinic for the evidence-based, biologically focused treatment of women with desire, arousal, and orgasm sexual health concerns. As discussed earlier, treatment is holistic and is based on the history, physical examination, and laboratory tests.

Phase 1

It is important to emphasize that no single type of hormonal intervention or regimen is effective in all women with sexual health concerns involving desire, arousal, and orgasm. Women who seek treatment may have symptoms of sexual health problems resulting partly from the onset of natural menopause or menopause induced by chemotherapy or surgery. Alternatively, they may be younger women whose labia minora have begun to atrophy because of the adverse effects of oral contraceptives on the sex steroid hormonal milieu. Infertility or endometriosis treatments may also disturb the sex steroid hormone milieu.

The hormonal abnormalities that are identified determine which of the following four biological treatment options women are offered in Phase 1. Based on blood test results, systemic androgen treatment may be achieved with DHEA alone, systemic testosterone alone, or a combination of both. Based on the history and physical examination, local estrogen treatment may be achieved with vestibular estradiol alone, intravaginal estradiol alone, or a combination of both.

Systemic androgens (DHEA and/or testosterone) have been shown to improve mood, energy, stimulation, sensation, arousal, and orgasm *(55–57)*. Limited clinical trials have examined the effects of DHEA therapy on sexual function in women. Baulieu and colleagues *(55–57)* administered 50 mg of DHEA or placebo to 140 women between ages 60 and 79 yr old for a period of 12 mo. DHEA treatment produced an approximate doubling of serum total testosterone concentration and significantly increased skin hydration and bone density. Libidinal interest was increased after 6 mo of treatment, and sexual activity and sexual satisfaction were increased after 12 mo *(55–57)*.

Testosterone has been used to treat women with sexual dysfunction for more than 50 yr *(58)*. Transdermal patches or gels, which are more consistently absorbed and avoid first pass through the liver, are currently being studied for their safety and efficacy in reducing sexual symptoms associated with testosterone insufficiency *(59,60)*. Recently, transdermal testosterone patches were compared to placebo in estrogenized women who had undergone oophorectomy and hysterectomy *(59)*. The study results showed that during a 12-wk period, the 300-μg testosterone patch was significantly more effective than the 150-μg patch or placebo in improving frequency of sexual activity, pleasure, and fantasy. Typically, testosterone is used in gel form (Food and Drug Administration-approved delivery system for men) and is applied to the back of the calf. One-tenth of the dose used in men is appropriate to start therapy for women.

One benefit of administering DHEA and testosterone is that a certain percentage of these hormones aromatize to an estrogen, thereby relieving hot flashes and night sweats without the administration of systemic estrogen.

Local estrogen, whether prescribed in the form of vaginal estradiol or a vestibular cream, improves perfusion, lubrication, tissue tone, and elasticity and restores the normal pH and vaginal health *(42,61,62)*. Vaginal estradiol also relieves dyspareunia, atrophic vaginitis, and vaginismus. Some systemic absorption occurs with all local estrogens, but this absorption is less than that occurring with oral therapy. Daily application of a film of vestibular estrogen is recommended as well, because it promotes the health of the frenulum (the most sensitive part of the external genitalia), labia minora, urethral meatus, hymenal tissue, and vestibular glands.

Women with sexual dysfunction who are placed on Phase 1 treatment need to undergo surveillance blood tests after 3 mo of therapy to monitor levels of estradiol, progesterone, DHEA, testosterone, androstenedione, dihydrotestosterone, follicle stimulating hormone, luteinizing hormone, prolactin, and thyroid-stimulating hormone, as indicated.

Women with sexual health concerns regarding desire, arousal, and orgasm whose symptoms of distress are not satisfactorily resolved with Phase 1 treatments may consider progressing to Phase 2 treatments.

Phase 2

In Phase 2, women receive systemic estrogen and/or systemic testosterone. Several clinical trials have shown that the distressing symptoms of vaginal atrophy associated with low estrogen states are ameliorated after estrogen therapy. In healthy menopausal women,

low doses of systemic bioidentical nonsynthetic 17-β estradiol reduced vaginal atrophy compared with placebo *(63)*. Systemic estrogen therapy can also successfully improve hot flashes, night sweats, and sleep disturbances that negatively affect body image, mood, and sexual desire. All efforts are made to keep serum estradiol levels between 30 and 50 ng/dL. Risks of systemic estrogen use include breast cancer, heart attack, and stroke. The concept of maintaining estradiol values at low levels is to reduce the risk of side effects while achieving a minimum efficacious dose.

In women with an intact uterus, systemic estrogen should always be opposed by a progesterone. All efforts are made to use a bio-identical nonsynthetic progesterone and keep values in the range of 1 ng/dL.

Phase 3

In Phase 3, attention is given to the possible role of dopamine agonists in facilitating desire and orgasm sexual responses. Sexual motivation is encouraged, sustained, and ended by numerous central nervous system neurotransmitter and receptor changes that are induced partly by the action of sex steroids, androgens, estrogens, progestins, and the central neurotransmitter dopamine *(64,65)*. The activation of dopamine receptors may be a key intermediary in the stimulation of incentive sexual motivation and sexual reward. In turn, these neurotransmitter and receptor changes activate central sexual arousal and desire. Contemporary animal research reveals that dopamine neurotransmitter systems may play a critical intermediary role in the central regulation of sexual arousal and excitation, mood, and incentive-related sexual behavior—particularly in the motivational responses to conditioned external stimuli. In summary, the complex central neurochemical actions of steroid hormones stimulate sensory awareness, central sexual arousal, mood, and reward and relate them to relevant individual sexual experiences involving a partner, a place, and an action.

Bupropion may have a beneficial effect on women with hypoactive sexual desire disorder. In a placebo-controlled trial, bupropion produced an increase in desire and frequency of sexual activity compared to placebo *(65,66)*. However, frequency was correlated to total testosterone level at baseline and during treatment. A traditional starting dose is 100 mg of bupropion per day, generally administered in the morning.

Vasodilators

Basic science studies investigating the physiology of sexual function using female animal models have supported the role of nitric oxide–cyclic guanosine monophosphate–PDE-5 pathways in the peripheral arousal physiology of the clitoral corpus cavernosum *(67,68)*, corpus spongiosum, vaginal epithelium, and vaginal lamina propria.

There have been several clinical studies on selective PDE-5 inhibitors during recent years; these studies have been conducted with either pre- or postmenopausal women with arousal sexual health concerns as well as in healthy women without sexual dysfunction. Many studies did not account for the hormonal milieu of the subjects in the inclusion and exclusion criteria. An important point in treating women with arousal sexual health concerns is that an adequate sex steroid (androgen and estrogen) hormonal milieu is critical for benefits from selective PDE-5 inhibitor treatment *(16)*. Several studies assess the safety and efficacy of selective PDE-5 inhibitors in subjects with normal hormonal milieus.

A double-blind, crossover, placebo-controlled safety and efficacy study with a selective PDE-5 inhibitor was performed in premenopausal women with normal ovulatory cycles

and normal levels of steroid hormones who were affected by female sexual arousal disorder without hypoactive sexual desire disorder. Subjects were observed to benefit from treatment with the active selective PDE-5 inhibitor and showed improvement in sexual arousal, orgasm, frequency, and enjoyment of sexual intercourse compared to subjects treated with placebo *(69)*.

A double-blind, placebo-controlled safety and efficacy study with a selective PDE-5 inhibitor was performed in postmenopausal women with female sexual arousal disorder who had adequate serum estradiol and free testosterone values. Women with female sexual arousal disorder without hypoactive sexual desire disorder who were administered the active drug showed a significantly greater improvement in sexual arousal, orgasm, intercourse, and overall satisfaction with sexual life compared to those administered placebo. No efficacy was shown for women with concomitant hypoactive sexual desire disorder *(70)*.

Another study was performed using selective PDE-5 inhibitors in women with psychotropic-induced sexual dysfunction. Women who had normal premorbid sexual function and who had developed sexual dysfunction—particularly anorgasmia with or without other sexual disturbances (i.e., loss of libido, lubrication difficulties, uncomfortable or painful intercourse)—were treated with a selective PDE-5 inhibitor. The subjects showed improvement of the presenting condition (usually depression, anxiety, or both) and experienced sexual side effects continuously for more than 4 wk. Patients took selective PDE-5 inhibitors and reported a complete or very significant reversal of their sexual dysfunction. This included return of effective duration and intensity of adequate arousal, lubrication, and orgasmic function *(71)*.

SEXUAL PAIN MANAGEMENT

Medical Therapy for Genital Sexual Pain Disorders

Biological pathophysiologies resulting in woman's sexual health problems associated with sexual pain may occur in the clitoris, urethra, bladder, vulva, vestibule, vagina, and pelvic floor muscles. It is not within the scope of this chapter to detail the entire management of women with genital sexual pain disorders. Interested readers can refer to the reference text *Women's Sexual Function and Dysfunction: Study, Diagnosis and Treatment (17)*.

Clitoris, Prepuce, and Frenulae

Careful inspection of the glans clitoris should be performed in women with focused clitoral pain, clitoral itching, or clitoral burning. Failure to visualize the whole glans clitoris with the corona is consistent with some degree of prepucial phimosis (mild, moderate, or severe), based on the elasticity of the prepuce and its ability to retract on examination *(72)*. Because phimosis may create a closed compartment, phimosis is often the underlying pathology in clitoral glans balanitis associated with recurrent fungal infections. Initial treatment may be conservative with topical estrogen and/or testosterone creams to determine whether the prepuce can be made more elastic and retractile *(73)*. Topical antifungal agents such as nystatin or oral antifungal agents such as fluconazole may be considered *(74)*. Infections can also be related to herpes virus, and appropriate treatment (e.g., with acyclovir) should be administered. If conservative treatment fails because of the phimotic prepuce, surgical management by dorsal slit procedure should be considered.

Urethral Meatus

Gentle retraction of the labia minora should provide full view of the urethral meatus. Prolapse of the urethral mucosa out the urethral lumen is highly associated with estrogen deficiency states such as following bilateral oophorectomy, natural menopause, or following chemotherapy for malignancy. Clinical symptoms include urgency, frequency, and discomfort of urination, and spotting of blood may be observed following urination or excretion. The abnormal voiding history is often accompanied by a unique sexual history. Women with urethral prolapse often have the ability to have full sexual pleasure and satisfaction during self-stimulation of the clitoris, but during sexual activity with the partner or with a mechanical device, she experiences pain and/or urgency to urinate and/or inability to have orgasm secondary to distracting pain. Conservative treatment options include topical or systemic estrogens, although the risks and benefits of estrogen treatment need to be fully discussed *(75)*.

Vulva/Vestibule

Genital sexual pain in the vulva/vestibule may be related to various specific disorders. Generalized vulvodynia *(76)* refers to a diffuse, constant, burning pain anywhere on the vulva, from mons to anus, which is hyperpathic and greatly out of proportion to the stimulus. Afflicted patients have a constant or sporadic awareness of the vulva with widespread ("everything hurts") vulvar soreness, rawness, constant irritation, various paresthesias, aching, and/or stinging. Generalized vulvodynia may be considered as primary if it occurs with the first penetrative sexual encounter or with a tampon or speculum examination. Generalized vulvodynia may be considered as secondary if it occurs after previous nonpainful vaginal penetrations. The diagnosis of generalized vulvodynia is made by ruling out such diagnoses as candida vaginitis and chronic genital dermatitis conditions during physical examination and laboratory testing. Q-tip testing shows all vulvar areas positive for pain and/or tenderness. The treatment of any genital sexual pain disorder involves the multidisciplinary team approach; this is especially true regarding the disabling condition of generalized vulvodynia. Patient management includes education and support, especially regarding avoidance of contacts and practice of healthy vulvar hygiene, pelvic floor physical therapy treatment, management of concomitant depression, and management of any associated neurological, dermatological, gynecological, orthopedic, or urological conditions. Medical management includes amitriptyline and/or gabapentin.

Vulvar vestibulitis syndrome is one of the most likely causes of dyspareunia, especially in women younger than 50 yr *(77,78)*. Vulvar vestibulitis syndrome may include the following. On history, there is severe pain on vestibular touch or attempted vaginal entry. On physical examination, there is erythema of various degrees within the vestibule. During Q-tip testing, there is tenderness to pressure that is "localized" within the vulvar vestibule. Often, the tender localized region is along the labial hymen junction associated with the presence of minor vestibular glands. With vulvar vestibulitis syndrome, genital sexual pain may also be experienced with the use of tampons, during speculum examination, when wearing tight pants, or when straddling while cycling or horseback riding. Although there is no known pathophysiology, there are several possible pathophysiological factors, including exposure to human papillomavirus, the irritant oxalate, abnormal immunological conditions, psychopathology, and an abnormal sex steroid hormonal

milieu. The treatment of vulvar vestibulitis syndrome includes conservative measures such as education, support, counseling, physical therapy, and/or biofeedback. Elimination of the pain trigger should be performed. Topical estrogen and topical xylocaine creams and/or ointments should be considered. Systemic medications include tricyclic antidepressant or gabapentin. Correction of the sex steroid hormonal milieu should be considered. Unlike generalized vulvodynia, in women with vulvar vestibulitis syndrome, surgery such as vestibulectomy can be considered if medical management fails.

The symptoms of atrophic vaginitis include vaginal dryness, dyspareunia, stinging, bleeding, and dysuria *(79)*. On physical examination, women with atrophic vaginitis reveal vaginal mucosal changes. The classic, healthy-looking vagina has a pink hue with vaginal folds and rugae that reveal a shiny lubricating substance when touched with a Q-tip and that do not bleed when rubbed with a Q-tip. In atrophic vaginitis, the vagina transforms to an unhealthy pale complexion, with a lack of vaginal folds and rugae, a lack of lubricating substance on the surface, and bleeding tissue following minimal contact. On wet mount, the microscopic examination reveals parabasal cells, increased white blood cells, and absent background flora of lactobacilli. The vaginal pH is elevated to approx 6.0 to 7.0. The conservative treatment involves the use of local topical vestibular and/or intravaginal estrogen. There are multiple products on the market, including intravaginal rings, intravaginal pills, and creams. There are also multiple estrogen alternatives, such as soy, although there are limited double-blind, placebo-controlled safety and efficacy trials using these products.

Disorders of the female pelvic floor—especially bladder/urethra and sexual dysfunction—are common. Normal function of the pelvic floor musculature is essential in maintaining appropriate sexual function. Both "low tone pelvic floor dysfunction" and "high-tone pelvic floor muscle dysfunction" can be closely associated with women's sexual health concerns. Hypotonus of the pelvic floor muscles secondary to childbirth, trauma, and/or aging is related to urinary incontinence during orgasm, vaginal laxity, and/or thrusting dyspareunia secondary to pelvic organ prolapse *(80)*. Hypertonus of the pelvic floor secondary to childbirth, postural stressors, microtrauma, infection, adhesions, and surgical trauma can contribute to symptoms of urinary retention, reduced force of stream, dysuria, urgency, penetrative dyspareunia, and/or vaginismus *(81)*.

Hypersensitivity disorders involving the GU tract represent a spectrum of symptoms and conditions that include chronic bacterial cystitis; urgency and frequency syndrome; sensory urgency; urethral syndrome; interstitial cystitis; and vulvar, vaginal, perineal, and pelvic pain. Hypersensitivity disorders (associated with hypertonus of the pelvic floor musculature) account for some of the concerns of female patients who present for evaluation of sexual health concerns. Sexuality is adversely affected for the majority of women with hypersensitivity disorders of the bladder, bowel, and vulva and high-tone pelvic floor dysfunction. Conservative therapy for pelvic floor dysfunction is aimed at muscle re-education. A pelvic floor rehabilitation program aimed at facilitating sexual comfort and pleasure for patients can be designed. Massage of the pelvic floor can be performed to elongate shortened muscles and decrease high-tone spasm in such patients.

Weakness and laxity of the pelvic floor muscles represent a spectrum of symptoms and conditions that include women with pelvic organ prolapse, with or without urinary or fecal incontinence. Risk factors include age, heredity, vaginal birth trauma, previous pelvic/vaginal surgery, history of radiation therapy, menopausal status, lifestyle factors such as strenuous lifting, and chronic medical conditions (including obstructive pulmo-

nary disease, obesity, and constipation). Stress incontinence that occurs with increased intra-abdominal pressure and maneuvers such as sneezing, coughing, and straining is related to abnormalities in urethral closure and poor pelvic muscle support. Sexuality is often adversely affected for women with severe low-tone pelvic floor dysfunction, especially in those with severe incontinence and prolapse, where symptoms become a source of anxiety and interfere with the overall sense of sexual satisfaction. Conservative therapy for low-tone pelvic floor dysfunction is also aimed at muscle re-education. Pelvic floor muscle strengthening exercises, augmented with biofeedback and/or electrical stimulation to the pelvic floor, can be initiated. If this and other conservative treatment options fail, then surgical procedures (including sling and tension-free vaginal tape placement) provide cure rates as high as 95% when performed in appropriate candidates.

SURGICAL THERAPY FOR GENITAL SEXUAL PAIN DISORDERS

Surgical Treatment for Vulvar Vestibulitis Syndrome

Surgical intervention for management of women with vulvar vestibulitis syndrome is offered to those who have failed initial conservative treatment focused on medical, psychological, and/or physical therapy. Surgery is based on the hypothesis that the pathophysiology of vulvar vestibulitis syndrome is associated with inflamed, irritated, and hypersensitive vestibular glandular tissue and related increased nerve density in the vestibular mucosa. Therefore, surgical success is based on excision of this abnormal glandular and nerve tissue in the vestibule *(82–84)*.

In women with vulvar vestibulitis syndrome, the first surgical excision and reconstructive procedure consisted of a semicircular segment of perineal skin, the mucosa of the posterior vulvar vestibule, and the posterior hymeneal ring. The reconstruction consisted of undermining 3 cm of the vaginal mucosa and approximating this directly to the perineum. Subsequent variations and modifications have evolved. Specifically, in contemporary "vulvar vestibulectomy," the posterior incision extends only to the posterior fourchette and does not include excisions of perineal skin. A "complete vulvar vestibulectomy" includes excision of the vestibular mucosa adjacent to the urethral meatus/Skene's glands region anteriorly, excision of vestibular mucosa laterally and posteriorly; reconstruction includes the posterior vaginal flap advancement. A "modified vulvar vestibulectomy" limits the excision of vestibular mucosa to the posterior vestibule. Both procedures are usually performed under general or regional anesthesia. During vestibulectomy, the vaginal advancement may cover the ostia of the Bartholin glands; however, the risk of postoperative Bartholin gland cysts is only 1%. A "vestibuloplasty" or "excision of vestibular adenitis" consists only of excision of localized painful areas of vestibular mucosa, without vaginal advancement, and can be performed with local anesthesia. Most surgeons choose the procedure based on the individual needs and symptoms of the patient. The complications of surgery for vulvar vestibulitis syndrome increase with the invasiveness of the procedure performed. Specific complications include bleeding, infection, increased pain, hematoma, wound dehiscence, vaginal stenosis, scar tissue formation, and formation of Bartholin duct cysts. As with all surgery, the risk of these complications can be reduced with appropriate surgical techniques. Various closure techniques have been described to minimize the risks of postoperative complications. Specifically, the vaginal advancement flap should be anchored by multiple subcutaneous mattress sutures of 3–0 Vicryl placed in an anterior–posterior direction and should be approximated to the perineum with interrupted stitches of 4–0 Vicryl *(82–84)*.

OTHER SURGICAL PROCEDURES

Distressing and disabling clitoral pain may occur secondary to phimosis of the clitoral prepuce and recurrent fungal balanitis of the clitoral glans or frenulae. If conservative treatment fails, then a dorsal slit procedure of the prepuce may be indicated to relieve the woman of the closed compartment perpetuating the recurrent fungal clitoral glans infection *(72)*.

Distressing and disabling vestibular pain, urinary urgency and frequency, and genital sexual pain may occur secondary to urethral prolapse. If conservative treatments fail, then surgical excision of the prolapsed urethral mucosa may be indicated *(80)*.

Distressing vulvar/vestibular discomfort may occur secondary to a Bartholin's cyst. If conservative treatments fail, then marsupialization of the cyst may be indicated to enable drainage of the highly viscous and mucinous cyst fluid *(85)*.

CONCLUSIONS

It is entirely appropriate to have a detailed chapter on women's sexual health concerns in a text dealing with male sexual function. Sexual dysfunctions are shared experiences. Increasing numbers of health care professionals manage both men and women with sexual health concerns because these health care professionals want to maximize the sexual health care delivery to each patient they treat. In the future, it will become increasingly more difficult to provide sexual health care to only one member of the couple.

The basic premise of biologically focused management of women's sexual health concerns regarding desire, arousal, and orgasm is that physiological processes can be altered by pathology. Determining how a woman's specific medical conditions modulate her sexual health requires much investment in basic science investigation. From the perspective of biology-focused clinicians, the essential principle guiding medical decision-making is identification of the underlying pathophysiology of the sexual dysfunction. If the biological basis of the desire, arousal, and orgasm dysfunction can be diagnosed, then management outcome may be successfully directed to the source pathophysiology. Two of the many challenges facing health care professionals today are improving their ability to accurately diagnose women with sexual health concerns involving desire, arousal, and orgasm and ensuring that they offer women the best evidence-based available treatment options. To achieve these goals, biologically focused clinicians need to be familiar with evidence-based, state-of-the-art data and current biologically focused management strategies.

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11 Evaluation of the Patient With Erectile Dysfunction

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SUMMARY

Evaluation of the male with erectile dysfunction (ED) has evolved over the past two decades. Although a complex array of diagnostic studies are available and may be employed in the appropriate subject, for the great majority of men these invasive, expensive, and on occasion painful studies are not necessary. Clearly, most men have a physiological etiology to their dysfunction and in fact, most of these men have a vascular cause. It seems that the fundamentals of medicine provide the most useful information, including a thorough medical history and physical exam as well as blood testing of serum glucose, lipids, and, when a hypogonadal etiology is suspected, semen testosterone.

There are several circumstances in which a more detailed analysis is in order, including patients who fail first-line therapy with oral pharmacotherapy and those with primary or traumatic ED. This chapter provides an up-to-date review of the diagnostic approach to the man with ED.

Key Words: Erectile dysfunction; male sexual health.

INTRODUCTION

Erectile dysfunction (ED) can deeply affect quality of life. Therefore, it is not surprising that men seek medical evaluation when they experience ED, especially now that it is almost universally known that effective oral medication is available by prescription. ED was previously believed to result from psychological factors, but an organic cause is now identifiable in most men, although a secondary psychological factor frequently exacerbates ED *(1)*. ED is currently categorized as vasculogenic, neurogenic, endocrinological, psychogenic, or mixed in origin.

Using a rational approach in the treatment of ED would suggest that the underlying cause should be determined so that the appropriate therapy can be selected. This implies that different treatments are available for the different etiologies of ED. In the current era of phosphodiesterase (PDE)-5 inhibitors, most men with varying etiologies for ED

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respond to oral or injection therapy. Therefore, the issue is whether it remains necessary to identify the specific cause in each man who presents with ED before proceeding to treatment.

Certainly, most men with ED do not require an extensive evaluation. These men are typically older, with easily identifiable risk factors for a vascular or neurological etiology, such as diabetes mellitus, coronary artery disease, hypertension, smoking, or dyslipidemia. Additionally, a significant number of men do not want extensive testing to determine the etiology of their ED but prefer a brief, minimal evaluation. For these men, a reasonable evaluation should consist of a history and physical exam, including blood pressure determination, fasting glucose and lipid profile, and, if symptoms suggest hypogonadism, a serum testosterone level.

However, a portion of men do not have an identifiable cause for ED or are refractory to conventional PDE-5 therapy. These men tend to be younger and have no significant medical history, or they are older men whose presumed cause for ED should have responded to PDE-5 medications. This is the population in which further testing is often productive in determining the cause and appropriate treatment of their condition.

Evidence has been accumulating that in addition to being a significant condition, ED appearing in otherwise healthy men may be an indicator of serious systemic conditions that have not yet manifested in other ways. These patients may respond to PDE-5 therapy, even in the absence of additional evidence for a vascular or neurological cause. By evaluating these patients for the presence of underlying conditions known to cause ED rather than simply treating the sexual dysfunction, undiagnosed systemic processes such as diabetes, hypertension, dyslipidemia, and cardiovascular disease may be identified earlier. Potentially, other complications associated with these conditions may be avoided through earlier recognition.

ROUTINE PATIENT ASSESSMENT

History

Taking a detailed history usually strongly suggests the underlying cause(s) for a patient's ED and obviates the need for extensive testing. However, the first step in evaluating a patient presenting with ED is to verify that his complaint is actually an inability to achieve or maintain an erection sufficient for sexual activity. Patients may report "erectile dysfunction" when they actually have conditions more accurately described as a penile deformity, such as Peyronie's disease *(2)*, or premature ejaculation. Asking questions such as "Do you have difficulty with penetration?" or "Do you have difficulty maintaining an erection?" may not properly discriminate between these various erectile difficulties. Therefore, careful questioning is essential.

Self-administered questionnaires may be useful in the initial evaluation of ED and can be completed in advance of the actual patient encounter. The International Index of Erectile Function (IIEF) is a widely used and validated 15-item questionnaire that evaluates five factors (domains) of sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction *(3)*. For the purposes of evaluating ED, the five questions comprising the erectile function domain (IIEF-EF) are most relevant, although useful information can be derived from the entire questionnaire. The responses can be used to gage the nature and severity of the patient's ED and loss of libido, if indicated.

The clinician should then take a directed history of the patient's complaint. Determining his previous level of sexual function is a starting point, as is noting the mode of onset (abrupt vs gradual) and duration of ED. The clinician should elicit possible precipitating factors, such as a change in health or emotional stress from loss of employment or relationship difficulties. The history should also indicate the patient's interest in sexual activity. The clinician should not assume that the patient has a normal libido because he is seeking evaluation for ED. The presence or absence of nocturnal or morning erections should also be ascertained, because a man with rigid erections upon wakening likely has a psychogenic etiology for his ED. The diagnostic and treatment approach for these men is often different than for men with an organic etiology.

Risk Factors

Once the patient's complaint has been elucidated, the clinician should take a thorough medical history, giving particular attention to conditions and behaviors associated with ED. Identifying risk factors helps identify the causes of the patient's ED, allow for modification of those risk factors, and guide appropriate therapy.

Vascular Disease. Diabetes, hypertension, dyslipidemia, and smoking are all risk factors for developing vascular disease, the most common cause of ED *(4–6)*. Obviously, a history of angina, myocardial infarction, stroke, or peripheral arterial disease strongly suggests a vascular origin of the patient's ED, but it is also important to remember that medications used to treat these conditions may have a role in the patient's ED. Interestingly, numerous risk factors for developing atherosclerotic disease and resultant ED are also independent risk factors for ED. Obesity, smoking, and dyslipidemia have all been shown to be associated with ED in the absence of demonstrable vascular disease. Individuals improving in these parameters appear to improve regarding their erectile function, possibly by improving endothelial function *(7–9)*.

Diabetes. The association between ED and diabetes is well-established *(10)*. The risk of ED in patients with diabetes approaches 50% and does not simply result from the increased risk for macro- and microvascular disease in patients with diabetes. These patients are also at risk for neuropathies, and hormonal abnormalities have been found in diabetics at a higher rate than in the general population *(11)*. Poor glycemic control (as demonstrated by an elevated $HgbA_{1C}$) level correlates with more severe ED *(12,13)*. To date, no studies have shown that tightening blood glucose control alone can improve ED, although it may slow progression.

Neurological Conditions. Several chronic neurological disorders have been associated with ED. Multiple sclerosis (MS) and Parkinson's disease are both associated with high rates of ED *(14–16)*. Stroke is also frequently followed by a decline in erectile function in patients who were sexually active before the event *(17)*. All of these conditions frequently co-exist with depression, which may exacerbate ED *(14,17)*. Conversely, depression in these patients may result from sexual dysfunction. Multiple systems atrophy (or Shy Drager syndrome) often causes ED *(17)*. Epilepsy is also associated with ED, but anticonvulsants frequently used to treat seizures may be the cause of impotence *(18,19)*. A herniated lumbar disk can be a reversible cause of neurogenic ED *(20)*.

Trauma and Priapism. A history of trauma should be elicited—particularly blunt pelvic, perineal, or genital injuries. Pelvic fractures can result in ED in as many as 30% of cases because of neurological or vascular injury *(21,22)*. Penile fractures may also result in ED, even when repaired at the time of injury *(23,24)*. Long-distance bicycling can

transiently affect the pudendal artery and nerve, causing perineal and penile numbness; however, it has an uncertain relationship to ED *(25,26)*.

Prolonged episodes of priapism may result in ED from ischemic fibrosis of corporal tissue. The fibrosis may cause dysfunction of the veno-occlusive mechanism. Treatment of priapism may also account for subsequent ED, particularly when cavernosal shunting is performed.

Renal Failure. Renal failure is associated with ED in up to 50% of patients *(27)*. These patients usually have numerous other risk factors, such as diabetes or hypertension, but end-stage renal disease is a risk factor. Mechanisms include hyperprolactinemia and resistance to the action of androgens *(28)*. Renal transplantation improves ED in many, but not all, of these patients *(27,28)*. Those who fail to improve after transplantation often have pre-existing irreversible vascular disease.

Surgical Causes. A complete surgical history should be documented. Radical prostatectomy—either retropubic or perineal—has been the surgery classically associated with ED, but several other procedures also result in ED. Abdominoperineal resections for colorectal cancer frequently injure the pelvic plexus, the origin of the cavernosal nerves *(29)*. Vascular surgery also can affect erectile function. Revascularizations involving the iliac arteries may decrease penile blood flow if inflow to the internal iliac arteries are bypassed *(29)*. Renal transplantation using the internal iliac artery can have a similar effect *(28)*. Although only one intact internal pudendal artery is theoretically necessary to maintain adequate penile blood flow, patients who undergo vascular or renal transplanation surgery often have diffuse, bilateral atherosclerotic disease, which compromises the intact contralateral artery.

Medications. Medications should be listed with an attempt to correlate when their use was initiated in relation to when ED occurred. A wide range of medications have been associated with ED. Antihypertensives are frequently responsible, especially diuretics and β-blockers, although calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are less likely to cause ED *(30)*. In men with marked vascular disease, vasodilation that allows increased penile blood flow does not occur because of damage to the penile vasculature. Instead, these men rely on elevated pressures to force blood to the penis through nondilating vessels. Blood pressure medications may then reduce penile perfusion as a consequence of their antihypertensive effects rather than as a result of their specific mechanisms of blood pressure reduction.

Psychotropic medications—particularly selective serotonin re-uptake inhibitors and monoamine oxidase inhibitors—often affect sexual function. They are known to decrease libido and to diminish orgasmic function in addition to causing ED. Antipsychotics can cause ED by elevating prolactin levels, and the anti-epileptics carbamazepine and phenytoin also appear to affect the pituitary–gonadal axis *(27,28)*.

Anti-androgens are an obvious cause of ED. Leuprolide, goserelin, flutamide, and bicalutamide are common examples of medications with a primary anti-androgen mechanism. It is also important to consider medications with secondary anti-androgen effects, such as spironolactone, cimetidine, and ketoconazole.

A vast array of medications has been implicated in the etiology of ED. When possible, it is better to use an alternative with a lesser probability of causing ED for men who are interested in maintaining sexual activity. Staying alert to the development of ED in a patient after prescribing a medication that has the potential of causing ED is beneficial for earlier recognition and avoidance of iatrogenic ED.

Lower Urinary Tracts Symptoms. Recent studies have shown a correlation between obstructive voiding difficulties and diminished erectile function *(31)*. Speculation suggests that lower urinary tract symptoms and ED may both derive from age-related smooth muscle dysfunction *(32)*. This finding remains to be proven, and it is unclear whether treating urinary symptoms improves ED. Therefore, inquiry into the presence or absence of voiding difficulties is presently of uncertain value to the work-up of ED.

Psychological Causes. A psychosocial evaluation is important in identifying psychogenic reasons for a patient's complaint of ED. Both depression and antidepressants can affect erectile function. Caution must be exercised when attributing ED to depression, because problems with sexual function can actually be a cause of depression. Psychogenic ED should be a diagnosis of exclusion in all but the most clear-cut cases. Marital discord or other disturbances to emotional relationships sometimes cause ED. A clue from the history may be the onset of the patient's ED. The onset of psychogenic ED tends to be more sudden, whereas the onset of organic ED tends to be more insidious *(33)*.

Many chronic diseases and their treatments, such as chemotherapy for malignancy *(34)*, can contribute to organic ED and also have a profound effect on self-image, resulting in diminished sexual and erectile function. Addressing these issues in addition to the organic cause of ED may have a beneficial effect.

Physical Exam

A physical exam should be performed on all patients and may provide insight into the cause of the patient's ED. The exam may reveal unexpected findings but is more likely to confirm suspicions suggested by the history.

The clinician should take a resting blood pressure prior to the exam. Body habitus and general virilization should be noted. The clinician should examine the penis for the presence of a Peyronie's plaque. The scrotal contents should be checked, although anything other than remarkably small testes is most likely not contributory because a normal serum testosterone may be found even in men with marked atrophy of the testes. Biothesiometry, which evaluates vibratory sensation on the penile shaft and glans with a small hand-held device (*see* Fig. 1), measures the integrity of the sensory innervation of the penis. Sensation and motor strength of perineum and lower extremeties should be evaluated to check for possible spinal compression. The bulbocavernosal reflex may be checked to assess the sacral reflex.

It has been our experience that diminished femoral and/or popliteal pulses is the most commonly useful physical finding. This finding suggests that vascular disease, specifically arterial insufficiency, is the likely cause or at least has a role in the patient's ED. If these large vessels have diminished pulsatility, it is likely that the cavernosal arteries, which are 0.5 to 1.0 mm in diameter, are also compromised.

Laboratory Testing

Controversy exists regarding what constitutes adequate and cost-effective laboratory testing for ED, particularly regarding hormonal evaluation (which is discussed in more depth in Chapter 6). Besides endocrine testing, a reasonable laboratory evaluation includes a basic metabolic profile, urinalysis, and a fasting blood glucose level and lipid profile. These tests may reveal an underlying cause, such as poor renal function, diabetes, or dyslipidemia. In fact, as many as 12 to 16% of men presenting for ED evaluation have been found to have undiagnosed abnormal glucose levels *(35,36)*.

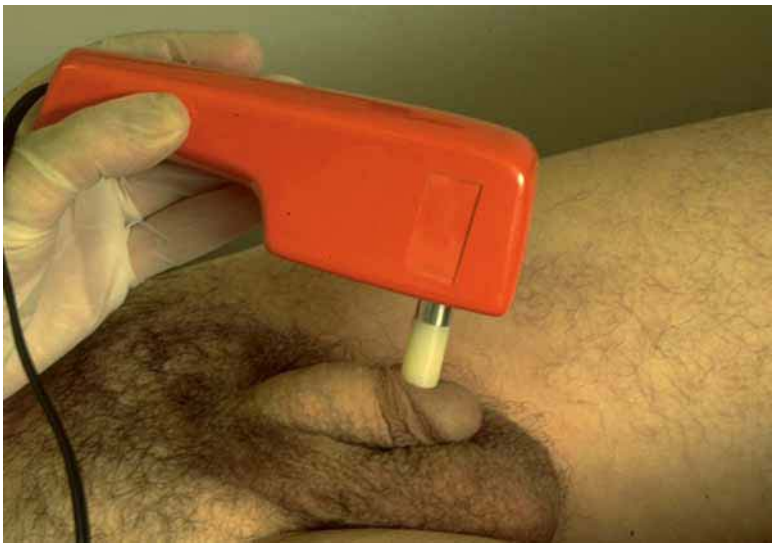

Fig. 1. A biothesiometer for assessing penile sensation.

ADDITIONAL TESTING

If the history, physical exam, and laboratory values fail to establish the probable etiology of the patient's ED, then additional testing may be warranted. Patients who have failed PDE-5 inhibitor therapy may also require and benefit from additional testing to more completely establish the cause of their ED and direct subsequent treatment.

Vascular Evaluation

Penile erection is a fundamentally vascular event, although neural inputs are necessary to trigger the vascular response. Normal vascular function leading to erection involves sufficient arterial inflow, corporal smooth muscle relaxation allowing sinusoidal filling, and trapping of blood within the corpora. The penile blood supply derives from the paired internal pudendal arteries that originate from the internal iliac arteries. Often, additional penile blood flow comes from an accessory pudendal artery branching from the external iliac artery. The internal pudendal artery gives rise to the common penile artery, which then branches into the spongiosal, cavernosal, and dorsal penile arteries. The cavernosal arteries supply the corpora cavernosa (the primary erectile bodies), and the dorsal penile and spongiosal arteries supply the glans and corpus spongiosum, respectively. The cavernosal arteries course slightly off-center through each corporal body and are the origin of the intrapenile helicine arteries, which fill the endothelium-lined sinusoidal spaces inside the corpora. Collaterals—especially those between the dorsal and cavernosal arteries—are present in most men. Variability of vascular anatomy, such as a unilateral origin of both cavernosal arteries, is also quite common *(37)*. Venous drainage begins with channels inside the corpora that coalesce into emissary veins. These veins perforate the tunica albuginea and join the deep dorsal penile vein, which also drains the glans. Venous drainage of the proximal corpora travels through the cavernosal and crural veins. During erection, sinusoidal filling, which results from trabecular smooth muscle relaxation, compresses the venous channels inside the corpora and limits flow through the emissary veins, thereby diminishing venous outflow and sustaining erection.

The knowledge of the specific physiological mechanisms responsible for normal erectile function has been established only in the past 20 to 30 yr. The awareness of the mechanisms of arterial and corporal smooth muscle relaxation, sinusoidal filling, and resulting venous occlusion has allowed tests to be developed that are able to assess the various aspects of penile vascular function. Vascular insufficiency is the most common cause of organic ED *(38)*, and, therefore, vascular evaluation has a particularly important role in the assessment of ED. Vascular insufficiency is divided into arterial and venous insufficiency. Arterial insufficiency describes poor inflow, usually from atherosclerotic disease or traumatic disruption of arterial supply. Venous insufficiency (leakage) describes the inability to trap blood within the corpora, either because of the presence of aberrant venous channels or because of an intrinsic tunical or smooth muscle abnormality. Persistent venous leakage resulting from insufficient sinusoidal filling and compression of venous channels is more often to the result of arterial insufficiency or incomplete smooth muscle relaxation rather than a primary veno-occlusive abnormality.

Intracavernosal Injection and Stimulation Test

The first test used to assess a patient's response to pro-erectile stimuli is often an intracavernosal injection of vasoactive medication combined with erotic and manual self-stimulation (combined injection and stimulation [CIS] test). Papaverine (30–60 mg), phentolamine (1–2 mg), and alprostadil (prostaglandin E_1, 10–20 μg) have been used alone or in combination. The purpose of the medications, in combination with erotic stimuli, is to cause maximal corporal smooth muscle relaxation and overcome inhibitory adrenergic input from the sympathetic nervous system *(39,40)*. To decrease sympathetic inhibition, the setting for any test that evaluates erectile function should minimize anxiety. Therefore, dim lighting, audiovisually stimulating materials, and privacy are helpful. Using a 27- or 30-gauge needle to inject the medication at the lateral aspect of the base of the penis limits pain and lessens the chance of injury to the neurovascular bundle, which travels along the dorsum of the penis.

CIS testing is a safe and minimally invasive method of determining the relative overall integrity of the vascular system of the penis, although priapism requiring injection of a vasoconstricting agent such as phenylephrine is an occasional side effect. A normal response to intracavernosal injection, which may require one or two repeat administrations of medication, indicates that the patient should be offered oral PDE-5 inhibitor therapy. A normal response also suggests that injection therapy is a therapeutic option if oral therapy fails. This study does not discriminate between psychogenic, vasculogenic, and neurogenic ED *(41)*.

After a normal response to injection, a patient may be satisfied that he can achieve normal erections, albeit with the aid of medication. If the patient is not interested in determining the specific cause of his ED, no further testing is necessary. In the case that a patient is interested in elucidating the etiology of his ED, or in the event of an abnormal response to injection, additional information is needed. An abnormal response to intracavernosal injection can be caused by extreme anxiety, moderate-to-severe arterial insufficiency, and/or veno-occlusive dysfunction. Without additional testing, the specific cause cannot be identified from CIS testing alone.

Penile Color Duplex Doppler Ultrasonography

Penile color duplex Doppler ultrasonography (CDDU) combined with an intracavernosal injection and erotic stimulation is relatively noninvasive and is significantly more

informative than injection alone. It directly assesses the arterial supply and indirectly measures veno-occlusive function. Using established parameters, patients are categorized as having normal or abnormal arterial or venous flow velocities, and the findings from CDDU correlate well with findings from penile angiography *(42,43)*.

The cavernosal arteries are evaluated at the base of the penis, preferrably from the ventrolateral position. CDDU allows the ultrasonographer to directly image the cavernosal arteries, thus preventing inadvertent evaluation of the dorsal penile arteries. This marks a significant improvement over earlier Doppler evaluations of penile blood flow, such as the penile–brachial index *(44)*. The imaging component of CDDU also allows for measurement of the change in cavernosal arterial diameter in response to intracavernosal injection. Abberant vasculature or tunical plaques may also be visualized by CDDU.

Penile blood flow during tumescence and erection changes with time, and this has important implications in CDDU testing *(45,46)*. Early in the erectile phase, cavernosal artery systolic velocities are high, but they taper as the cavernosal bodies engorge and intracavernous pressure rises, increasing resistance to flow. Similarly, diastolic arterial flow is also higher during early cavernosal filling and falls as intracavernous pressure increases. Arterial diastolic inflow serves as a proxy measurement for venous outflow during CDDU *(47)*.

A 10-MHz probe is used to measure the cavernosal artery peak systolic flow velocity (PSV) and end diastolic flow velocity (EDV). The timing of measurement is crucial. The arterial flow should be measured during the tumescent phase before full rigidity is achieved, typically at around 3 to 5 min after intracavernosal injection (Fig. 2; ref. *38*). If arterial systolic flow is measured too late (i.e., when full penile rigidity has already been achieved), then the PSV will be low, giving the false impression of arterial insufficiency. Conversely, if the arterial diastolic flow is measured too early (i.e., before full rigidity is achieved), then the EDV will be high, giving the false impression of venous leakage. Therefore, correlating the PSV and EDV values with a direct assessment of the patient's erection is absolutely necessary to ensure valid measurements.

A cavernosal artery PSV of 25 to 30 cm/s is typically used as a cut-off for normal arterial inflow, and an EDV above 5 cm/s is considered by most authors to be indicative of venous leakage *(38,43,48,49)*. Asymmetry of cavernosal arterial flows may suggest the presence of vascular disease *(50)*. Unlike intracavernosal injection testing, useful information may be obtained from patients who fail to achieve a rigid erection during CDDU. Some have low PSV values in this setting, whereas others fall into the normal range. A poor erection and a low PSV is indicative of arterial insufficiency, but a poorly sustained erection with a normal or high PSV and an elevated EDV may indicate venous leakage (*see* Fig. 3).

CDDU has several advantages compared with penile angiography. Because it is less invasive than angiography, CDDU has a much lower risk of complications. It is also less painful and, therefore, limits anxiety, which increases sympathetic inhibition of smooth muscle relaxation. CDDU is a better functional test because it allows quantification of penile blood flow that is more easily correlated with the response to intracavernosal injection. However, there are disadvantages to CDDU. Results are operator-dependent, and assessment of venous insufficency is indirect because venous outflow is not directly observed.

Dynamic Infusion Cavernosometry and Cavernosography

Dynamic infusion (pharmaco)cavernosometry and (pharmaco)cavernosography (DICC) is a somewhat invasive radiological study primarily used to assess the integrity of the veno-occlusive mechanism in a patient who complains of ED. It is usually reserved

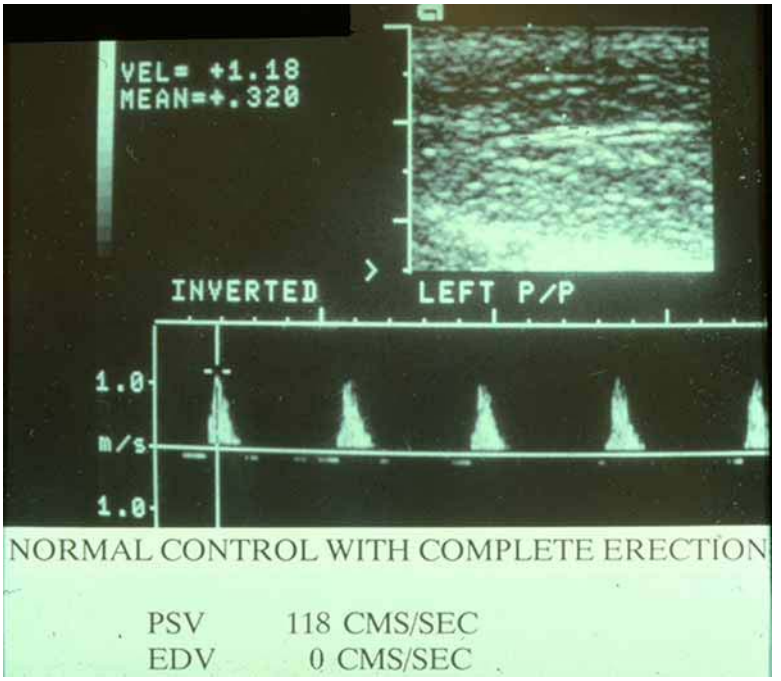

Fig. 2. Normal duplex ultrasound results with a normal peak systolic and end diastolic flow velocities.

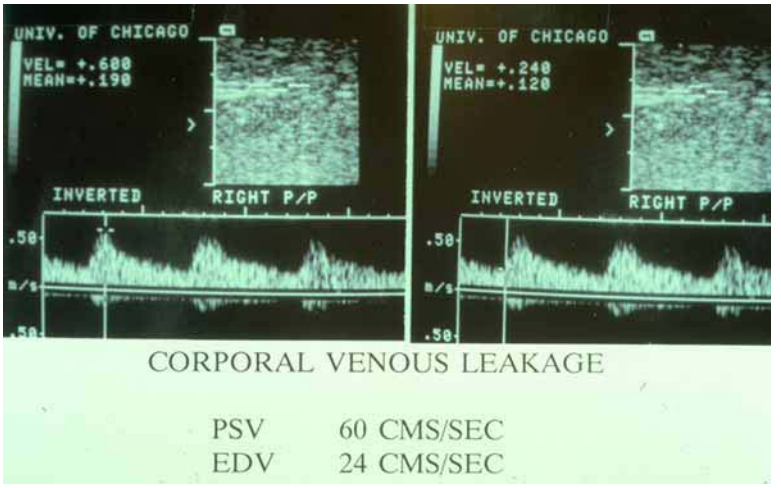

Fig. 3. Abnormal duplex ultrasound results from a man with venous leakage showing a normal peak systolic flow velocity and an elevated end diastolic flow velocity.

for patients that have characteristics of primary veno-occlusive dysfunction or for men in whom vascular reconstruction is being considered, particularly after trauma. Characteristics that suggest venous leakage include elevated EDVs in the presence of good arterial inflow on duplex ultrasound examination or a history of rapid detumescence after achieving a rigid erection. Cavernosometry allows for the quantification of various measures of veno-occlusion. Cavernosography provides visualization of the venous channels responsible for veno-occlusive dysfunction, including abnormal superficial dorsal,

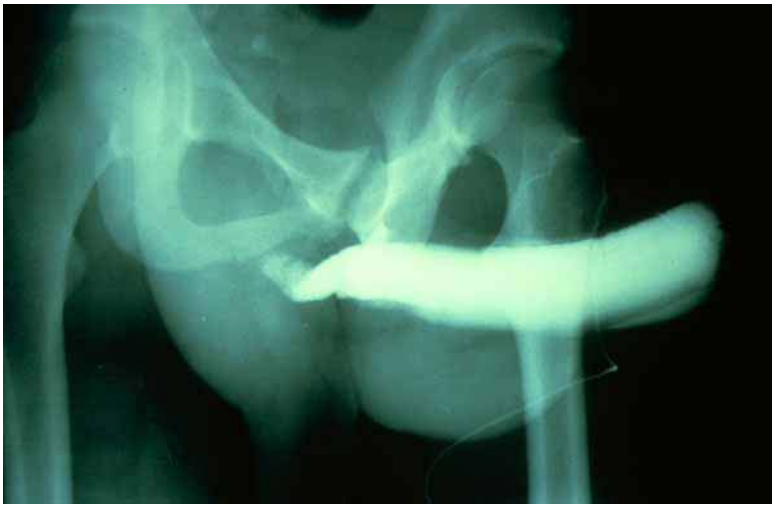

Fig. 4. A normal cavernosogram.

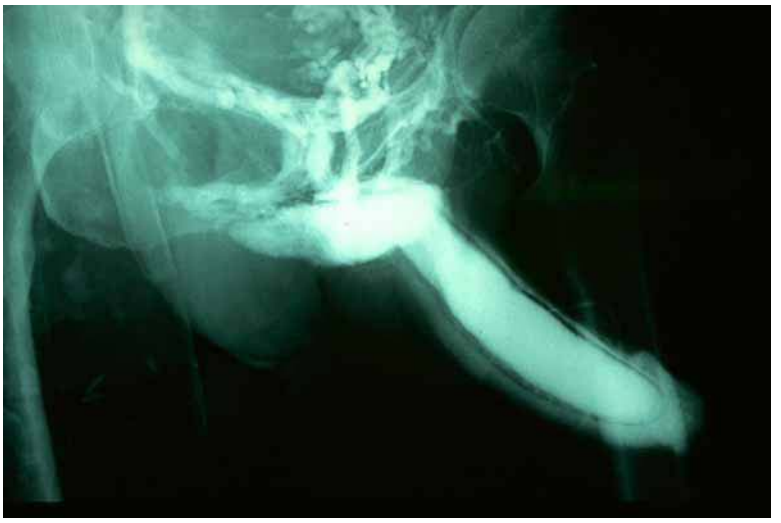

Fig. 5. An abnormal cavernosogram showing massive venous leak. Note the visualization of the glans, spongiosum, and deep dorsal penile and pelvic veins.

deep dorsal, cavernosal, and crural venous drainage or drainage from aberrant veins, if present (*see* Figs. 4 and 5).

Like most tests that assess erectile function, intracavernous infusion of papaverine is used to elicit maximum corporal smooth muscle relaxation. This is particularly important in DICC testing, because veno-occlusion absolutely depends on sinusoidal dilation and filling. Insufficient smooth muscle relaxation, either from primary smooth muscle dysfunction or anxiety, is the major cause of false-positive DICC testing *(51,52)*. The vasodilator is infused through a 21-gauge butterfly needle placed into one of the corpora. A second 21-gauge needle is placed into the contralateral corporal body for manometric monitoring. If an erection is not achieved following papaverine infusion, then normal saline is infused at a progressively higher rate until a rigid erection (approx 100–150

mmHg) is achieved. Once measurements have been obtained, dilute contrast is infused and radiographs are taken to visualize the routes of abnormal venous drainage. Visualized venous outflow should be minimal when intracorporal pressures are elevated to values typical of an erection (⊕80 mmHg), unless veno-occlusive dysfunction is present *(53)*.

The measure derived from DICC that is most commonly used to assess cavernosal veno-occlusive function is "flow-to-maintain" infusion rate. The flow-to-maintain rate is the rate at which the solution is infused after erection has been achieved to maintain the intracorporal pressure between 90 and 100 mmHg. Widely varying normal values have been reported, ranging from 3 to 30 mL/min *(54–57)*. Additional measures are also used to assess veno-occlusive function. If venous leakage is present, the infusion rate necessary to first achieve erection may be elevated. The 30-s decompression rate assesses the loss of intracavernous pressure in the first 30 s after the infusion is stopped upon reaching the intracorporal target pressure (~150 mmHg) and is greater if veno-occlusion is abnormal. The postinfusion equilibrium pressure is the plateau pressure inside the corpora after the infusion of saline is stopped and is lower with abnormal venous leakage.

It is accurate to say that patients with a primary veno-occlusive disorder have higher flow-to-maintain rates *(58)* and more rapid decompression and lower equilibrium pressures than patients without a venous leak *(54)*. However, cutoff values have not been established to identify those patients who will benefit from venous ligation procedures to treat venogenic ED. Additionally, some normal potent men have been shown to have venous outflow during erection that can be visualized during cavernosography *(57,59)*. These findings, coupled with the often disappointing results of penile vein ligation surgery, have led to the conclusion that many men with identifiable venous leakage during DICC have veno-occlusive dysfunction secondary to an intrinsic corporal abnormality, rather than primary venous leakage *(52,60,61)*. Consequently, DICC testing has diminished in importance as part of the vascular evaluation of impotent men.

Penile Angiography

Penile (pharmaco)angiography is the gold standard for evaluation of the penile arterial blood supply and serves as the basis for validation of duplex ultrasound evaluation of penile blood flow. Currently, penile (pharmaco)angiography is not commonly performed because of its invasiveness compared to the other readily available tests. Nevertheless, angiography has a role in selected situations for the evaluation of a man with suspected vasculogenic ED, particularly in patients with posttraumatic ED who are candidates for revascularization.

The procedure involves selective catheterization of the internal pudendal artery by a catheter introduced into the femoral artery. Intra-arterial and intracavernosal injections of a vasodilating agent are used to dilate the distal portion of the penile vascular tree. Visualization of the intrapenile arteries is best during the tumescent phase of erection *(62)*. In atherosclerotic disease, lesions are typically seen in the internal pudendal artery and at the base of the penis *(63,64)*. Lesions from pelvic and perineal trauma often are found at the root of the penis near the urogenital diaphragm, although more distal lesions from penile injury have been described (*see* Fig. 6; refs. *23, 63,* and *64*).

Angiography has numerous limitations partly resulting from its invasiveness and the setting in which it is conducted. Anxiety and pain increase sympathetic tone, limiting cavernosal smooth muscle relaxation. Angiography is primarily an anatomic mapping study rather than a functional test, therefore it is well-suited to the discovery of discrete traumatic lesions that may be repaired or bypassed during revascularization.

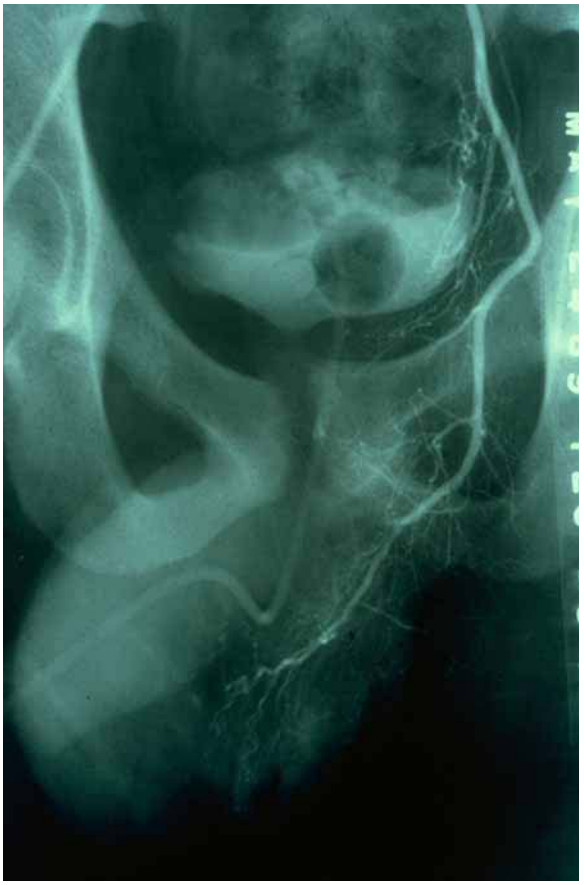

Fig. 6. A right penile arteriogram after a pelvic fracture. Note the nonvisualization of the right common penile artery. Only a scrotal branch from the internal pudendal artery is opacified.

Neurological Evaluation

Neural input to the vascular components of the penis is necessary for spontaneous erectile activity and is mediated by the cavernosal nerves, which are branches from the pelvic plexus and contain autonomic fibers. Somatic sensory afferent signals are carried from the dorsal penile nerves to the spinal cord by the internal pudendal nerves. The dorsal penile nerves do not directly affect erectile tissue but may play an important role in maintaining erection during sexual activity by generating pro-erectile signals from the central nervous system (CNS; ref. *65*). Their dysfunction may result in a poorly sustained erection. Injury or dysfunction of either set of nerves from trauma or chronic disease such as diabetes can severely affect erectile function. Control of ED by the CNS can also be affected by acute injury from stroke and spinal cord injury or by chronic conditions such as Parkinson's disease or MS.

Specific neurological evaluation is not routinely performed beyond the neurological component of the physical exam. This is largely because findings from neurological evaluation often do not change subsequent management of ED. In fact, patients with a neurological etiology for ED often have excellent responses to vasoactive injection therapy because the vascular bed is intact. The same situation exists in men with psychogenic ED, and the two may present in a similar manner. If the history does not distinguish between

Fig. 7. A Rigiscan® Plus device.

these two possible causes, neurological testing may be valuable. Neurological testing is also useful in other specific situations, such as in research and medico–legal disputes.

Nocturnal Penile Tumescence and Rigidity Monitoring

Nocturnal penile tumescence and rigidity monitoring (NPTR) is a noninvasive method to determine whether a patient has nocturnal erections. It is not specifically a neurological test, but it is well-suited to distinguish between neurogenic and psychogenic ED, because both sets of patients often have normal vascular responses to intracavernous injection. Men with a psychogenic etiology for ED should demonstrate normal or near-normal nocturnal erectile patterns, whereas men with a neurological cause should have abnormal patterns.

The RigiScan® device is the most commonly used method for the ambulatory measurement of nocturnal erectile activity (*see* Fig. 7). It consists of two loop-strain gages placed at the base and the tip of the penis that are attached to a recording device worn on the leg during sleep. The device measures spontaneous increases in penile circumference (tumescence); during an erectile event, it applies a radial force to the erect penis and measures its rigidity as a percentage of a standard noncompressible rod. The recording device is capable of detecting the degree and duration of increases in tumescence and rigidity compared to baseline (*see* Fig. 8). Measurements are typically taken over two or three nights because patients with documented normal erectile function have been shown to have abnormal results during a single night of testing but have normal results with repeated monitoring *(66)*. Patients should not drink alcohol or use sedatives or other sleeping aids during testing.

The results of NPTR may be evaluated with different methodologies. The least complex method classifies men as normal if they have an erection with 70% rigidity for at least 5 min *(67)*. A more sophisticated method integrates the degree of rigidity and tumescence with the duration of erectile events over the course of a night *(66)*. Each night's erectile activity is described by rigidity activity units and tumescence activity units at the penile base and tip. When nocturnal erections have been monitored over several nights, the best tip rigidity activity units scores are used. The scores can be assessed by a nomogram that allows the patient's scores to be expressed as percentiles compared to a normal population.

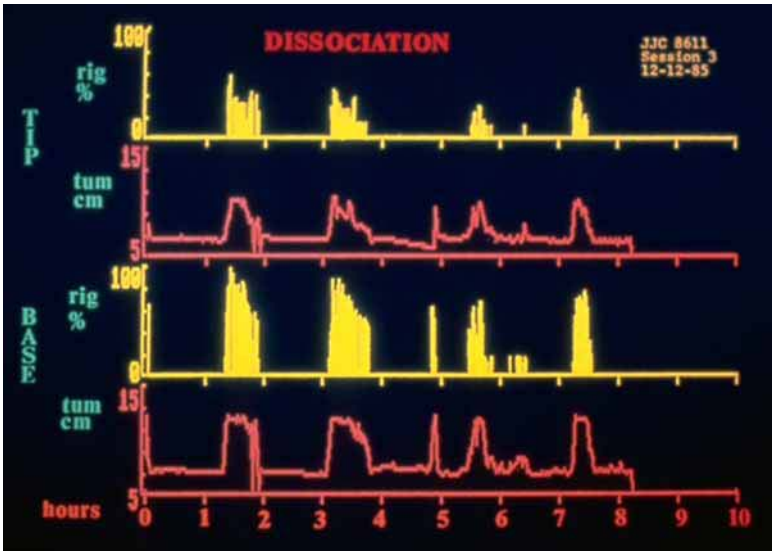

Fig. 8. A graph showing nocturnal penile tumescence and rigidity monitoring results in a normal male.

NPTR is best used to differentiate between organic and psychogenic ED, although patients with penile sensory deficits may have normal NPTR results *(68)*. NPTR does not reliably distinguish between the various organic etiologies, and other tests are necessary when psychogenic ED has been ruled out.

Neurophysiological Testing

Several other neurophysiological tests have been developed to identify neurological deficits in men with ED. They are typically reserved for patients who have exhibited abnormalities on physical exam and biothesiometry. The tests assess the function of the afferent and efferent neural tracts involved in erection.

Evoked potentials (EPs) are used to assess the pudendal somatosensory nerve signals originating in the dorsal penile nerves and carried to the CNS by the pudendal nerves *(15, 65,68)*. The time it takes for a signal from an electrode on the penis to be detected in the CNS is measured. Delayed or absent EPs indicates either central or peripheral neuropathy *(65,68)*. MS is a common cause for a CNS process to trigger ED that demonstrates EP abnormalities *(15,16)*. In sacral reflex testing, the time it takes for a signal from an electrode on the penis to elicit an anal sphincter contraction is measured. Sacral reflex testing specifically assesses peripheral nerve function. If sacral reflexes are normal but EP testing is abnormal, then the lesion can be localized to the CNS because central pathways are more extensively involved in EPs than in sacral reflexes. The presence of abnormalities in both tests suggests peripheral neuropathy with or without CNS dysfunction *(65,68)*.

Although methods for direct assessment of the cavernosal nerves are not available, corpus cavernosum electromyography has been used to detect differences in electrical activity of the corporal smooth muscle between men with and without ED *(69–71)*. Measurable differences appear to exist, with potent men tending to show decreased corporal electrical activity during erection and men with ED having persistent electrical activity. These differences may result from disrupted autonomic neural input or an intrinsic abnor-

mality of the corporal smooth muscle. Differing patterns of corpus cavernosum electromyography may be able to distinguish specific causes of smooth muscle dysfunction *(69–71)*.

Neurophysiological testing is not common for many reasons. It requires specialized equipment and techniques and, therefore, is expensive and not widely available. Many patients with neurogenic ED often have a diagnosed neurological condition, such as MS, that predicts abnormal neurophysiological test results. Finding neurophysiological abnormalities in these patients does not change management of their ED. In one study, neurophysiological abnormalities in patients with MS did not correlate with the presence or absence of ED *(15)*. Neurophysiological testing also does not appear to offer the possibility of detecting occult systemic neurological processes *(68)*. Until specific therapies are available for men with neurological ED, neurophysiological testing will remain primarily a research tool.

HEALTH BENEFITS OF ED EVALUATION

Determining the specific cause of ED in each patient does not necessarily alter treatment, because vasculogenic, neurogenic, and psychogenic ED each frequently respond to PDE-5 inhibitor or vasoactive injection therapy. Identifying the cause of ED offers the chance of diagnosing systemic conditions that may severely affect a man's health and longevity *(72)*. Accumulating evidence suggests that ED may predict the presence of coronary artery disease in asymptomatic men. In one study of 300 consecutive men presenting to an emergency department with chest pain, two-thirds of the patients reported symptoms of ED preceding diagnosis of coronary artery disease by an average of more than 3 yr *(73)*. Others have suggested that ED may serve as a useful marker for coronary artery disease in diabetic patients without symptoms of myocardial ischemia *(74)*. Additionally, arterial insufficiency found on CDDU has been shown to correlate with ischemic heart disease *(75)*. Other studies have demonstrated that ED is the presenting sign of type 2 diabetes mellitus in up to 12% of patients with the disease *(35,36)*.

CONCLUSION

In the evaluation of ED, no single test provides all of the information necessary to determine the cause. Rather, the patient history suggests the likely etiology and provides the context in which test results should be interpreted. It is also important to remember that different causes of ED can co-exist, which can make interpretation of test results difficult. Vascular disease is the predominant cause of ED, but neurological, endocrinological, and psychogenic causes should be considered. A reasonable and cost-effective approach is to conduct a thorough history and physical exam with basic laboratory testing. In instances where ED is not explained by findings from this initial work-up or when patients request a more detailed investigation, results from additional testing may provide an explanation for ED. In some men, determining the cause of ED may also identify serious systemic processes that have ED as their initial manifestation.

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12 Oral Therapy for Erectile Dysfunction

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SUMMARY

Oral medications are first-line treatment for erectile dysfunction (ED). They are attractive to patients and physicians because of the ease of use and discrete nature of delivery compared with other treatment options. Among all the treatments for ED, the oral agents have been the most rigorously studied. Effective oral therapy for ED was first introduced in 1998 with the approval of the first phosphodiesterase type 5 inhibitor, Viagra®, and was soon followed by vardenafil (Levitra®) and tadalafil (Cialis®) in 2003. Oral pharmacotherapy has important considerations, including time to onset, food interactions, duration of action, drug–drug interactions, systemic side effects, and clinical efficacy. This chapter focuses on the efficacy of oral pharmacotherapy for the treatment of ED and includes discussions on historical treatments, homeopathic remedies, drug discovery, pharmacology of phosphodiesterase type 5 inhibitors, pharmacokinetics and dynamics, clinical trials experience, and future directions.

Key Words: Phosphodiesterase type 5; sildenafil; vardenafil; tadalafil; erectile dysfunction; pharmacotherapy; oral medications.

INTRODUCTION

Effective oral therapies are the most recent treatment option for erectile dysfunction (ED). The oral therapeutic route for the treatment of ED is one that is met with little resistance from patients and physicians because of the benign nature of delivery. Compared with existing alternative treatments, it is the most effective noninvasive therapy.

The ideal oral agent should be well-tolerated, maximally efficacious, and easily complied with; it should also provide rapid response and have no drug–drug interactions or systemic side effects. This chapter provides the background in oral therapies and focuses on the phosphodiesterase (PDE)-5 inhibitors, their unique properties, and the vast clinical experience.

HISTORY

Oral remedies to enhance sexual function were described even as early as medicinal therapies existed. Earliest reports have been with various Chinese herbal remedies. In

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the United States, the goal of earlier therapies focused on sexual drive and hormonal modulation ("aphrodisiacs").

In the late 1960s, Afrodex® (a combination of methyltestosterone, strychnine, and yohimbine) was widely used and was later withdrawn by the Food and Drug Administration (FDA) because of efficacy issues. Yohimbine, derived from the bark of the Yohim African tree, has shown to be an inhibitor of monoamine-oxidase and acts centrally. Although studies have shown response in psychogenic ED, the 1996 American Urology Association Guidelines advised that Yohimbine was no better than placebo *(1)*.

In 1973, Rytter described the combination of bamethan sulfate, synephrine, and coffeinum purum for the treatment of "impotentia erectionis" *(2)*. In the late 1970s, L-dopamine was examined.

Trazadone, known for its association with priapism, works both centrally and peripherally as an antidepressant. Several studies have shown an effect on nocturnal and sexually stimulated erections, although these have had marked sedative effects *(3)*. Oral prostaglandin E_1 has also been a candidate. Apomorphine (Uprima®), approved in Europe, is a centrally acting dopaminergic agonist. This agent was developed with a unique sublingual delivery system, but in 2000, it was voluntarily withdrawn from FDA review *(3)*. Phentolamine mesylate (Vasomax®), an α-adrenergic blocking agent, was also withdrawn secondary to toxocological issues.

The modern era of PDE-inhibitor-based oral therapy did not begin until 1998, with the introduction of sildenafil (Viagra) to the US market. In 2003, Vardenafil (Levitra) and tadalafil (Cialis) were subsequently introduced in the United States.

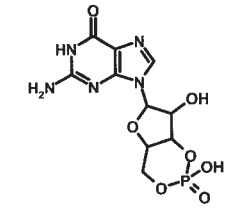
SCIENTIFIC DISCOVERY

Similar to many useful medicinal treatments, the discovery of the class of agents was serendipitous. Initially focused on developing an effective anti-angina treatment, scientists at Pfizer Pharmaceuticals quickly discovered the unique properties of the type 5 subtype of PDE inhibitors. Furthermore, the discovery of the importance of nitric oxide (NO) in the sexual stimulation pathway by Ignarro and Rajfer helped define the physiology of penile vascular smooth muscle relaxation *(4)*. In 1998, the first PDE-5 inhibitor approved by the FDA was sildenafil citrate (Viagra).

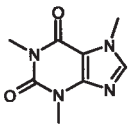
PHARMACOLOGY OF PHOSPHODIESTERASE INHIBITORS

To understand why PDE inhibitors are effective in treating ED, one must be familiar with the mechanism of tumescence. Penile erection is achieved through a complex pathway triggered by tactile or psychogenic stimulation, resulting in arterial and smooth muscle relaxation within the penis. NO has been identified as a critical signal and prerequisite in the tumescence pathway. NO is synthesized in nerve terminals of the autonomic pathway and endothelial cells of blood vessels and cavernosal lacunar spaces. NO activates soluble guanylate cyclase of smooth muscle cells (SMCs), which results in increased intracellular cyclic guanosine monophosphate (cGMP) levels; cGMP is responsible for SMC relaxation in the corporal bodies and penile arterioles *(5)*. PDEs are responsible for intracellular degradation and hydrolysis of cGMP. Figure 1 shows the complex pathway of tumescence and roles of NO and PDE-5.

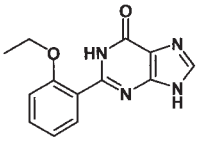
The enzyme PDE is responsible for catalyzing the hydrolysis of cGMP and/or cyclic adenosine monophosphate, both of which are effective cellular signaling pathways. As a family, 11 different PDEs have been described. PDE-mediated medications have been used to treat a broad array of conditions, including asthma, cardiovascular diseases, and ED.



cGMP
Substrate of PDE5



Caffeine



Zaprinast
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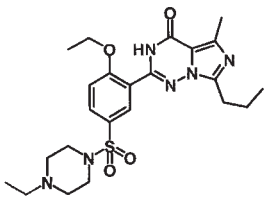
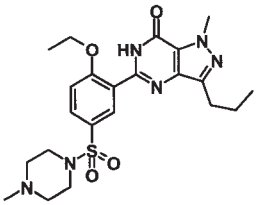
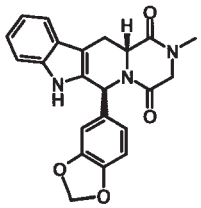


Vardenafil



Sildenafil



Tadalafil

Fig. 1. Chemical structures of the phosphodiesterase type 5 (PDE-5) inhibitors that have been developed—caffeine, zaprinast, sildenafil, vardenafil, and tadalafil—and the PDE-5 substrate, cyclic guanine monophosphate. cGMP, cyclic guanosine monophosphate; PDE-5, phosphodiesterase type 5. (From ref. *4*.)

Table 1
Comparison of Selectivity Ratios of PDE-5 Inhibitors

PDE family	*Sildenafil*	*Vardenafil*	*Tadalafil*	*Tissue distribution*
PDE-1	80	257	>10,000	Brain, lung, heart, VSMC
PDE-2	>7500	>10,000	>10,000	Brain, heart, liver, adrenal, CC, olfactory
PDE-3	4400	3600	>10,000	Heart, lung, liver, pancreas
PDE-4	1800	5700	>10,000	Immunocytes, lung, brain
PDE-5	1	1	1	VSMC, SMC, lung, CC, platelets
PDE-6	10	224	780	Retina
PDE-7	5160	N/A	>10,000	Skeletal muscles, T-cells
PDE-8	>10,000	N/A	>10,000	Testes, ovary, intestine
PDE-9	2796	N/A	>10,000	Liver, kidney
PDE-10	1123	447	>10,000	Brain, testes
PDE-11	346	03	5.5	Testes, brain, CC, skeletal muscle, prostate

Data from refs. *6* and *10*.
SMC, smooth muscle cell; VSMC, vascular smooth muscle cell; CC, corpus cavernosum.

Twenty-one PDE genes have been identified, resulting in more than 60 different PDE enzymes classified into 11 families. The primary tissue distribution of receptor subtypes has been well-described (Table 1). Notably, PDE-5-subtype receptors are distributed throughout vascular SMCs, SMCs, lung, corpus cavernosum, and platelets. Regarding adverse effects, PDE-6 is highly specialized and is found only in photoreceptors of the retina *(6)*.

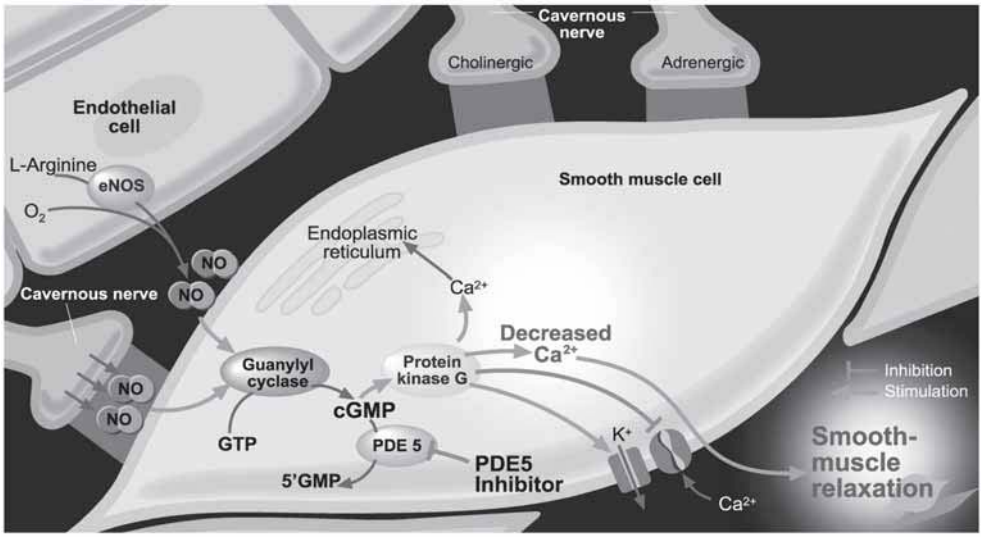


Fig. 2. Mechanism of erection, from neuronal signaling to the cellular mechanism. (From ref. *4*.)

To summarize, for PDE-5 inhibitors to improve and achieve erections, there must be an intact neuronal pathway that induces a minimal NO response for cGMP turnover *(5)*. Figure 2 reveals the importance of neural initiation.

PHARMACOKINETICS AND PHARMACODYNAMICS: DOSING ISSUES AND LIMITATIONS

As selective inhibitors of the enzyme, PDE-5, sildenafil, tadalfil, and vardenafil each have unique properties reflective of their chemical composition. Changes in side-chain structures can allow essentially identical structures to behave and react differently in vivo. Figure 3 shows the chemical structures of the PDE-5 inhibitors developed to date.

Acting systemically, PDE-5 inhibitors not only work on penile smooth muscle vasculature but also on arterial and venous smooth muscles throughout the body. Consequently, men using organic nitrates or other NO donors are prohibited from the concomitant use of PDE-5 inhibitors because of the potential for significant drops in systemic blood pressure *(6)*.

Potency and selectivity of PDE-5 differ and may not necessarily result in differences in clinical efficacy. Potency is a measure of affinity to a receptor at a given concentration; more potent drugs require less dosing/concentration. Selectivity is the concentration needed to inhibit PDE-5 compared to the other PDE subtypes. Theoretically, these measures may affect adverse effects. Compared in the same assay, vardenafil is most potent and selective, followed by sildenafil and then tadalfil *(8–11)*.

The three major clinical considerations with the currently available PDE-5s are onset of action, efficacy, and duration. Regarding objective parameters, the maximal plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and half-life can be directly compared. These values do not necessarily equate with clinical effects (*see* Table 2; ref. *5*) However, they serve as guidelines to help predict clinical response with daily use.

Sildenafil (Viagra)

Onset of action for sildenafil was recently clarified, and it can now be touted as the fastest-acting agent on the market. A double-blind, placebo-controlled trial of 228 men

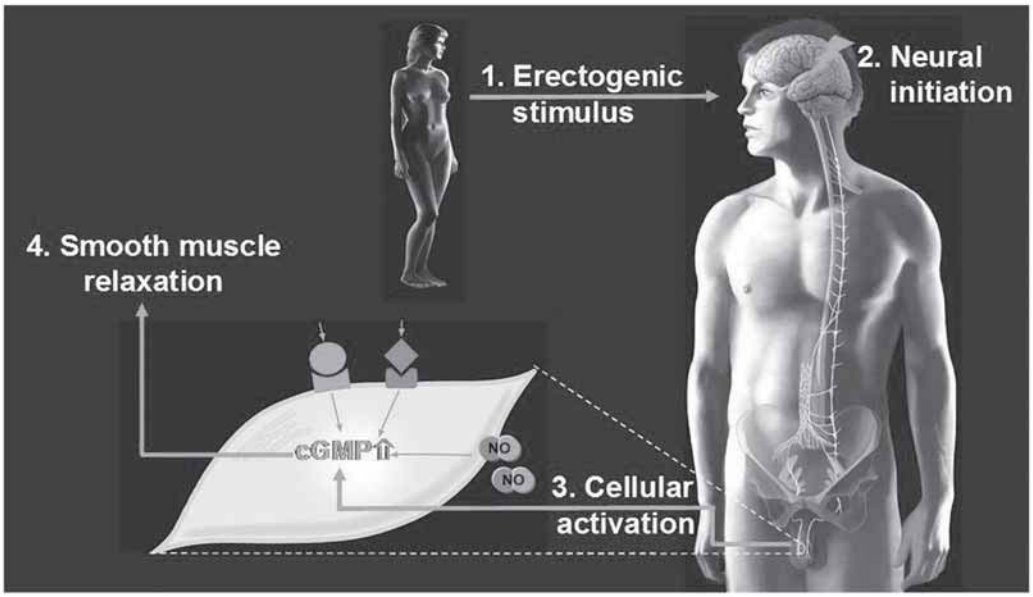


Fig. 3. Cyclic guanine monophosphate (cGMP) signaling in smooth muscle cells of corpus cavernosum and effect of phosphodiesterase type 5 inhibition on corpus cavernosum cGMP levels. eNOS, endothelial nitric oxide synthase; NO, nitric oxide; GTP, guanosine triphosphate. (From ref. *4*.)

Table 2
Comparison of Pharmacokinetic Parameters of PDE-5 Inhibitors

Indicator	*Sildenafil*[a,b]	*Vardenafil*[a,c]	*Tadalafil*[a]
T_{max} (h)	<1	<1	2
Half-life (h)	3–5	3–5	17.5
ΔC_{max} with high-fat meal (%)[d]	↓29	↓18–50	No change
Metabolism	Hepatic	Hepatic	Hepatic

[a]Data from ref. *10*.
[b]Data from ref. *13*.
[c]Data from ref. *20*.
[d]Change in maximum plasma concentration in fed (high fat) vs fasted state.

randomized to either 100 mg of sildenafil or placebo demonstrated erections sufficient for intercourse in as little as 14 min (35%), with the majority (51%) responding in 20 min *(12)*. This is significantly shorter than the previously described onset of between 30 and 60 min. Times were self-reported/self-recorded into a diary using a stopwatch. The reported half-life of sildenafil is 3 to 5 h, and the duration of action may be 8 to 12 h beyond administration. In the presence of high-fat food intake, absorption may be adversely affected *(13)*.

Tadalafil (Cialis)

Tadalafil (also known as the "weekend" pill in Europe) derived its nickname secondary to the long half-life, which has translated into clinical efficacy of 12 to 36 h after initial dosing *(14,15)*. Tadalafil is rapidly absorbed and achieves C_{max} at a median of 2 h, with a half-

life of approx 17.5 h (mean). Tadalafil absorption is unaffected when taken with food. In the presence of substantial alcohol consumption (>5 units), there is a potential for increased systemic vasodilation leading to orthostasis, dizziness, and headaches *(16)*.

Tadalafil is metabolized mainly by the cytochrome p450 3A4 (CYP3A4), and, therefore, in the presence of inhibitors of this pathway (ketoconazole), tadalafil dosing should not exceed 10 mg and should be dosed at a maximum of every 72 h *(16)*. Patients with hepatic impairment should not exceed 10 mg of tadalafil, and in the setting of hepatic failure, they should not be administered at all. Patients with moderate-to-severe renal insufficiency should not exceed 5 mg daily or 10 mg every 48 h. Although no age-adjusted dosage is required, there is an observed lower oral clearance in patients older than age 65 yr, suggesting some caution *(16)*.

Clinically, patients can expect to see onset of action as early as 16 min after administration, with maximal rigidity achieved in 45 min *(17)*. The prolonged half-life of tadalafil translates into clinically long durations of action. In one study, after oral dosing, 60 and 64% of men reported successful intercourse (Sexual Encounter Profile [SEP] question 3) at 24 and 36 h, respectively, *(14)*. An integrated analysis of 11 clinical trials with more than 2000 men confirmed the prolonged efficacy of tadalafil, with a mean successful intercourse attempt of 65.5% per patient (<60 min) to 73.4% (24–36 h) after a single dose of 20 mg *(15)*.

Vardenafil (Levitra)

Vardenafil is rapidly absorbed with T_{max} of approx 45 min and a plasma half-life of 4 to 5 h *(18)*. There is evidence of prolonged half-life and higher C_{max} levels in older men (>65 yr), suggesting a lower starting dose of 5 mg with upward titration *(19)*. Vardenafil pharmacokinetics were unaltered in the presence of a moderate-fat meal or alcohol intake (0.5 g/kg of ethanol; refs. *20* and *21*). It is metabolized by the CYP3A4 with mostly hepatic elimination. In the setting of hepatic impairment, doses need to be limited. The dose should start low (5 mg) only in cases severe renal insufficiency (CrCl < 30 mL/min).

Onset of action for vardenafil suggests clinical efficacy before T_{max} levels are achieved. Using the SEP Q3, the earliest recorded time was 10 min, with significant differences compared with placebo (25 min) after dosing *(22)*.

SAFETY PROFILE OF PDE-5 INHIBITORS

Generally, all PDE-5 inhibitors share similar adverse effects as a manifestation of the mechanism of action, including headaches, flushing, and dyspepsia. The cardiovascular profile and effects of PDE-5 inhibitors have been well-characterized by various studies. Most of the long-term data are a reflection of the first approved product—sildenafil citrate. Table 3 provides an overview of major adverse effects reported in clinical use of PDE-5 inhibitors.

Cardiovascular Effects

To summarize nearly 90 publications related to sildenafil, it is a modest peripheral dilator with a mean maximal drop in systolic and diastolic blood pressures of 8 and 6 mmHg, respectively. Sildenafil does not produce reflex tachycardia, changes in cardiac contractility, or electrophysiological cardiac conduction problems. Moreover, in normal patients, there is no significant effect on pulmonary hemodynamics *(24)*.

Table 3
Side Effects of PDE-5 Inhibitors

Drug (dose)	*Adverse event (% reporting)*
Sildenafil[a] (25, 50, 100 mg)	Headache (7–25)
	Flushing (7–34)
	Dyspepsia (1–11)
	Nasal congestion (4–19)
	Visual effects (1–6)
Tadalafil[b] (2.5, 5, 10, 20 mg)	Headache (11–14)
n = 1561	Flushing (4)
	Dyspepsia (7–10)
	Nasal congestion (4–5)
	Back pain (4–6)
	Myalgia (4–5)
Vardenafil[c] (5, 10, 20 mg)	Headache (8–17)
n = 1385	Flushing (6–13)
	Dyspepsia (2–6)
	Nasal congestion (1–8)

[a]Ref. *23*.
[b]Ref. *45*.
[c]Ref. *43*.

Of the three agents, vardenafil is associated with minor QT prolongation and, therefore, should be avoided in patients taking class IA or II antiarrhythmics and congenital QT prolongation *(25)*.

Visual Disturbances

At higher doses, sildenafil causes mild and transient visual symptoms in a minority of patients (mainly blue tinge to vision, increased brightness of lights); this results from PDE-6 isoenzyme inhibition. This PDE-6 effect has no significant acute or chronic effects in normal vision or in men with macular degeneration, diabetic retinopathy, or treated glaucoma *(26)*. Tadalafil lacks selectivity for the PDE-6 isoenzyme and, therefore, visual disturbances have not been reported *(27)*.

Recent media and attention have focused on a link between nonarteritic anterior ischemic optic neuropathy (NAION) and PDE. This is unrelated to the PDE-6 isoenzyme effects and is a phenomenon of decreased blood flow to the optic nerve that occurs in men older than 50 yr who have risk factors that mirror ED (diabetes, hypercholesterolemia, hypertension, ischemic heart disease). Pomeranz et al. *(29)* first reported this phenomenon in a two-case series of five and seven men using sildenafil. There has been no definite causal link in a review of 103 clinical trials with more than 13,000 men analyzed. The FDA currently has no specific warning, other than to seek medical help if visual changes occur while on a PDE-5 inhibitor.

Myalgias

PDE-11 inhibition with associated myalgias presenting as back pain or limb pain are unique to tadalafil. This has been reported in as many as 12% of patients in at-home studies

(16). These myalgias are not life-threatening and are not associated with rhabdomyolysis, as seen with statins.

Adverse Events Experienced in Clinical Trials and Long-Term Safety

In placebo-controlled clinical trials involving more than 7000 men, the incidence of myocardial infarction and all-cause mortality was the same between groups treated with sildenafil and placebo. Some suggested these patients were low-to-moderate risk in comorbidities and, therefore, did not reflect the majority of patients seeking therapy for ED in the general population. To address this suggestion, Shakir *(30)* reported on more than 22,000 men with ED from the National Health System in the United Kingdom and found no difference in cardiovascular morbidity or mortality compared to age-matched males.

Padma-Nathan et al. *(31)* conducted a 4-yr safety profile of sildenafil and demonstrated excellent safety. Adverse events included headache (13–16%), flushing (10%), and dyspepsia (7%). Myalgia occurred in less than 1% of men who took sildenafil *(31)*.

Data from five phase III trails of vardenafil lasting up to 26 wk were pooled in a recent analysis of safety and tolerability. Withdrawal secondary to adverse effects was less than 4%. The respective incidence of headache, flushing, and rhinitis were 15.6, 11.7, and 10.3%, respectively. Abnormal vision was reported by 11 patients (0.65%; ref. *32*).

The long-term safety of tadalafil has been assessed in an ongoing open label study of 1173 patients. Headache and dyspepsia were most frequently reported (15 and 11% respectively).

DRUG INTERACTIONS AND CONTRAINDICATIONS

The concomitant use of oral PDE-5 inhibitors with compounds of the nitroglycerin class is an absolute contraindication that has been well-demonstrated in vitro as well as in vivo. The combination results in an amplified effect on the NO–cGMP pathway, resulting in hypotension.

This is a class effect *(16,25,33)*. Because of its long half-life, tadalafil needs to be dosed at least 48 h apart from a nitrate product *(16)*.

There is evidence that α-blockers used in combination with oral PDE-5 inhibitors may cause a precipitous drop in blood pressure with clinical symptoms of orthostasis. All three agents have been cleared by the FDA for concomitant use with α-blockers, although this clearance has been with precautions. Current recommendations state that patients on α-blockers should be started on the lowest available dose of a PDE-5 inhibitor and titrated upward, and current PDE-5 users need to titrate α-blocker therapy appropriately *(16,25,33)*.

CLINICAL EXPERIENCE AND POSTMARKETING ANALYSIS

Normal, Healthy Male

In the presence of normal healthy tumescence, there is evidence that sildenafil and other PDE-5 inhibitors may shorten postejaculation refractory times. Twenty healthy male volunteers received 100 mg of sildenafil and underwent penile duplex ultrasound. There was a marked reduction of postejaculatory refractory times: 10.8 vs 2.6 min for placebo and sildenafil, respectively *(34)*. This was confirmed in a larger study of 60 men

in Italy, in which 40% (12 of 30) of patients given sildenafil subjectively reported noticeable reductions in postejaculatory refractory times compared with 13% (4 of 30) of patients given placebo *(35)*.

Moreover, there are increasing data to suggest some effect on premature ejaculation. Proposed mechanisms include modulation of the contractile properties of the vas deferens, seminal vesicles, prostate, and urethra; a state of peripheral analgesia; and prolongation of erections *(36)*. Two clinical trials have examined the use of sildenafil in combination with a selective serotonin re-uptake inhibitor for the treatment of premature ejaculation *(37,38)*. Initial results have been encouraging.

PDE inhibition has not yielded clinically detectable effects on semen parameters, hormones, or adverse effects on fertility rates in healthy males *(34,39,40)*.

Organic and Psychogenic ED

Use of PDE-5 inhibitors in the general population has demonstrated success across all objective measuring tools: erectile function domain of the International Index of Erectile Function (IIEF-EF), SEP question 2 ("Were you able to insert your penis into your partner's vagina?") and question 3 ("Did your erection last long enough to have successful intercourse?"), and responses to the Global Assessment Questionnaire. Subpopulation analyses for patients with advanced age, hypertension, coronary artery disease, diabetes, and hyperlipidemia have been reported for all three PDE-5s, with favorable results. Moreover, there are no reported differences in treatment efficacy across racial lines *(7,41)*.

Since its approval, sildenafil citrate has demonstrated long-term efficacy and safety. Carson et al. *(42)* performed a recent meta-analysis of 11 studies with a total population of approx 2667 men and demonstrated significant improvements in EF compared with placebo, regardless of age, racial background, body mass index, comorbidities, etiology, or severity or duration of ED. Only 6.7% of patients discontinued sildenafil in the 3-yr study because of treatment-related issues. Efficacy was maintained over the long term, and patient satisfaction and improvement was more than 96% *(42)*.

In patients with significant comorbidities that would suggest a poor response (such as diabetes, ischemic heart disease, or hypertension), clinical trials demonstrated good response compared to placebo *(43)*. Even in the presence of two or more antihypertensive agents, sildenafil has demonstrated statistically significant improvements in EF, SEP question 3 and question 4, improved erections, and more intercourse attempts *(42)*.

The North American Pivotal trial supported the successful use of vardenafil using a broad population of men with various comorbidities and severity of ED. This 26-wk placebo-controlled trial of 805 men examined three outcomes: EF domain score of IIEF, SEP question 2, and SEP question 3. Vardenafil was significantly better than placebo across all measures of efficacy, and patient self-reported diaries reflected the outcome *(44)*.

Multiple integrated analyses of placebo-controlled clinical trials of tadalafil have been reported. Across each measure of efficacy (EF domain, SEP questions 2 and 3, and the Global Assessment Questionnaire), tadalafil at doses of 10 and 20 mg showed significant improvements over placebo, regardless of ED severity or comorbidities *(15,45,46)*. Pooled data of 2102 men from 11 double-blind, placebo-controlled trials demonstrated efficacy over placebo in all measured domains and across all subpopulations (obesity, hypertension, diabetes, heart disease, hyperlipidemia, ethnicity, age, ED severity, ED duration, tobacco use, and prior sildenafil use; ref. *47*).

Postprostatectomy ED: Treatment and Prevention ("Rehabilitation")

Studies evaluating patients after non-nerve-sparing and nerve-sparing radical prostatectomies have reported variable rates of response. These studies are largely affected by patient age, pre-operative erection status, comorbidities, surgical technique, and post-operative recovery.

Studies have shown the highest available dose of the PDE-5 inhibitors (100 mg sildenafil, 20 mg tadalafil, or 20 mg vardenafil) to be maximally efficacious at 12 mo from nerve-sparing radical prostatectomies.

Sildenafil response rates based on surgical technique are reported as bilateral nerve-sparing (33–80%), unilateral nerve-sparing (0–80%), and non-nerve-sparing (0–20%; refs. *42, 48,* and *49*). Response to sildenafil can be expected to be poor (26%) within the first 6 to 9 mo after surgery; however, 18 to 24 mo after prostatectomy, treatment success significantly improved to 60% *(48,49)*. Tadalafil has also demonstrated significant improvements in ED after nerve-sparing radical prostatectomies, with a five-point increase over placebo in the EF domain of IIEF and better rates of successful intercourse attempts (41 vs 19%). In a larger scale study, 440 men who had nerve-sparing radical prostatectomies were randomized to placebo vs 10- or 20-mg doses of vardenafil; objective (EF score, SEP questions 2 and 3) and subjective measures (patient satisfaction, sexual experience) were better compared with placebo *(50,51)*.

Prevention of ED after nerve-sparing radical prostatectomies has been a subject of more recent efforts. Padma-Nathan et al. *(52)* recently presented data regarding the daily use of 50 or 100 mg of sildenafil vs placebo for 9 mo after nerve-sparing radical prostatectomies. The sildenafil group reported significantly higher rates of erections (4 vs 27%). Proposed mechanisms include improved oxygenation with nocturnal erections and/or neuronal regeneration *(52)*.

Postbrachytherapy or External Beam Radiation for Prostate Cancer

There is a clear but controversial association of ED after radiation treatment for prostate cancer. Rates of ED depend on the type, dosage, and delivery method for localized radiation. Higher rates of ED are observed with conventional external beam irradiation, followed by conformal therapy and then brachytherapy. Rates of ED vary widely and progress over time.

Hisasue et al. *(53)* compared conformal therapy with conventional radiation and found rates of EF to be 47.6% at 1 yr; however, the rate for conformal therapy significantly dropped to 19% at 3 yr. Little et al. *(54)* conducted a quality-of-life questionnaire to be given 2 to 3 yr after external radiotherapy and found a reduction in EF from a baseline of 84% pretreatment to 49% at 2 yr and 41% at 3 yr.

Shemtov et al. *(55)* reported that successful therapy with sildenafil after irradiation is more effective after brachytherapy compared to external beam radiation External radiotherapy patients tended to be older, although comorbidities were well-matched. Raina et al. *(56)* reported long-term potency after iodine-125 seed radiotherapy at a rate of 29%; this improved to 70% when patients treated sildenafil were included.

OPTIMIZING ORAL THERAPY: FAILURES OF PDE-5 INHIBITOR

Patients who demonstrate no appreciable response to oral therapy with sildenafil have become a new challenging subpopulation. Based on the review of the different pharma-

cokinetic parameters of each PDE-5 inhibitor, patients should be adequately counseled on the proper use of each agent. The differences in the pharmacokinetics of the various agents present different tactics to optimize absorption, onset of action, and duration.

Sildenafil and vardenafil users should avoid high-fat meals with oral intake, whereas tadalfil patients have no restrictions. However, tadalafil should be avoided in the presence of significant alcohol consumption (>5 units) because of safety concerns. Secondary to the long half-life, tadalafil is expected to have a delay in onset of action compared to the other two agents. Concomitant medications (rifampin, phenytoin, carbamezapine, etc.) that are known to induce hepatic metabolism should be avoided in daily use.

Initially, simple patient re-education and counseling and an adequate trial of use demonstrated that a significant portion (55%) of initial nonresponders could be salvaged *(57)*. Later, the Patient Response with Vardenafil in Sildenafil Nonresponders trial demonstrated up to a fourfold improvement in successful intercourse completion rates over baseline and reduced mean IIEF-EF scores from severe to mild-to-moderate *(58)*. They suggested that an additional 50% of patients could be salvaged with oral therapy by switching to vardenafil alone. Recent data suggest salvage rates to be much lower and not statistically significant *(59)*. In clinical practice, most patients are offered and have tried all the PDE-5 agents with proper drug-specific counseling before accepting a failure to this modality.

PATIENT COMPLIANCE

Overall, the dropout rates for the three PDE-5 inhibitors secondary to adverse effects have been quite low (<5%). Large-scale studies have proved the tolerability of these agents. Klotz et al. *(60)* recently presented data on why patients abandon successful therapy with sildenafil. The authors found that only 161 of 234 patients (69%) with successful response refilled their prescriptions within 6 mo of receiving the first prescription. A telephone survey of the 73 patients (31%) revealed lack of opportunity or desire for sexual intercourse (45%) as the primary reason for not refilling the prescription, followed by lack of partner interest (23%), high cost of medication (12%), and adverse effects (5%; ref. *60*).

PATIENT PREFERENCE ISSUES

In the era of direct-to-patient advertising with high-profile celebrity endorsements, patients are entering physicians' offices with preconceived expectations for the various PDE-5s. Several industry-sponsored trials have demonstrated certain factors that affect patient preference and perceived response. Various independent clinical trials comparing the three PDE-5s have also emerged from international data. Accurate patient preference studies should adhere to the following basic guidelines: (a) double-blinding; (b) nonbiased drug administration instructions; (c) crossover design; (d) equivalent dose comparisons; (e) standardized assessment; (f) declaration of patient demographics; and (g) rigorous statistical analysis *(61)*.

Three open-label crossover trials of sildenafil and tadalafil have demonstrated definite patient preference when accounting for time constraints, spontaneity, and sexual self-confidence *(62–64)*. Moreover, these trials have demonstrated several important patient issues: (a) a time to coital attempt after oral therapy greater than 4 h predicts preference for tadalafil *(62)*; (b) successful sildenafil users change dose-attempt behavior when switched to tadalafil *(64)*; and (c) the Psychological and Interpersonal Relationship

Scales questionnaire suggests "time concerns" and "sexual self-confidence" as main preference factors *(62,63)*.

Industry-sponsored open-label studies have examined patient preferences between the three available PDE-5s in the clinic and university settings *(65–68)*. Claes and Zermann *(66,68)* demonstrated no appreciable difference in patient preference among the various agents. Stroberg demonstrated patient preference of tadalafil over sildenafil at a ratio of 9:1 *(65)*. Overall, these studies demonstrated that patients who are naïve to PDE-5 inhibitorsare harder to find and that when "time concerns" are emphasized, patients prefer tadalafil.

A few double-blind crossover trials have been conducted to compare patient preference of sildenafil to patient preference of tadalafil *(69,70)*. Von Keitz et al. *(70)* conducted four treatment arms with a sham to protect the blind and evaluated patient drug preference and dosing instruction preference. They found that 132 of 181 (73%) patients chose tadalafil over sildenafil in the extension arm. Moreover, 24 of 36 (67%) patients preferred tadalafil dosing instructions. Govier *(69)* demonstrated patient preference for 20 mg of tadalafil over 50 mg of sildenafil when dealing with initiation of ED treatment.

Another important confounding variable when dealing with patient preference is patient education. We *(71)* suggested a standardized approach to educate patients about onset and duration of action (i.e., "expect that each of the three drugs will be active in your system by 1 to 2 h and may linger for some time") to minimize suboptimal medication trials.

FUTURE TARGETS AND HOMEOPATHIC REMEDIES

Herbal, vitamin, and mineral products are constantly scrutinized for prevention and treatment of medical ailments; they are more readily accepted by patients because they are perceived as being harmless and generally beneficial. The treatment of ED is not immune from this phenomenon. Compounds examined include: (a) L-arginine, a precursor to NO; (b) gingko biloba; (c) Korean red ginseng; (d) pycnogenol (e) yohimbine; and (f) zinc *(72–74)*.

There are at least six PDE-5 compounds in preclinical or clinical development. The focus of the upcoming PDE-5 inhibitor compounds is to offer a unique pharmacokinetic profile. Centrally acting agents under investigation, such as apomorphine (Uprima) and PT-141 (Melanotan II), rely on dopaminergic and melanocortin pathways, respectively *(75)*. A combination of yohimbine and L-arginine (NMI-870) is in phase I development. Selective potassium-channel activators (Pinacidil) are also being developed. Opening potassium channels results in smooth muscle relaxation and erections.

CONCLUSION

Oral pharmacotherapy with PDE inhibitors has become the cornerstone of treatment for ED in the new millennium. Patients and physicians readily accept this secondary to the minimally invasive nature of treatment and good clinical efficacy with minimal side effects.

Urologists and primary care physicians need to be well-versed in the dosing limitations and drug–drug interactions of the various agents.

As a class, the PDE-5 inhibitors have demonstrated excellent efficacy and safety data with long-term follow-up. The presence of comorbidities should not exclude patients from an adequate trial of PDE-5s. Overall, all three agents (sildenafil, vardenafil, tadalafil) are expected to have similar efficacy, although no direct comparative trials have been con-

ducted with drug-specific dosing limitations. The flexibility that tadalafil offers translates into real world use that is reflected in patient preference studies. Although sildenafil is the prototype for the class, various compounds are being developed that reflect the characteristics of tadalafil—short onset of action with prolonged duration and good efficacy.

Future therapies are being investigated that will further improve on existing treatments and possibly offer patients various benign oral medications.

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13 Intracavernosal Injection of Vasoactive Agents

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SUMMARY

The National Institutes of Health consensus statement on impotence estimates that the number of men with erectile dysfunction in the United States is approx 20 million, presenting with varying degrees of erectile dysfunction. Although significant improvements in the pathophysiology have resulted in newer treatment modalities for the management of erectile dysfunction, intracavernosal vasoactive pharmacotherapy has been successfully utilized as a second-tier modality. These methods, the use of injection pharmacotherapy, account for approx 40% of all treatment options for the management of male sexual dysfunction. Tremendous progress in the use of monotherapy, and subsequent bimix, in conjunction with triple injection therapy, has resulted in improved modalities of treatment satisfaction.

Key Words: Erectile dysfunction; penile injection therapy; prostaglandin E1; trimix.

INTRODUCTION

Erectile dysfunction (ED) affects 20 to 30 million American men and has an unfavorable impact on quality of life, with alterations on mental well-being and family/social relationships *(1,2)*. ED may present as early as age 40, with a prevalence estimated at 5%; the incidence increases as age increases *(1)*. With the advent of sildenafil and other phosphodiesterase (PDE)-5 inhibitors, oral medications are often prescribed as first-line therapy for ED. Of men with ED, 30% do not respond to oral medications and 15% are unable take these oral medications because of contraindications *(3)*. Some patients prefer injection therapy because of its predicability in time-to-onset and its reliability in rigidity compared with oral medications *(3)*.

This chapter focuses on the history of intracavernosal therapy, different injectable agents available as monotherapy or in combination therapy, their medication profile, and side effects. It also includes the 2004 American Urological Association's Clinical Guidelines for the Treatment of Organic Erectile Dysfunction, specifically for vasoactive agents *(4)*.

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HISTORY

The use of intracavernosal pharmacotherapy began in 1982, when Virag published the erection-inducing properties of papaverine *(5)*. Independently, Brindley *(6,7)* observed that the self-injection of an irreversible-adrenergic antagonist, phenoxybenzamine, into the corpora produced a rigid erection, on demand. Additionally, authors have reported the erectile potential of the α-adrenoceptor blockers phenoxybenzamine and phentolamine as well as the combination of papaverine–phentolamine for self-injection into the cavernous bodies *(8)*. The work of Zorgniotti and Lefleur *(8)* with combination intracavernosal pharmacotherapy was a breakthrough for self-injection therapy because it was a new minimally invasive modality in the management of ED.

In 1986, at the Second World Meeting on Impotence in Prague, Adaikan and Ishii *(9,10)* introduced alprostadil for self-injection therapy, and it became the primary agent in intracavernosal pharmacotherapy for ED. Its reliability was confirmed in 1988 by the work of Porst and Stackl *(11,12)*. In 1995, the US Food and Drug Administration approved alprostadil for injection therapy for its use in the treatment of ED.

Injectable agents had some side effects, such as penile discomfort and fibrosis. The development of combination therapy began when researchers were evaluating methods to enhance efficacy and concomitantly lower adverse events. This led to the trimix combination of prostaglandin E $(PGE)_1$–papaverine–phentolamine in 1990, following the publication of Goldstein, which presently is the most popular combination pharmacotherapy in the United States *(13)*.

Other injectable agents followed, but not all were widely accepted in the United States. These agents were more commonly used in Europe. In 1989, the relatively selective α_1-adrenoceptor moxisylyte (thymoxamine) arrived in France, but it was soon withdrawn from the market *(14)*. Other drugs were introduced, including vasoactive drugs such as calcitonin gene-related peptide (CGRP), linsidomine (SIN-1), vasoactive intestinal polypeptide (VIP), and sodium nitroprusside, but these did not gain wide market appeal *(15–20)*. Two exceptions exist: the combinations of papverine–phentola-zamine and VIP–phentolamine were approved for use in Europe *(21)*.

The ideal injectable agent should be widely available, user-friendly, and inexpensive. It should be able to achieve an excellent response rate with minimal side effects, regardless of the varying etiologies of ED. These agents may be used as either monotherapy or combination therapy.

ALPROSTADIL

Mechanism of Action

Alprostadil (PGE_1) is currently the most commonly used intracavernosal agent, used either alone or with other agents in combination therapy. It acts via direct stimulation of the cyclic adenosine monophosphate (cAMP) pathway to decrease intracellular calcium concentrations, allowing for relaxation of arterial and cavernosal smooth muscle tissues *(22)*. PGE_1 is metabolized primarily by the lung and is excreted by the kidney *(23,24)*. PGE_1 can be combined with α-cyclodextrin (Edex™; Schwarz-Pharma) to enhance solubility and delivery; in 1998, the Food and Drug Administration approved this combination *(24)*. PGE_1 has a half-life of 30 to 60 s (Table 1).

Success Rate

Long-term follow-up of 4 to 5 yr of alprostadil usage is available *(26–29)*. A review of these studies has shown that the efficacy rate of alprostadil during in-office titration

Table 1
Pharmacological Profile of Alprostadil *(3)*

Sites of action	*Adenylate cyclase causes 3'5'-cAMP ″*
	Presynaptic on α1-adrenoceptor to cause noradrenaline ⎫ Angiotensin secretion to cause muscle tone ⎭ Stimulation of Maxi-K^+ channels to cause hyperpolarization Neuromodulation of pre-optic area Inhibition of transforming growth factor-β1 to cause collagen ⎭
Dosage	2.5–40 μg
Pharmacokinetics	Metabolism intracavernosal and during lung passage Half-life: 30–60 s PGE_0 active metabolite
Efficacy	70–80%
Side effects	Pain 10–20%, priapism <1%, fibrosis 5–11%
Target group	Nonresponders to or contraindications for oral therapy (sildenafil, apomorphine) In combination with oral drug therapy for patients with severe ED (salvage therapy)

Table 2
Success Rates of Self-Injection Therapy
With Alprostadil (Viridal/EDEX in the European Prospective 4-Yr Trial *[25,28]*)

Year follow-up	*Number of injections*	*Number of successful coitus*	*Percentage*
First year	6935	6293	91
Second year	3937	3691	94
Third year	3233	3050	94
Fourth year	2781	2679	96
Total	16,886	15,713	93

varied between 70 and 75% in more than 10,000 patients *(30)*. Success rates, defined as successful coitus per injection, varied between 89 and 97%, which is higher than any reported efficacy rate among the available marketed vasoactive drugs (Table 2; refs. *26* and *29*).

Dosing

PGE_1 is more effective than papaverine alone, especially in patients with vasculogenic impotence. Following intracavernosal dosages of 5 to 40 μg, 70% of men experienced satisfactory erections *(30)*. For non-neurogenic patients, test dosing may safely begin with 10-μg injections, increasing in increments of 5 to 10 μg until the desired effect is achieved. The initial dose in neurogenic patients should be decreased to 1.25 μg, followed by increases of 1.25 to 2.5 μg if the test dose is ineffective.

Side Effects

Side effects of PGE_1 include penile pain (occurring in 25% of patients), which can be alleviated by the concurrent injection of lidocaine, sodium bicarbonate, or neurotropin (Table 3; refs. *24–26,30,32,33*). Another side effect is prolonged erections (occurring in 4% of patients; refs. *25* and *26*). PGE_1 has a lower incidence of prolonged erection

Table 3
Side Effects of Vasoactive Drugs in Retrospective Studies *(29)*

Drug	*No. pts/no. publications*	*Priapism (%)*	*Fibrosis (%)*	*Pain (%)*	*LFTs ″ (%)*
Papaverine	1527/15	7.1	5.7	4	1.6
Pap/Phentol	2263/22	7.8	12.4	11.6	5.4
PGE_1	2745/10	0.36	0.8	7.2	0

LFT, liver function test; PGE_1, prostaglandin E_1.

(1–4%) compared with papaverine or papaverine–phentolamine but has the disadvantage of penile pain at the injection site, storage requirements, and higher cost. Edex (Schwarz-Pharma) and Caverject™ (Upjohn-Pharmacia, North Haven, CT), with the exception of the 40-μg dose, can be stored at room temperature. The 40-μg strength must be stored at 2 to 8°C (36–46°F) until dispensed. After dispensation, the 40-μg-strength alprostadil may be stored at or below 25°C (77°F) for 3 mo or until the expiration date, whichever occurs first *(34)*.

When reconstituted and used as directed, the deliverable amount of alprostadil is 5, 10, 20, or 40 μg, respectively. The reconstituted solution should be used within 24 h when stored at or below 25°C (77°F) and should not be refrigerated or frozen. Only the accompanying diluent or bacteriostatic water for injection with benzyl alcohol should be used when reconstituting alprostadil *(34)*.

PAPAVERINE

Mechanism of Action

Papaverine hydrochloride is the first agent widely used for intracavernosal self-injection. It inhibits PDE, which prevents the breakdown of cAMP and leads to the subsequent decrease in calcium concentration. This results in relaxation of all vascular structures in the penis. The longer half-life of papaverine compared with other intracavernosal agents may explain the higher incidence of prolonged erections with papaverine or papaverine–phentolamine combinations. Papaverine is metabolized by the liver and, as monotherapy, it is associated with mild elevation of liver transaminases *(31)*.

Dosing

Papaverine is stable in solution and loses 10% of its potency over a 4-yr period *(3)*. It should be stored at a pH between 3.0 and 3.7, and papaverine precipitates at pH levels greater than 5.0 *(3)*. Maximum plasma levels are achieved within 10 to 30 min, and it has a half-life of 1 to 2 h *(3)*. Papaverine may be stored at room temperature.

Success Rate

Smaller doses may be required in patients with neurogenic impotence secondary to spinal cord injury or other neurological disorders. The usual dose of papaverine is 1 to 30 mg. A satisfactory response has been shown in 44% of patients with a 7.5-mg dose and in another 41% with 1- to 15-mg *(31)*. Patients with psychogenic ED also achieve excellent results using single-agent papaverine, and some eventually experience spontaneous return of erections *(31)*. Patients older than 70 may use papaverine safely with

Table 4
Pharmacological Profile of Papaverine *(3)*

Sites of action	*Nonselective phosphodiesterases causes 3'5'-cAMP ″*
	Inhibition of L-type Ca^{2+} channels causes intracellular Ca^{2+} ⎫ Inhibition of angiotensin II secretion to cause muscle tone ⎭
Dosage	30–110 mg
Pharmacokinetics	Metabolism through the liver Half-life: 1–2 h
Efficacy	27–78%
Side effects	Pain 4%, priapism 3–18%, fibrosis 5–30%, elevation of liver enzymes 1.6% *(15,17,18)*
Target group	Nonresponders to or contraindications for oral therapy (sildenafil, apomorphine) In combination with oral drug therapy for patients with severe ED (salvage therapy), usually in combination with other intracavernosal agents

Table 5
PGE vs Papaverine *(14)*

	PGE_1	*Papaverine*
Response		
Full erection[a]	34 (26%)	17 (13%)
Sufficient for penetration	20 (16%)	14 (11%)
Total	54 (42%)	31 (24%)
Adverse effects		
Prolonged erection	0	1
Fibrosis of corpora	0	25
Discomfort on injection	11 (8.5%)	6 (4.7%)
Day of injection		
Attempted intercourse	24 (19%)	15 (12%)
Successful intercourse	12 (9%)	6 (5%)

[a] $p < 0.025$.
PGE_1, prostaglandin E_1.

similar side effects as in younger patients, although dose increases may be necessary to achieve the desired response (Tables 4 and 5; ref. *31*).

Side Effects

Side effects of papaverine include priapism (7.1%), fibrosis (5.7%), pain (4%), and elevation of liver enzymes (1.6%; ref. *35*).

PHENTOLAMINE

Mechanism of Action

Phentolamine is a nonselective inhibitor of the α-adrenergic receptor, inhibits smooth muscle contraction, and has a direct relaxant effect on smooth muscle and antiserotonin-

Table 6
Pharmacological Profile of Phentolamine *(3)*

Sites of action	Nonselective $\alpha_{1\text{-}2}$-adrenoceptors blockade leading to noradrenaline ⎫
	Maxi K^+ stimulation causing hyperpolarization
	NO-synthase stimulation leading to intracellular NO ⎭
Dosage	30–110 mg
Pharmacokinetics	Metabolism through the liver
	Half-life: 30 min
Efficacy	27–78%

ergic activity (Table 6). The plasma half-life is 30 min, and it is extensively metabolized by the liver before excretion by the kidneys.

Dosing

Phentolamine is used in combination products and is not used as a single-dose agent.

Success Rate

As monotherapy, phentolamine does not result in adequate erections. Its clinical use is limited to combination products to achieve a desired synergistic effect, most commonly with papaverine and PGE *(31)*.

COMBINATION PRODUCTS

Papaverine and Phentolamine (Fig. 1)

The combination of papaverine and phentolamine was the first combination to be used in humans and was popularized in 1986 by Zorgniotti and Lefleur *(7)*. Papaverine–phentolamine is more effective than papaverine alone but has a higher or equal rate of fibrosis and prolonged erections. Priapism had a reported incidence of 6 to 15%, and fibrosis occurred at a rate between 18 and 57% *(35–39)*. Elevation of liver enzymes was seen in 5.4% of subjects *(33)*. This combination is not commonly used because more effective combination therapies are available. It is equally as effective as PGE monotherapy, but the latter has side effects of increased penile pain with decreased incidence of fibrosis and priapism.

Fig. 1. *(Opposite page)* Mechanisms of action of pharmacotherapies for ED. Intracellular mechanisms of various neurotransmitters, vasoactive factors, and sites of action of pharmacotherapy. NO, synthesized via nonadrenergic, noncholinergic (NANC) nerves of endothelial cells, diffuses into smooth muscle cell, a process that activates guanylate cyclase and increases intracellular cyclic guanosine monophosphate (cGMP) synthesis. Sildenafile inhibits PDE-5 and blocks this breakdown. PGE_1 and vasoactive intestinal peptide bind to specific G protein-coupled receptors, which activate adenylate cyclase and increase intracellular cyclic adenosine monophosphate (cAMP) synthesis. Forskolin directly activate adenylate cyclase. Increased cAMP and cGMP levels eventually lead to smooth muscle relaxation. Both cAMP and cGMP are hydrolyzed to adenosine monophosphate (AMP) and guanosine monophosphate (GMP), respectively, by PDEs terminating their effects. Papaverine nonselectively blocks both cAMP and cGMP PDEs. α_1-adrenergic receptors normally signal through $G_{q/11}$ heterotrimeric proteins, an outcome that activates protein kinase C-γ (PLC), liberates inositol triphosphates (IP_3), and results in the elevation of intracellular calcium (Ca^{2+}) and smooth muscle contraction. Phentolamine blocks this process, as shown. ACh, acetylcholine; ATP, adenosine triphosphate; GTP, guanosine triphosphate. (From ref. *62* with permission.)

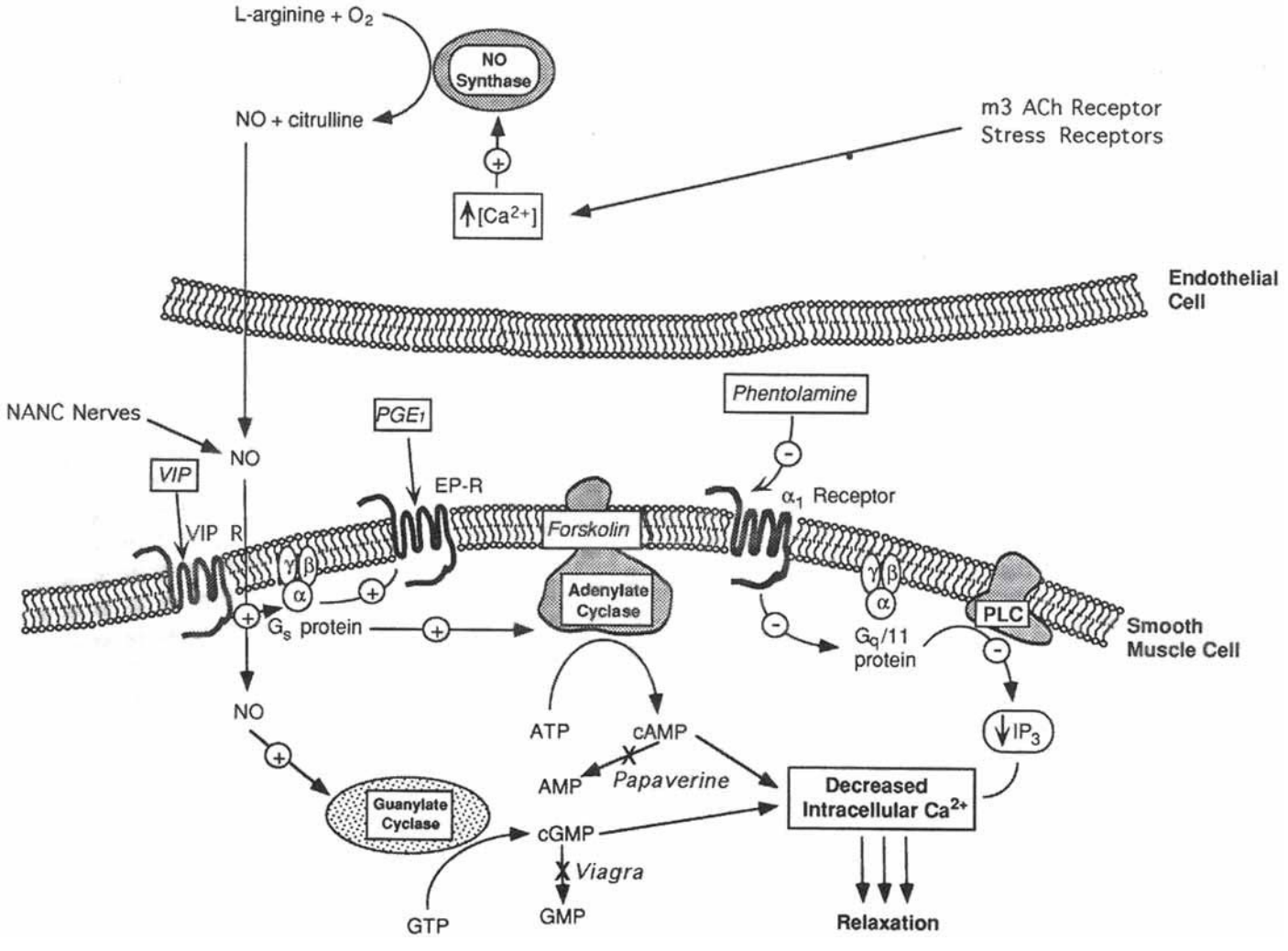
L-arginine + O_2
NO Synthase
NO + citrulline
m3 ACh Receptor
Stress Receptors
↑[Ca^{2+}]
Endothelial Cell
NANC Nerves
NO
VIP
VIP R
PGE1
EP-R
Phentolamine
α_1 Receptor
Forskolin
Adenylate Cyclase
G_s protein
G_q/11 protein
PLC
Smooth Muscle Cell
ATP
cAMP
AMP
Papaverine
↓IP_3
Decreased Intracellular Ca^{2+}
Guanylate Cyclase
cGMP
Viagra
GMP
GTP
Relaxation

Table 7
Pharmacological Profile of VIP/Phentolamine *(37,59)*

Sites of action	VIP: adenylate cyclase ♦ 3'5'-cAMP ″ Phentolamine: nonselective $\alpha_{1\text{-}2}$-adrenoceptors blockade leading to noradrenaline ⌡ Maxi K^+ stimulation causing hyperpolarization Endothelin-antagonism, blockade of 5-HT-receptors
Dosage	25 μg of VIP/1–2 mg of phentolamine
Pharmacokinetics	Metabolism through the liver Half-life: 30 min
Efficacy	60–70% mixed patients with ED partially nonresponders to PGE_1
Side effects	Flushing 70–80%, priapism <1%, fibrosis unknown
Target group	Nonresponders to or contraindications for oral (sildenafil, apomorphine) therapy, principally all patients with ED

VIP, vasoactive intestinal polypeptide; PGE_1, prostaglandin E_1; ED, erectile dysfunction.

Triple Mixture Therapy

The combination of papaverine, phentolamine, and PGE_1 (popularized as "trimix") was developed to reduce the dosages of individual agents, decrease side effects of each agent, and improve efficacy. Dosages of each compound varied from 4.4 to 15 mg of papaverine, 0.15 to 0.5 mg of phentolamine, and 1.5 to 20 μg of PGE_1 per milliliter *(40–42)*.

In nonselected patients with ED, response rates using the trimix combination were approx 80 to 90%, which is 10 to 15% higher than after 20 μg of alprostadil alone *(38)*. Rigid erections following trimix administration were achieved in 50 to 62% of so-called nonresponders, suggesting that trimix can be useful rescue therapy for patients who do not respond to monotherapy with alprostadil or the combination of papaverine and phentolamine (Table 5; refs. *13* and *41*).

The trimix combination produces a response in 30 to 40% of patients who have not responded to 40 μg of alprostadil. Trimix can be prepared by mixing 1 ampule of Androskat (30 mg of papaverine, 1 mg of phentolamine) with 10 to 20 μg of Caverject (Upjohn-Pharmacia). This combination should be used within 30 d because of the 30% degradation of PGE_1 concentration within 60 d *(43)*.

Trimix self-injection therapy is an excellent option for patients who do not respond to alprostadil or for those who experience painful erections after using alprostadil alone. Trimix has a similar side effect and risk profile as papaverine and phentolamine, especially regarding priapism and fibrosis (Table 3).

VIP–Phentolamine (Fig. 1)

VIP alone does not produce rigid erections; however, when combined with phentolamine, rigid erections occurred. In a prospective trial of 289 patients given VIP–phentolamine, 77% responded with erections adequate for intercourse. The rate of priapism was 0.6% *(44)*. The biggest advantage of this combination therapy is its availability in a ready-to-use, automatic, single-injection device with a 29-gage needle. Many patients may prefer this combination, because alprostadil requires reconstitution prior to use (Table 7).

Table 8
Nonmarketed Vasoactive Drugs With Potential for Self-Injection Therapy *(3)*

Compounds	*Dosage*	*Results (efficacy)*	*Conclusion*
PGE_1/CGRP	20 μg/5 μg	30% of nonresponders to 40 μg of PGE_1	Salvage-therapy potential
Linsidomine (SIN-1)	1 mg	35–74%	Inferior to PGE_1
Sodium nitroprusside	300–600 mg	64–84%	More side effects than PGE_1
Triple-drug (trimix): Pap/Phentol/PGE_1	30 mg/1 mg/20 μg	80–90%	Salvage therapy

PGE_1, prostaglandin E_1; CGRP, calcitonin gene-related peptide.

NEWER AGENTS

Other agents, either alone or in combination, are available internationally or are undergoing experimental trials. These include the nitrodonors SIN-1 and sodium nitroprusside, VIP, forskolin, moxisylyte, and CGRP (Table 8).

Linsidomine

SIN-1 generates nitric oxide (NO) nonenzymatically, resulting in the stimulation of guanylate cyclase that leads to 3'5'-cyclic guanosine monophosphate accumulation. Success rates of up to 69% (78 of 113) were reported in one group *(16,45)* but not in others *(17,46)*. A small comparative trial of 40 patients showed 35% efficacy rates of partial or full rigidity following administration of 1 mg of SIN-1, compared with 82.5% efficacy rates following administration of 20 μg of alprostadil *(4)*. Although side effects are lower, the efficacy rate is significantly lower, so further research was not conducted toward market development.

Sodium Nitroprusside

Sodium nitroprusside, another nitrodonor, was compared with alprostadil *(47)*. In a study of 95 patients, 49% had partial and 15% had complete rigidity after taking 300 to 400 mg of sodium nitroprusside. After administration of 20 μg of alprostadil, 54 and 20% responded, respectively. Global response rates of 84% were achieved with 600 mg of nitroprusside. This study showed that alprostadil produced better response rates and sodium nitroprusside was linked to hypotonic blood pressure reactions in up to 15% of patients, which prohibited sodium nitroprusside from further testing and marketing.

Vasoactive Intestinal Peptide

VIP acts through stimulation of adenylate cyclase, forming increased concentrations of cAMP; however, it does not appear to act through the release of NO. In vivo studies in dogs showed modest effects on arterial inflow but much more pronounced effects on decreasing venous outflow. As single-agent therapy, VIP failed to produce satisfactory responses. A recent study of patients in whom previous intracavernosal therapy had failed revealed that the combination of VIP and phentolamine produced an erection sufficient for sexual intercourse. Minor side effects occurred, including flushing, bruising, and pain at the injection site, but no episodes of priapism were reported. Further trials with VIP in combination with other agents are in progress.

Forskolin

Forskolin is a naturally occurring plant alkaloid that induces smooth muscle relaxation by direct activation of the catalytic domain of the enzyme adenylate cyclase. Conversely, PGE_1 and VIP indirectly stimulate adenylate cyclase by interacting with specific G protein-coupled receptors. Forskolin acts synergistically with PGE_1 to increase cAMP levels and induce smooth muscle relaxation. Short-term clinical investigations in 31 men with vasculogenic ED refractory to high-dose trimix used a four-agent mix consisting of papaverine, phentolamine, PGE, and forskolin. Favorable results were reported in 61% of patients, with no apparent immediate or short-term effects *(48)*.

Moxisylyte

Moxisylyte (thymoxamine) is a selective α_1-receptor blocker. It relaxes smooth muscle and decreases sympathetic tone. It is not widely used in the United States because of clinically relevant drops in blood pressure and orthostatic symptoms of dizziness in 5 to 8% of patients *(49,50)*. Compared with 20 μg of alprostadil, efficacy rates of those patients who had received moxisylyte were lower. The success rates were 75% in the office and 85% at home with self-injection of alprostadil compared with 40% in the office and 61% at home with self-injection of moxisylyte *(47,48)*. Although the advantages of moxisylyte include low risks of priapism (<1%) and fibrosis (<2%), it has a lower efficacy rate (Table 9; refs. *25* and *49*).

CGRP Combined With PGE_1

CGRP is a potent vasodilator that allows for increased blood flow and tumescence but not rigidity at intracavernosal doses of 500 μg *(19)*. In a study of 65 patients given CGRP (5 μg) combined with PGE_1 (10 μg) 91% of whom were nonresponders to 30 mg of papaverine and 1 mg of phentolamine, 55% experienced rigidity *(51)*. In another study, 30% patients who had no response to either 40 μg of PGE_1 or 80 mg of papaverine or the combination of 60 mg papaverine with 2 mg of phentolamine experienced rigid erections following treatment with 5 μg of CGRP and 20 μg of PGE_1 *(52)*. No further reports have been published regarding the validity and safety of the CGRP–PGE_1 combination.

PRACTICAL ISSUES ON SELF-INJECTION THERAPY (TABLE 10)

Anticoagulated Patients (Table 11)

Patients who are anticoagulants do not have any contraindications to using self-injection therapy. The risk of bleeding is not higher than the normal patient population *(53)*.

Transplant Recipients

There is no increased risk of infection or fibrosis in patients who have received kidney transplants *(54)*.

Diabetic Patients

Focal fibrotic changes are more frequently observed in insulin-dependent diabetic patients when compared with nondiabetic patients *(55)*.

RELATIVE CONTRAINDICATIONS

Relative contraindications to self-injection therapy include penile fibrosis, coagulopathy, uncontrolled psychiatric disorders, regular use of monamine oxidase inhibitors,

Table 9
Pharmacological Profile of Moxisylyte (thymoxamine) *(24,52,53)*

Sites of action	Selective α_1-adrenoceptor blockade
Impact on erection	Sympathetic tone ↓ Smooth muscle tone ↓
Dosage	10–20 mg
Pharmacokinetics	Metabolism through the liver and excreted by the kidney
Efficacy	20–40%
Side effects	Priapism <%, fibrosis <1%, hypotonic reaction/dizziness 5–8% *(15,17,18)*
Target group	Patients with contraindications to sildenafil and inconvenient painful reactions to PGE_1

PGE_1, prostaglandin E_1.

Table 10
Biological Effects of Marketed Vasoactive Drugs for Self-Injection Therapy in Erectile Dysfunction *(3)*

Compound	*Site of action*	*Effect on cavernous tissue*
Alprostadil (PGE_1)	Adenylate cyclase	3'5'-cAMP ″
	Presynpatic α1 receptors (inhibition)	Noradrenaline release ↓
	Angiotensin II secretion (inhibition)	Smooth muscle ↓
	Maxi-K^+ channels (stimulation)	Hyperpolarization
	TGF-β1 (inhibition)	Collagen-production ↓
Papaverine	Phosphodiesterase (nonselective)	3'5'-cAMP/cGMP ″
	L-type Ca^{2+} channels (inhibition)	Intracellular Ca ↓
	Angiotensin II secretion (inhibition)	Smooth muscle ↓
Phentolamine	$\alpha_{1\text{-}2}$-adrenoreceptors (blockade)	Noradrenaline effects ↓
	Maxi K^+ channels (stimulation)	Hyperpolarization
	NO-synthase (stimulation)	Intracellular NO ″
VIP	Adenylate cyclase	3'5'-cAMP ″
Moxisylyte	α-adrenoreceptors	Noradrenaline effects ↓

Table 11
Self-Injection Therapy in Special-Risk Groups

Risk group	*No. of patients*	*Reference*	*Conclusion*
Anticoagulants (warfarin)	33	*51*	No increased risk of bruising
Kidney transplant	26	*52*	No increased risk of infection or fibrosis
Diabetes mellitus	16	*53*	Considerable increased risk of pain (19 vs 3%), cavernitis (19 vs 0%), and fibrosis (25% vs 3%)
Non-diabetics	29		

Table 12
1996 AUA Clinical Guidelines
for the Treatment of Organic Erectile Dysfunction (Specific to Vasoactive Agents) *(55)*

Recommendations

Vasoactive drug injection therapy

Standard: The physician should inform the patient using vasoactive drug injection therapy that a prolonged erection can occur and that the patient should present for treatment after a prolonged erection of four hours. The physician should be familiar with the methods used to reverse a prolonged erection and should inform the patient of how to contact the treating physician or a knowledgeable substitute at any time.

Guideline: For patients beginning initial therapy, PGE_1 (alprostadil) monotherapy is preferred. For patients who fail PGE_1 therapy because of pain or inadequate erection, other drugs should be considered.

Guideline: For combination therapy, papaverine/phentolamine and papaverine/phentolamine/PGE_1 appear equally efficacious and safe. For PGE_1/phentolamine combination therapy, insufficient data have as yet been reported in the literature; but panel opinion is that this combination appears to be an effective therapy.

Standard: the least flexible of the three levels. The outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions and there is virtual unanimity about which intervention is preferred.

Guideline: intermediate flexibility of the three levels. The outcomes of the interventions are sufficiently well known to permit meaningful decisions and an appreciable but not unanimous majority agrees on which intervention is preferred.

Option: the most flexible of the three levels. The outcomes of the interventions are not sufficiently well known to permit meaningful decisions, preferences among the outcomes are not known, patient preferences are divided among alternative interventions, and/or patients are indifferent about the alternative interventions *(55)*.

and severe cardiovascular disease that could be exacerbated by a complication of the injection *(56)*. Patients taking monamine oxidase inhibitors are at risk for hypertensive crisis if adrenergic agents are used to treat prolonged erection. Patients with chronic systemic illness should be followed in conjunction with their primary physician. Poor manual dexterity or morbid obesity, which could preclude self-injection, may be overcome by teaching the injection technique to an able and willing partner (Table 12; ref. *57*).

MANAGEMENT OF COMPLICATIONS RESULTING FROM SELF-INJECTION THERAPY

Priapism

Erections lasting longer than 4 to 6 h should be treated to prevent tissue damage and to preserve future erectile function. Porst observed more than 150 patients with drug-induced priapism and found that direct injection of a sympathomimetic antidote was sufficient if the priapism lasted less than 12 h *(11)*. For erections lasting between 12 and 18 h, evacuation of the entrapped hypoxemic blood with the insertion of a butterfly needle was performed first. If re-oxygenation has not been re-established after 10 to 15 min, then injection of a sympathomimetic agent is appropriate. The recommended agents and doses are 5 to 20 mg of etilefrine or 0.1 to 0.5 mg of phenylephrine, because these drugs have the least impact on cardiac β-receptors *(58)*. If the erection persists after 15 min, despite penile massage to promote circulation of the medication, then a repeat dose should

Table 13
Dosages of Vasoactive Agents

PGE_1 (alprostadil)	2.5–40 μg
Papaverine	30–110 mg
Phentolamine	Not used as monotherapy
VIP/phentol	25 μg/1–2 mg
Linsidomine (SIN-1)	1 mg
Sodium nitroprusside	300–600 mg
Triple-drug (Trimix): Pap/phentol/PGE_1	30 mg/ 1 mg/ 20 μg
Forskolin	5–20 μg
Moxisylyte	10–30 mg
PGE_1/CGRP	20 μg/ 5 μg

PGE_1, prostaglandin E_1; VIP, vasoactive intestinal polypeptide; CGRP, calcitonin-gene-related peptide.

Table 14
Formulation of Papaverine/Phentolamine/PGE_1 Solution *(55)*

Vasoactive agent	*Dose (mL)*
Papaverine HCl (30 mg/mL)	2.50
Phentolamine (5 mg/mL)	0.50
Alprostadil (500 μg/mL)	0.05
0.9% saline for injection	1.20
Total volume	4.25

be injected into the opposite cavernous body. If this fails, then evacuation should be performed. If the blood pressure increases during injection, then oral or fast-acting nifedipine can be used.

Fibrosis

Fibrotic changes are mild or moderate and are usually small nodules in the tunica albuginea or penile septum. If the patient notices fibrosis, then he should be re-instructed in the correct injection technique and should avoid the fibrotic area. If fibrotic plaques are present, then injection therapy should be temporarily discontinued for 3 to 4 mo. Upon re-evaluation with office intracavernosal injection, physicians can determine whether the patient may continue with self-injection therapy or should proceed with surgical intervention, such as corporoplasty or penile prosthesis.

CONCLUSIONS

Although the use of oral medications for the treatment of ED has become increasingly popular, intracavernosal injection therapy continues to be indicated for certain patient populations.

- Approximately 15 to 20% of patients with ED have contraindications to sildenafil-like nitrate or NO-donor medications. This includes patients with severe cardiac disease or antihypertensive polypharmacotherapy.

- Of alprostadil responders, 15% did not respond to sildenafil. This is more common in patients who have had cavernous nerve impairment, such as patients who have had pelvis surgery, trauma, or insulin-dependent diabetes mellitus *(3)*.
- Approximately 30 to 40% of patients also prefer self-injection therapy to sildenafil *(3)*.
- In approx 50% of patients who do not respond to sildenafil or injection therapy alone, the combination of both methods can work to prevent them from using vacuum therapy or undergoing a penile prosthesis *(59,60)*.

As the physiology of erections has been clarified, improvements in the formulation and agents used in "vasoactive cocktails" have progressed. To achieve a favorable outcome, a thorough knowledge of vasoactive agents and their efficacy and side effects, as well as a multifactorial assessment to ED, is paramount. The success of home self-injection therapy also requires detailed instruction, guidance, and follow-up.

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14 Topical and Intra-Urethral Therapy

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SUMMARY

The management of erectile dysfunction (ED) has been completely transformed with the advent of effective oral therapy that occurred after the introduction of sildenafil in 1999. However, until the mid-1990s, the only practical method of delivering vasoactive substances to the penile erectile tissues was by direct injection into the copora cavernosa. Despite the introduction of orally effective agents, intracavernosal injection (ICI) continues to enjoy widespread acceptance by patients and urologists alike. However, despite its initial acceptance as a treatment alternative, 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 drop out rates approaching 50% at 1 yr. This *de facto* dissatisfaction with proven effective treatments is the rationale for alternative routes for the delivery of vasoactive substances.

Intra-urethral 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. Intra-urethral prostaglandin suppositories via the use of a commercial delivery system (Medicated Urethral System for Erection [MUSE]) gained Food and Drug Administration 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 erectile dysfunction 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 while being perceived as minimally invasive because they do not require needles or intra-urethral instrumentation. Topical and intra-urethral therapy may also provide benefits to patients unresponsive to systemic therapy or who use medications that cannot be taken along with such oral treatments (nitrate use).

Key Words: Erectile dysfunction; penis; topical delivery; intra-urethral delivery; MUSE.

INTRODUCTION

It is clear that there must be integrity of the neurovascular input to the corporal bodies for current oral therapies to be most effective. Men whose nerves are not spared during

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radical prostatectomy generally respond more poorly to oral therapies than those whose nerves are spared *(1–6)*. Therefore, there will continue to be a role for locally applied therapy in this subset of patients. Patients often inquire about less invasive therapies for the treatment of erectile dysfunction (ED) using oral, topical, or intra-urethral methods at the time of treatment discussion. Therefore, it is important that the practitioner be aware of the issues pertaining to such alternative therapies.

INTRA-URETHRAL THERAPY

General Principles of Intra-Urethral 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 *(7,8)*. The absorptive nature of the urethral mucosa was also demonstrated in several reports of systemic effects from urethrally instilled lidocaine, which is now commonly used as a local anesthetic for endoscopic procedures *(9–11)*. Reports of priapism secondary to self-introduction of various substances to the urethra emphasized this as a potential route for drug therapy of ED *(12,13)*. 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 micro-environment theoretically appears more suitable for absorption than skin because of the presence of complex columnar cells rather that stratified squamous epithelium. Indeed, the absorption of intra-urethral prostaglandin is rapid, with less than 20% of the medication remaining in the urethra 20 min after dosing *(14)*. Additionally, 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. Corporal spongiosography has shown retrograde filling of the cavernous bodies through the deep dorsal vein and its circumflex braches after intra-urethral application of prostaglandin E $(PGE)_1$ *(15)*. Regardless of the exact transfer mechanism, intra-urethral introduction of prostaglandin results in a rapid onset of hemodynamic effects in the penile vasculature—namely, increased corporal blood flow and increased arteriolar diameter, similar to those seen in intracavernosal injection (ICI) *(16)*.

INTRA-URETHRAL THERAPY FOR ED: BACKGROUND

The use of intra-urethral delivery of a vasoactive substance as a therapeutic maneuver for ED was first published in 1993. Wolfson et al. *(17)* used PGE_2 vaginal suppositories to create a PGE_2 cream and then instilled this into the urethral meatus in 20 men with ED. Treatment response was determined after 20 min and was 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, several pilot studies using various formulations of PGE_1 showed promising results. Concurrently, a commercially available delivery system was developed using alprostadil (Medicated Urethral System for Erection [MUSE]). The system consists of a polyproplyene applicator with a hollow stem that is 3.2 cm in length and 3.5 mm in diameter, with a tip containing a semisolid pellet of medication. The stem is inserted fully into the urethra, a button is depressed to dispense the medicated pellet, and the applicator is removed. It is important to have men urinate immediately before application because the residual urine helps facilitate insertion of the applicator and helps disperse the medicine. The applicators are avail-

able in 100-, 250-, 500-, and 1000-μg dosages. Although there is emerging interest in newer intra-urethral therapies using nitric oxide donors and other compounds, MUSE remains the only intra-urethral therapy approved by the Food and Drug Administration (FDA).

INTRA-URETHRAL PGE_1

Description

Alprostadil is a synthetic form of the naturally occurring 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 result from increasing the intracellular concentrations of cyclic adenosine monophosphate (cAMP). Alprostadil interacts with specific membrane-bound receptors that stimulate adenylate cyclase and elevate intracellular cAMP, leading to activation of protein kinase and resultant smooth muscle relaxation *(18)*. There is also evidence that PGE_1 may activate certain calcium-sensitive potassium channels, resulting in cellular hyperpolarization *(19)*. Alprostadil may also antagonize the vasoconstrictive actions of norepinephrine by preventing the its neuronal release and may enhance the actions of nonadrenergic, noncholinergic vasodilatory transmitters. In treating ED, 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. Therefore, the lacunar spaces expand and blood becomes trapped 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, thus blocking venous outflow. This process is also referred to as the corporal veno-occlusive mechanism. More recently, PGE_1 has been shown in vitro to induce vascular endothelial growth factor and endothelial nitric oxide synthase expression *(20)*. Vascular endothelial growth factor and endothelial nitric oxide synthase are believed to have protective/restorative effects on erectile function through different mechanisms *(21,22)*. Pilatz et al. *(23)* showed a cytotoxic effect of papaverine on human cultured cavernosal endothelial cells, an effect that was not observed with PGE_1. Alprostadil does not directly affect ejaculation or orgasm.

Pharmacokinetics

Alprostadil has been administered by intravenous infusion, intracavernous injection, and via a urethral suppository and topical administration. Intravenous administration of alprostadil requires a continuous infusion of the drug because approx 80% of the dose is metabolized in one pass through the lungs, mostly by β and θ-oxidation. After cavernosal or intra-urethral 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 10 times the 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 intra-urethral forms. Once alprostadil is in the systemic circulation, it 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 produced better responses than prazosin alone. More than 50% of men receiving a 500-μg dose of alprostadil achieved rigid or full erections *(24)*.

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 *(25)*. This was a two-tiered study consisting 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; of these, 96% reported the results of in-home therapy. There was a statistically significant difference in the percentage of men who took alprostadil and experienced successful intercourse compared to those who took placebo (64.9 vs 18.6%). Moreover, in men with responses, 7 of 10 administrations were followed by intercourse. There were no differences in efficacy resulting from 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 (compared with 11% achieved erection after taking placebo) *(26)*. It should be underscored that the reported response rates from these studies include only those patients who demonstrated erections on in-office testing, making the overall response rate 42 to 44%. Fulgham et al. *(27)* reported on their series of MUSE use in a practice setting in which only 30% of patients achieved erections sufficient for intercourse and the discontinuation rate was greater than 80%. Werthman et al. reported other concerns about the efficacy of MUSE by demonstrating full-sustained erections in only 7% of 100 consecutive patients *(28)*. Notably, 49% of this same group responded with full-sustained erections when using ICI, suggesting the superiority of the latter technique over 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 intra-urethral alprostadil in certain clinical situations or cause-specific cases of ED. MUSE has shown reported efficacy as "rescue" therapy for those who have failed other treatments. Engel and McVary *(29)* reported on a subset (452 patients) of the original MUSE study cohort who had received prior ICI therapy. They found that 58% of men who described ICI as "not effective" achieved an erection sufficient for intercourse after intra-urethral therapy in the clinic, and 47% of these men achieved intercourse at home, indicating that intra-urethral 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. A postmarketing study revealed that 57% of men who failed sildenafil therapy or discontinued its use because of side effects achieved an erection sufficient for intercourse with MUSE *(30)*. The etiologies of the ED were not stratified, and 27% of the men required the use

of a penile constricting ring (Actis). Nevertheless, these data underscore the fact that even in the era of oral treatments, intra-urethral therapy may have an important role. There is also evidence supporting the efficacy of MUSE in men with a failed penile prosthesis. Benevides and Carson *(31)* reported erections sufficient for intercourse in 7 of 11 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 *(31)*.

Costabile et al. (*32*) performed a retrospective analysis of the MUSE trial and found that intra-urethral therapy was successful in achieving erection in 70% of men in whom radical prostatectomy was the cause of their ED. However, because of 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, more than 78% of these patients reported no residual erectile function after surgery, indicating that this is a viable option in this subset of patients. Caution in interpretation is again warranted because of the two-tiered structure of the trial and the *ad hoc* nature of the report.

In a retrospective review of a single surgeon experience, Raina et al. *(33)* recently showed that MUSE was an effective treatment for postprostatectomy ED. Although their data were still retrospective in nature, they did reveal a response rate of 55% and a long-term compliance rate of 63%. More importantly, there were no significant differences noted in response rates between men with nerve-sparing procedures vs those without.

Finally, intra-urethral therapy has been studied in patients with spinal cord injury and has been found as 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. *(34)* showed that larger doses of alprostadil (1000 μg) were needed for erection in patients with spinal cord injury, and although vaginal intercourse was possible, patients were less satisfied than they were after intracavernosal injections. 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 intra-urethral alprostadil have included the addition of a proximal penile constriction ring (Actis device) and the combination of PGE_1 with other available agents. The Actis device is placed at the base of the penis prior to administration of MUSE and acts to enhance maintenance of erectile response by decreasing venous leakage and prolonging corporal exposure to the medication. It may also decrease the risk of transient hypotension resulting from any systemic absorption *(34)*. In a limited evaluation of eight patients failing MUSE alone, investigators found that six were able to obtain an erection sufficient for intercourse *(35)*. In a multicentered study of 144 patients, 71% were able to achieve erections sufficient for intercourse. This was compared with a historic control of 40%, suggesting a marked increase in response after use of this device *(36)*.

Peterson et al. *(37)* reported that the addition of 500 mg of prazosin to 125- and 250-μg doses of alprostadil improved response over each of the respective doses of alprostadil alone. However, this benefit was negated at higher doses of alprostadil.

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. *(38)* recently reported on the combination of sildenafil

and intra-urethral alprostadil. In this study, the International Index for Erectile Dysfunction questionnaire was used to evaluate patients who were not satisfied after initial treatment with either medication used as a monotherapy. A significant improvement was noted in scores for the combination group over each of the monotherapy groups. Nehra et al. *(39)* used a combination of 100 mg of sildenafil and 1000 μg of MUSE in 28 patients who had independently failed monotherapy with either agent. At a follow up of 30 mo, all 28 patients were reporting erections sufficient for intercourse, and 8 of the 28 patients had been able to reduce the sildenafil dose to 50 mg *(39)*. 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 intra-urethral prostaglandin vary and range from 30 to 70%. Response appears to be independent of the etiology of ED, with the possible exception of spinal cord injury. Patients with spinal cord injury do not appear to respond as well because of the reasons mentioned earlier. Combination therapies that include intra-urethral prostaglandin may hold more promise for the future.

Contraindications

Anticoagulant therapy, bleeding disorders, polycythemia, sickle cell disease, thrombocytosis, and multiple myeloma are conditions for which the treatment of impotence with alprostadil is contraindicated. Alprostadil is also contraindicated in patients who are prone to venous thrombosis or who have hyperviscosity syndrome and, therefore, are at increased risk of priapism. This includes patients with sickle cell disease, thrombocytosis, polycythemia, or multiple myeloma. In clinical trials of alprostadil urethral suppository, priapism (defined by rigid erection lasting longer than 6 h) and prolonged erection (rigid erection lasting at least 4 h but less than 6 h) were reported in 0.1 and 0.3% of patients, respectively. This compares favorably with the reported rates of prolonged erection and priapism associated with ICI (0.4 and 4%, respectively). No reports have indicated whether topical alprostadil has a similar range of priapism. Alprostadil in any form should be used cautiously in patients with cardiovascular disease. Symptomatic hypotension and syncope occurred in 3 and 0.4% of patients, respectively, during in-clinic dosing of alprostadil urethral suppository and therefore should not be used in patients who at risk or who have a history of syncope.

Drug Interactions

There are no drug interactions reported for any of the formulations of alprostadil. Prostin VR pediatric has been used with the standard therapy for neonates with restricted pulmonary or systemic blood flow, which includes antibiotics (penicillin and gentamycin), vasopressors (i.e., dopamine, isoproterenol), cardiac glycines, 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. Topical alprostadil is expected to behave similarly. The potential for pharmacokinetic drug interactions between alprostadil administered via injection, topically, or via urethral suppositories and other agents has not been formally studied.

Adverse Reactions

Adverse reactions of alprostadil are reported more frequently following intravenous administration; therefore, they may not be appropriate in a discussion of intra-urethral

or topical agents. Regardless, apnea has been reported in about 12% of neonates with congenital heart defects who were treated with alprostadil and was most notable in neonates who weighed 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, although hypotension is uncommon, it is a potentially serious adverse event, even with the use of intra-urethral suppositories. The patient with spinal cord injury appears to be particularly at risk; therefore caution should be used when counseling these patients *(34)*. Some have advocated the use of a constrictor ring at the base of the penis (Actis device) in conjunction with MUSE usage 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 administered intra-urethrally, 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 whether these adverse reactions in female partners resulted from medication or from 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. Regarding local penile therapy using direct smooth muscle relaxants, the durability and onset of action of such methods may not be useful attributes. There are several issues worth mentioning:

1. High systemic levels are undesirable because 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.
3. The vasoactive agent(s) need to reach the corpora cavernosa in a timely fashion with the effective (highest) concentration.

Referring to these principles, topical penile therapy has a unique set of anatomic and physiological issues that must be considered. 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 because it has direct venous communication to the corpora cavernosa *(40,41)*. The skin itself is a relatively impermeable tissue because of 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 *(42)*. 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. Exposure to the glans

affords a more easily "breached" layer. Other skin regions (e.g., back and palms) are particularly impermeable *(43)*. An additional factor confounding efficient delivery of drug is the rich vasculature of the deep dermis that may "steal" the drugs to the systemic circulation.

With the assortment of confounding factors mentioned earlier, one may wonder how gel applied to the penis could ever induce an erection. One attractive possibility is that 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, the gel could travel into the corpora cavernosa, similarly to the intra-urethral delivery of drug *(17,25)*. The known absorptive nature of the penile skin and glans make this a real possibility *(43)*. If this occurred, then delivery of the drug to the shaft of the penis would seem superfluous and might 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, therefore, 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 the drug to the penile tissues. Systemic levels have been measured, and the application of papaverine and minoxidil to thepenile skin have proved that absorption does occur. However, its presence in the systemic circulation does not prove its role in the erectile response *(44,45)*. All of the aforementioned possibilities are expected to be inefficient at transferring active agents and therefore require 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 *(46)* attempted to overcome the presumed permeation problem by performing a surgical procedure in which he made an excision of a small area of tunica and covered the defect with a patch of deep dorsal vein. The intention was to apply a local medication on the skin right above the defect. This concept did not progress—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 because the drug flux is likely to be low. Investigators are currently using permeation enhancers to increase drug flux speed. 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 to help 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 *(40,41,47,48)*. The task of these enhancers is to (a) disrupt the stratum corneum lipid bilayer; (b) interact with the membrane keratin; (c) produce a weak interaction with the drug molecule; and (d) reverse all actions in a short time.

The effectiveness of one of these agents, SEPA® (Macrochem Corporation, Lexington, MA), to enhance the transport of various agents through human or porcine skin in vitro has been well-established *(48,49)*. 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. *(50)* examined the effect of SEPA on stratum corneum by performing FT-IR spec-

troscopy, differential scanning calorimetry, and scanning electron microscopy on samples of isolated human stratum corneum. The changes that were noted suggested reversible conformational modification in stratum corneum lipids by SEPA, consistent with general lipid fluidization. The effect is reversed when SEPA is removed *in vacuo*, suggesting that the effects of SEPA are temporary, with readily and spontaneously restored lipid organization and barrier function. During the phase of lipid fluidization, drugs can diffuse through the stratum corneum at a much higher rate than normal. NexACT® (Nexmed Inc.) is another proprietary skin-enhancing technology that has been developed and is currently used in clinical trials to deliver locally applied ED therapy. In late 2002, clinical trials using these compounds were briefly halted because of FDA concerns over possible carcinogenicity in a transgenic mouse model. It was postulated that chronic skin irritation led to the increase in cancers seen in the mouse model and that the actual compound was not the cause of carcinogenicity. Those issues have been resolved and clinical trials have resumed, but this serves to underscore the hurdles encountered when trying to perfect skin-penetration-enhancing technologies.

TOPICAL THERAPY FOR ED: BACKGROUND

Various formulations using topically applied compounds to induce erection have been described. Organic nitrate donors were the first topical agents to be used in the treatment of ED *(51)*. Case reports have demonstrated that blood flow to the penis and tumescence are increased after application of a nitro-based paste *(52,53)*. 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 *(45,54)*. In one study, Cavallini *(53)* reported 2% minoxidil as superior to 10% nitroglycerin cream in inducing improved penile hemodynamics, with fewer side effects. Although topical alprostadil is by far the most thoroughly evaluated compound, it has not yet been approved by the FDA or European Union regulatory authorities. However, Alprox-TD® (Nexmed Inc.), a delivery system using alprostadil and the NexACT® skin enhancer, is now commercially available in China, and US and European phase III trials are complete or near completion. It is conceivable that this may become the first FDA-approved topical therapy for ED in the near future.

TOPICAL PGE_1

Alprostadil (PGE_1) is used in a gel form for topical application. The compound is essentially the same as that discussed in the section on intra-urethral therapy. Although applied topically, the mechanism of action is the same as previously cited—namely, it involves a PGE-receptor-mediated increase in intracellular cAMP, resulting in direct smooth muscle relaxation. The pharmacokinetics of alprostadil have been previously summarized. It is worth reiterating that the large majority of the drug is metabolized on the first pass through the lungs, and there are no reports of any significant systemic accumulation. Although there is no development of tolerance with the administration of intracavernous or intra-urethral alprostadil, this has not been reported with the use of the topical drug.

Response Rates

In a placebo-controlled phase I/II trial of a topical PGE_1 gel, Kim and McVary *(47,55)* first reported significant increases in systolic blood flow velocity, as measured by color

Doppler ultrasonography. In this largely neurogenic impotent population, only 2 of 10 patients responded with a clinical erection (no response in the placebo group). Becher *(56)* reported a double-masked placebo study that investigated the effect of a 0.2 and 0.4% alprostadil combined with a skin-penetration-enhancing gel in 52 men suffering from impotence . 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 to intracavernosal injection when measured with color Doppler, suggesting that the drug penetrates the skin and reaches the corpus cavernosum in a concentration sufficient to cause smooth muscle relaxation *(40)*.

McVary *(41)* reported a phase I/II single-blinded study with a formulation of alprostadil (0.5, 1.0, and 2.5 mg) using 5% SEPA as skin penetration enhancer. Application of the PGE_1 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 of PGE_1 doses was found in 67, 75, and 67% of patients, respectively (placebo: 17%; $p < 0.001$). This represented an advance over previous topical administration studies because significant erectile responses were obtained with gel applications.

Interestingly, most patients had modest or absent responses to gel application in the initial 25 min following application. This response was greatly augmented with the addition of visual or tactile stimulation, suggesting the role of topical gels in *facilitation* rather than *initiation* of erection. The facilitation was not observed in the placebo group. This augmentation of erectile response with tactile stimulation has been found with several oral, intra-urethral, and intracorporal injection treatments *(25,57,58)*. Importantly, Becher *(56)* performed a female safety study in 18 healthy volunteers using 1 g of a gel consisting of 0.4% alprostadil (4000 μg) applied on the vaginal wall and introitus. Ten postmenopausal and eight premenopausal women showed good tolerance to this formulation, although one patient experienced minor bleeding at the cervix. All patients showed labial and clitoral engorgement that was not referred to as uncomfortable.

In two multicenter, placebo-controlled, phase II trials, significant changes from baseline in erectile function scores were seen in patients treated with Alprox-TD® *(59)*. Response increased with dose escalation, and the response was greater in patients with severe ED (second trial). Results of recently completed phase III trials are eagerly anticipated.

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. No reports have indicated the risk of prolonged erection and whether topical alprostadil has a similar range of priapism as intra-urethral administration (0.1%). Topical alprostadil has not been shown to have a similar risk of syncope compared with intra-urethral use *(41,47)*. There are no drug interactions reported for any of the formulations of alprostadil. Similarly to MUSE, systemic drug interactions are unlikely because of the low systemic absorbance of topical prostaglandin.

Adverse Reactions

In addition to the aforementioned adverse events, topical alprostadil has unique reactions that must be mentioned. Discomfort at the application site was reported in 85% of participants after the topical application of an alprostadil/SEPA gel *(41)*. Most patients

(85%) who received the SEPA formulation—whether or not it contained PGE_1—experienced a sensation of warmth that abated within 5 to 20 min of application. This time frame suggests that the SEPA formulation was the mediating substance. About 20% of the patients classified this warmth as severe burning. Because 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 the glans penis. It is possible that application of the gel to the glans exclusive of the penile shaft may prevent this discomfort. It is likely to have been the function of both the carrier formulation and the active drug because 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 PGE_1 belongs, it is not surprising that an alprostadil gel influences other processes than erection when applied to the penis. Eicosanoids exist in nearly all somatic tissues and are known mediators of a large number of physiological 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 *(60)*. The role of prostaglandins in the sensory afferents of pain perception is well-documented, although intermediates such as calcitonin-gene-related peptide may be involved *(61)*. Interestingly, in a study by McVary et al. (*41*), there was no correlation between skin reaction, discomfort, side effects, or erythema with erectile response. This is important because the disassociation of the side effects from the positive attributes of erectile response allows 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 for the treatment of ED. Although little can be said about its role in that regard, there is an 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 in 1988 for the treatment of alopecia. Investigation of topical formulations for 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. Iit is instead converted to minoxidil *O*-sulfate by the hepatic enzyme sulfotransferase *(62)*. This metabolite has 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 or exhibit adrenergic neuronal blocking effects. Despite adrenergic denervation, minoxidil retains its activity. Minoxidil-induced delay in the hydrolysis of cAMP through the inhibition of PDE may contribute to the its vasodilatory action as well. All

direct vasodilators produce a sympathetic response, including an increase in heart rate, stroke volume, and cardiac output as well as a marked increase 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 stimulates hair growth, topical therapy does not cause hypertension. Minoxidil may either activate the hair follicle directly or may stimulate the microcirculation around the follicle, thereby 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. This presumably promotes the veno-occlusive mechanism and results in erection. This effect from topical minoxidil is interesting considering that it is a prodrug that requires hepatic metabolism to become active *(62)*. For this to be effective, the topically absorbed minoxidil must be metabolized through the liver then recirculated to the penis to be active. This appears to a substantial task. Issues regarding the site and efficacy of absorption were addressed earlier in this chapter.

Pharmacokinetics

Minoxidil can be administered topically or orally. Approximately 90% of an oral dose is absorbed from the gastro-intestinal 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 is widelydistributed 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 is 4 h, antihypertensive effects can last 2 to 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, has no tubular secretion, and, therefore, renal clearance depends on glomerular filtration. This filtration accounts for approx 10% of total clearance. Approximately 95% of a topical dose is eliminated after 4 d.

In topical administration of 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 fingertips, the hands should be thoroughly washed after application. Systemic effects resulting from topically administered Minoxidil are unlikely but 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 or cerebrovascular disease because of 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. Using Rigi-scans to measure penile circumference changes resulting from a topical 2% minoxidil solution, Cavellini

(54) reported a significant increase when compared with topical 10% nitroglycerin or placebo ointment. Similarly, he reported a significant increase in penile rigidity with topical minoxidil compared with the nitroglycerin or placebo controls. Doppler ultrasonography of cavernosal arterial flow was reported as greater with minoxidil than either control, but no quantitative information was supplied. No mention of sexual intercourse was reported. In a slightly different study design, Clark *(45)* reported on the treatment of ED in diabetic males using a 2% minoxidil combined with a penetration enhancer (SEPA). 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 has been used in its oral form. Little is known about results when minoxidil has been used topically for the treatment of ED. Regardless, drug interactions of minoxidil include antihypertensive agents, nitrates, diazoxide, diuretics, estrogen, nitroprusside, nonsteroidal anti-inflammatories, and sympathomimetics. Estrogens can cause fluid retention, thus increasing blood pressure and antagonizing the antihypertensive effects of minoxidil. Nonsteroidal anti-inflammatories 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 on its use. Systemic adverse reactions are unlikely from topical administration. Placebo-controlled trials with topical minoxidil only showed an increase in dermatological effects from the active drug. Oral minoxidil has been occasionally associated with the appearance of a bulbous rash and Stephen Johnson's syndrome. Topical minoxidil therapy produces local dermatological reactions, including contact dermatitis, local burning pruritus, erythema, and xerosis. Many adverse effects have been reported during the administration of topical minoxidil preparations, but no effects have been directly attributed to the drug.

TOPICAL PAPAVERINE

Introduction

Since Virag *(63)* introduced of injection of papaverine into the corporal bodies for the treatment of sexual dysfunction in the early 1980s, it has become a widespread and well-accepted method. 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 by inhibition of the oxidative-phosphorylation-mediated inactivation of cAMP (via PDE), and it interferes with calcium mobilization during muscle contraction. This results

in an increased half-life of the secondary messengers cyclic gunaosine monophosphate and cAMP. This relaxation is noted in the vascular system, bronchial musculature, the gastro-intestinal/biliary tracts, and the urinary tract (including the corpora cavernosa). If spasm exists, this relaxation may be prominent. The relaxation is direct and is unrelated to muscle innervation, because the muscle still responds to drugs and other stimuli that cause contraction. Papaverine has minimal action on the central nervous system, 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 were measured in a single study using a high-performance liquid chromatography assay *(44)*. After 60 min, mean serum levels had increased by 50%, suggesting that absorption occurred but did not occur 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. Conversely, papaverine is present in the blood at levels of 335 to 761 ng/mL within 3 min of 40 mg injected intracavernosally, as measured by similar techniques *(64)*. The pharmacokinetics and bio-availability of topical papaverine on animal models have been studied, in which 9 to 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 *(65)*.

Response Rates

Kim et al. *(44)* reported the use of topical papaverine in a phase I/II single-blinded, placebo-controlled trial of 20 patients with organic impotence. The formulation included 5.5% papaverine HCl gel and 7, 15, and 20% papaverine base gel as well as a proprietary skin-permeation enhancer. After the application of the gel at the penis, scrotum, and perineum, a dose-dependent hemodynamic effect was observed during duplex ultrasonography. Only three patients achieved full erections (also when exposed to placebo, suggesting reflex erection). The tolerability was good both locally and systemically. Similar findings were reported using up to 20% papaverine base gel *(66)*.

Contraindications

Intravenous injection of papaverine is contraindicated in the presence of complete atrial ventricular heart block. When contraction is depressed, the drug may provoke transient ectopic rhythms of ventricular origin (either premature beats or paroxysmal tachycardia). Papaverine does not have FDA approval for the treatment of ED by intracorporal injection or topical application. The intracorporal injection of papaverine is known to result in persistent priapism that requires either surgical or medical intervention. The impact that topically applied drugs would have on any of these types of complications is a matter of conjecture at this point. Based on the bio-availability 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 as with intracavernous injection *(67–69)*. Topical therapy was not

shown to have a similar risk in one study *(44)*. General discomfort, nausea, abdominal discomfort, anorexia, skin rash, malaise, vertigo, headache, intensive flushing of the face, perspiration, increased depth of respiration, increases in heart rate, slight increases in blood pressure, and excessive sedation have been reported side effects resulting from papaverine given by injection. Few of these have been reported when administered by topical methods.

TOPICAL NITROGLYCERIN

Introduction

The use of topical nitroglycerin is a standard treatment for unstable angina pectoris because predictable blood levels can be achieved. Several studies have attempted the use of nitroglycerin ointments, pastes, plasters, or patches for the treatment of ED.

Mechanism of Action

Relaxation of vascular smooth muscle is the principle pharmacological action of nitroglycerin. In a dose-dependent manner, nitroglycerin produces 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 and results in a more favorable supply–demand ratio. It is not known whether topical nitroglycerin for the treatment of erectile function can have similar effects on cardiac status. Contraindications for the use of topical nitroglycerin include patients who have allergic reactions to organic nitrates. These are extremely rare, but they do occur. Allergies to the adhesives used within the nitroglycerin patches have also been reported.

Pharmacokinetics

Nitroglycerin transdermal delivery systems are designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release is linearly dependent on the area of the applied system. In patch systems approved by the FDA, each square centimeter of applied system delivers approx 0.02 mg of nitroglycerin per hour. Generally, after approx 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 extra hepatic 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 that system's use. It is not known whether any of these pharmacokinetic issues are pertinent to topical nitroglycerin applied to the penis.

Response Rates

Owen et al. *(52)* reported a double-blind, placebo-controlled study using a 2% nitroglycerin paste applied at the penile shaft in 30 patients with impotence. The evaluation

included penile tumescence measurement and duplex ultrasonography. Although the patients who 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. *(70)* reported a study in 174 patients who underwent duplex ultrasonography for an ED workup and received a topical application of nitroglycerin paste at the penile shaft. There was a significant difference in the four vessels' diameters before and after the drug application.

Clinical evaluations in a home environment are limited. Nunez et al. *(53)* reported three successful cases involving use of 2% nitroglycerin paste. Sonksen *(71)* reported "clinical response" in 12 of 17 patients with spinal cord injury. However, only five achieved a "usable response" at home. Meyhoff *(72)* studied 10 patients with nitroglycerin patches; of these, 4 patients achieved a "usable" response and 3 preferred the patches to their usual intracavernosal papaverine treatment.

Adverse Reactions

The most frequent adverse reaction in patients who are administered nitroglycerin is headache, which occurs in approx 2% of patients. Other reactions that occur in less than 1% 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.

CONCLUSION

The advent of oral therapy for ED has obviously revolutionized the approach to treating this very prevalent disease. In addition to the increased public awareness of ED that came with the introduction of sildenafil and other oral agents, there has been a renewed interest in advancing the understanding of penile physiology, basic erectile pharmacology, and alternate drug delivery systems. The latter constitutes an evolving technology that is potentially useful for the treatment of ED. Intra-urethral drug delivery is now well-established and appears to function as a second- or third-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 to take advantage of its vascular communications with the corpora cavernosa. Although topical therapies are still experimental, introduction into the market may be on the horizon, and this form of therapy 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 intra-urethral agent has its place in the physician's armamentarium to treat patients with ED.

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15 Vacuum Erection Devices

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SUMMARY

Vacuum erection devices (VEDs) are safe, effective treatments for erectile dysfunction with few side effects. Vacuum negative pressure more than 100 mmHg causes a combination of arterial and venous blood to fill the corpora cavernosum. The use of an elastic band to trap the blood within the penis allows sufficient rigidity for penetration. Devices approved by the Food and Drug Administration have a vacuum pressure regulator to prevent injury resulting from excessive negative pressure. Nearly all patients with erectile dysfunction can obtain an erection, and even men with hematological defects can safely use a device. Since the advent of oral pharmacotherapy for erectile dysfunction, dropout rates for VED users have increased substantially. However, VED remains an effective and well-accepted treatment in certain populations. Adjunctive uses of the device to enhance erectile responses in men with intracavernosal injection, penile prosthesis, and after explantation of penile implant all have been proposed. The off-label use of the device to rehabilitate erectile function after radical prostatectomy or other causes of erectile dysfunction has not yet been proven effective. Overall, vacuum erection devices remain a cost-effective treatment for erectile dysfunction and an acceptable second-line therapy.

Key Words: Penile erection; vacuum erection device; erectile dysfunction.

INTRODUCTION

The ideal treatment for erectile dysfunction (ED) should demonstrate efficacy, safety, rapidity of onset, limited side effects, and ease of administration. Before the advent of oral pharmacotherapy, vacuum erection devices (VEDs) fulfilled many of the criteria for a successful treatment and achieved a moderately high diffusion to patients with ED. Although the use of all treatments other than phosphodiesterase type 5 inhibitors has declined since the approval of sildenafil citrate in 1998 *(1)*, second-line therapies are required in a considerable number of patients and include VEDs, intracavernosal and -urethral vasodilators, and penile implants. VEDs remain one of the currently available therapies that should be considered for the treatment of ED, as outlined in the Erectile Dysfunction

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Guideline Update Panel appointed by the American Urological Association (AUA) *(2)*. Low patient acceptability limits the widespread application or use of this therapy, but it remains an effective, inexpensive treatment option.

John King, a 19th-century American physician, advocated that a "glass exhauster should be carefully applied to the part, once a day." Thus, he was perhaps the first to suggest that continuous and repeated application of a vacuum device to the penis could prevent or reverse impotence *(3)*. Lederer added a compression ring to the vacuum device to facilitate an on-demand erection. In 1917, his "device for the artificial erection of the penis" was patented in the United States (Surgical Device, no. 1225341).

In 1974, Osbon *(4)* invented and developed the first VED to receive approval by the Food and Drug Administration (FDA). In 1986, Nadig and colleagues *(5)* reported on the efficacy and safety of the device. Subsequently, the FDA has approved use of numerous VEDs. Vacuum devices are currently recognized as a safe and inexpensive treatment for ED *(6–10)*. More than 175 citations in PubMed contain information about the rationale, engineering features, and therapeutic use of VEDs (www.ncbi.nlm.nih.gov/entrez, accession date July 7, 2005).

HEMODYNAMICS OF VACUUM-INDUCED ERECTION

Unlike penile erection in a healthy individual, the hemodynamics of a vacuum-induced erection does not depend on intact arterial inflow. VEDs cause rigidity through negative pressure suction and by trapping blood in the penis. In the majority of patients, vacuum negative pressure greater than 100 mmHg is necessary to achieve erection *(11)*. Researchers have not completely determined whether arterial blood contributes to the erection or only venous filling occurs. Numerous studies have suggested that transient increases in arterial blood flow occur during vacuum-induced erection *(12–14)*. Blood is trapped in several different compartments in the penis, including subcutaneous spaces and the corpora cavernosa. Reduced xenon washout of the corpora has been demonstrated with the Erec Aid© system (Endocare; ref. *15*). An elastic band, disk, or O-ring placed around the base of the penile shaft contains the blood within the penis and allows rigidity sufficient for penetration and sexual activity *(10)*.

Excessive negative pressure can be detrimental to the penis, and pressures should not exceed 225 mmHg. Because greater negative pressures can cause bruising and hematoma, a vacuum pressure regulator (limiter) is essential; therefore, only FDA-approved devices should be used. In the past, such VEDs were only available by prescription, but over-the-counter devices containing a vacuum limiter are also available and acceptable *(2)*.

The corporal diameters double after vacuum distension and placement of the constriction device *(13)*. The only absolute anatomical requirement for successful induction of erection with a VED appears to be the presence of cavernosal sinusoids capable of filling and distension. Patients with cavernosal fibrosis after priapism or prior infected penile implant experience a poor response to this therapy *(16)*.

Although normal arterial inflow may not be required for the effective use of a VED, a significant decline in amplitude of the pulse volume occurs after application of the constriction ring. Although one group using plethysmography *(11)* described persistent, albeit reduced, blood flow during constriction, others found no arterial flow after constriction using duplex Doppler ultrasonography *(13)*. Together, the data suggest that prolonged application of the constriction ring may lead to ischemia. Constriction sufficient to maintain rigidity can be maintained without risk for up to 30 min.

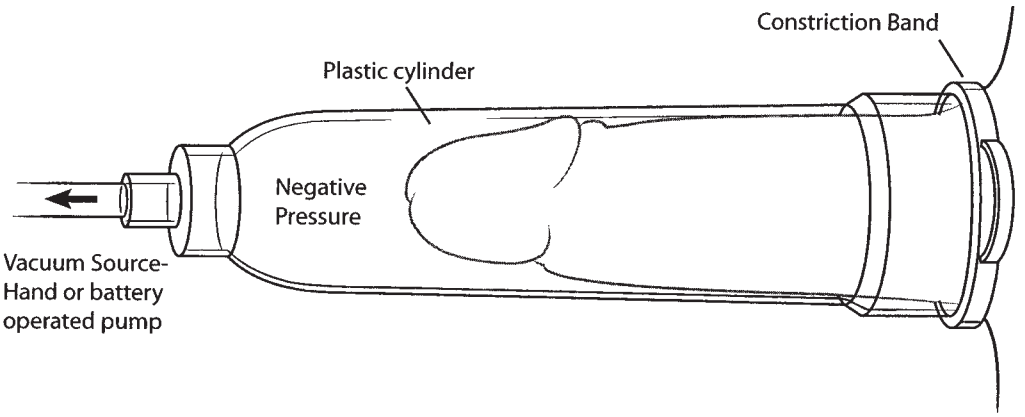

Fig. 1. Diagram of a VED showing cylinder and constriction ring. The vacuum pump, either hand- or battery-powered, may be self-contained or attached via tubing.

Table 1
Vacuum Erection Devices Approved by the FDA

Manufacturer	*Device name*	*FDA approval*	*Cost (US $)*
Endocare	Osbon ErecAid©	Yes	450–575
EuroSurgical	Post-T-vac	Yes	430
Owen Mumford	Rapport Premier/Classic	Yes	330
Augusta Medical	Touch II/Response II	Yes	300
Mediwatch	Erectease	N/A	385

DEVICE REQUIREMENTS

To ensure the presence of a negative pressure regulator and other design features, only FDA-approved equipment should be used. The VED must be of adequate length and diameter to accommodate the patient's penis. Men with Peyronie's disease may not be able to induce erection successfully because of penile deformity or pain resulting from bending of the erect penis in the cylinder. All VEDs consist of a transparent plastic cylindrical chamber, a manual or battery-powered vacuum, and a constriction device (Fig. 1). Metal or other inelastic rings are contraindicated *(10)*. Optimal sized openings allow the distended penis to fill the cylinder without allowing scrotal skin to be trapped in the device. Table 1 lists the currently available FDA-approved devices.

PATIENT SELECTION

VEDs allow almost all men with ED to successfully achieve erection *(10)*. Success depends on appropriate instruction; in a recent prospective study, nearly all postprostatectomy patients were able to obtain erection by the second demonstration *(17)*. Another study showed that men with diabetes achieved erection in the majority of cases *(18)*. Conversely, one study reported that men with extensive scarring and deformity of the penis are highly likely to fail with VEDs *(16)*. Nevertheless, even in this population, a trial may be worthwhile if surgical therapy with a penile implant is not an acceptable alternative. Men with a high-risk level for cardiovascular disease should not receive treatment for sexual dysfunction until their cardiac condition has stabilized *(19)*.

The time commitment to obtain and use the VED was calculated at 1 to 1.5 d; individual instruction by a physician or experienced medical assistant is likely to enhance successful

use of the device and should be provided *(10)*. Manual dexterity of the patient should be considered; a single-handed device incorporating the suction cylinder and pump in one piece may be more user-friendly, especially for novice users *(20)*. Printed material and videotape instructions are less effective in ensuring technical success than demonstration by a trained individual *(21)*.

Contraindications

Although the UK Panel on ED *(22)* mentions bleeding disorders as a potential reason not to use VEDs, one prospective study has shown no increased risk of complications of VED in patients taking warfarin *(23)*. The weight of evidence regarding hematological defects and VEDs suggests safety in the face of coagulopathy or anticoagulation therapy.

Instructions

After applying a water-soluble lubricant to the base of the penis and the contact area of the VED, the penis is placed in the chamber. By pressing the base of the chamber tightly against the pubic bone, patients are less likely to trap the scrotal skin or testes *(10)*. Improved penile rigidity results from the technique of double-pumping (applying the vacuum for 1 to 2 min, releasing pressure, and reapplying it for an additional 3 to 4 min). To maintain rigidity when the vacuum is released, the constriction device is placed around the base of the penis. In men with severe corporal veno-occlusive dysfunction, multiple constriction rings are necessary to maintain rigidity *(24)*.

EFFICACY

Regardless of the etiology of ED, most men who use a VED can achieve penile rigidity sufficient for vaginal penetration *(25–27)*. The AUA Guidelines Panel (Table 2; ref. *10*) summarized accrued results from nearly 20 clinical trials through 1994. No new evidence regarding efficacy or safety of the devices was reported in the 2005 Report of the Guidelines Update Panel (convened in 2000; ref. *2*).

Based on data collected before the sildenafil era, the overall probability of achieving return to intercourse with VEDs was 0.757, with a 0.253 probability of dropout. More evidence continues to accrue, including results of randomized controlled trials. Dropout rates have increased substantially (*see* Patient Satisfaction and Long-Term Use section). Efficacy of the VED has been demonstrated in numerous specialized patient populations, including patients with spinal cord injury *(28)*, cavernous veno-occlusive dysfunction *(24)*, postradical prostatectomy *(17,29)*, and diabetes *(18,26,27)*. VEDs remain effective and well-accepted in certain patients, usually older men in a stable relationship.

Specialized Uses

Adjunctive uses for VEDs have been advocated in case series and case reports as well as by expert opinion. Vacuum devices can enhance responses and erection quality in patients using intracavernosal injection (ICI) *(30,31)*. Using a VED in combination with ICI, one investigator recorded increased buckling pressure from 117 to 125 mmHg with ICI up to 565 mmHg *(32)*. Similar improvements have been observed in patients using intra-urethral pharmacological agents *(33)*.

Others have proposed using the VED to augment tumescence and improve erection quality in men with a penile prosthesis *(34)*. The device has also been used as a tissue expander after grafting procedures of the tunica albuginea. After surgery for Peyronie's

Table 2
Outcomes and Complications of VEDs

Outcome of treatment	*Number of studies Total (n)*	*Results Median, 95% CI*
Return to intercourse	18	0.757
	1943	0.668–0.828
Patient satisfaction	20	0.763
	859	0.686–0.826
Partner satisfaction	7	742
	218	0.582–0.867
Dropout[a]	22	0.253
	1072	0.218–0.291
Local AEs	18	0.095
	884	0.054–0.150
Discomfort/pain	20	0.188
	2481	0.135–0.254

Abbreviations: CI, confidence interval.
[a]Current reports suggest a much higher dropout rate.
(Drawn from ref. *10*.)

disease or penile augmentation, the device may both prevent graft contraction and improve the results of lengthening and girth enhancement of the penile shaft *(35,36)*.

Another indication for the use of VEDs is to expand fibrotic cavernosal tissue in anticipation of penile implant. Hakim (personal communication, 1996) has described daily use of the VED to enhance the probability of penile implant surgery in men with prior priapism or infected implant, in whom severe fibrosis makes the implant challenging.

The potential off-label use of the device to rehabilitate erectile function after radical prostatectomy or other etiologies of ED is intriguing. Hemodynamic effects of blood flow, pressure, or mechanical strain have been demonstrated in vitro with vascular smooth muscle cells, but in vivo or in vitro studies using cavernosal cells are lacking. One clinical study showed improvements in nocturnal penile tumescence after repeated use of VEDs *(37)*. However, this study has not been duplicated. Therefore, evidence to support the use of VEDs to prevent ED or restore erectile function is lacking. A randomized controlled trial of postoperative VED "rehabilitation" following radical prostatectomy is in progress (personal communication, David Talen, Endocare) and may help clarify this important question.

PATIENT SATISFACTION AND LONG-TERM USE

Erection with a VED differs from normal penile erection. Patients and partners may note lower skin temperature, glans coolness, cyanosis, venous distension, and abnormally increased girth. Destabilization of the phallus at the point of constriction can impede penetration. Although ejaculation is inhibited or altered by the constriction ring, a retrospective case series has reported orgasm in up to 74% of patients *(23,38)*.

Patient and partner satisfaction appear to be closely correlated (Table 2; ref. *10*) and depend on successful erection *(28)*. However, studies have not been performed using validated anonymous instruments to quantify erectile function or patient and partner satisfaction with the devices.

In the era of oral pharmacotherapy, use of VEDs has decreased significantly, with only a minority of patients choosing to use the devices and then continuing to use them in the long term *(17,39–41)*. In one study, men using VEDs were administered sildenafil; of those who successfully achieved erection with both therapies, two of three chose the phosphodiesterase-5 inhibitor rather than VED *(42)*. Men in a randomized controlled trial who failed sildenafil were more likely to choose ICI over VEDs. Notably, however, no statistically significant differences in patient or partner satisfaction were noted between the two treatments *(23,34)*.

Dropout rates have increased compared with earlier data, in which 35 to 60% of patients continued using the device at 1 yr of follow-up *(23,40,43)*. In two recent reports outlining a stepwise or progressive treatment regimen for ED in postprostatectomy *(29)* and diabetic men *(18)*, only 10 of 74 and 9 of 284, respectively, were using VED at the end of the study.

COMPLICATIONS

The original AUA Guidelines panel for ED calculated the probability of discomfort from the use of a VED as 0.188 *(10)*. Severe pain and dropouts resulting from severe pain are infrequently reported. Local adverse events occur with a probability of 0.095. These include petechiae, which may develop on the skin of the penis as a result of capillary rupture after using a VED. Ecchymosis and hematoma are uncommon but have been reported, particularly in men taking aspirin or other anticoagulant drugs. Men who use VEDs commonly report altered climax and impaired ejaculation. Several case reports have documented the onset of penile curvature after use of VEDs *(44–46)*.

Although it has been suggested that men with spinal cord injuries and other neurological impairments of penile sensation may have complications with use of the constriction ring *(47–49)*, one prospective study in this population showed no such adverse events *(28)*. Failure to remove the constriction ring in a timely fashion could embarrass the blood supply to the penile shaft skin or the entire distal penis *(50)*.

ROLE IN TREATMENT

All aspects of the VED, including advantages and disadvantages of the device, should be discussed in an unbiased fashion, because most men can achieve adequate rigidity regardless of the cause of ED *(10)*. The UK Guidelines *(22)* cited advantages of VEDs, including low incidence of side effects; capability of long-term use; and applicability to a wide range of patients, including those who have failed other therapy. According to the UK Guidelines, disadvantages include lack of application in patients with bleeding disorders; lack of spontaneity and cumbersome nature; uncomfortable erections or impaired ejaculation; pivoting at base of penis; cold penis for partner; and worse ability to attain orgasm compared with ICI, with lower satisfaction for patient and partner.

The VED is a cost-effective treatment for ED. As more men develop ED because of aging of the population and increased prevalence of diabetes, obesity, and cardiovascular disease, cost issues may become more important for patients and society. The typical cost of a device in 2005 ($400) was less than the yearly cost of oral pharmacotherapy (assuming four tablets of a phosphodiesterase-5 inhibitor are prescribed per month).

CONCLUSIONS

VEDs remain a reliable, efficacious, and safe second-line therapy for ED. Patient acceptance of the device has declined as other less-invasive options have been introduced, and only a minority of men with ED select this treatment. However, for men with refractory

ED or those for whom ICI is not acceptable, a VED is highly likely to induce an erection sufficient for sexual intercourse. Specialized indications for pre- and postsurgical tissue expansion, augmentation of ICI, and adjuncts to penile implants have been described. No rigorous scientific studies have substantiated the role of this modality as a hemodynamic intervention or prevention strategy, but it merits further investigation.

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16 Penile Implants

Steven K. Wilson, MD and John J. Mulcahy, MD, PhD

SUMMARY

Effective penile implants were introduced in the early 1970s and have provided a predictable and reliable treatment of erectile dysfunction. They can be placed in almost all circumstances in which more conservative treatments have been ineffective or are contraindicated. Manufacturers of these devices have improved their functioning and durability, and repair rates are low when compared with other mechanical products. Infection rates associated with implantation of these devices have declined because of the introduction of antibiotic-coated products, and salvage procedures have greatly reduced the need for implant removal under these circumstances. The satisfaction among both patients and partners using penile implants is in the range of 80–90%, a higher rate than that for any of the other treatments of erectile dysfunction.

Key Words: Penile implants; erectile dysfunction therapy; salvage of infected implants; penile implant categories; penile implant complications.

INTRODUCTION

The forerunners of today's penile prostheses were introduced to the marketplace more than 30 yr ago. It is a little known fact that the introduction of today's semi-rigid rod *(1)* and the three-piece inflatable *(2)* was almost simultaneous. Before the introduction of these, there was very little interest in erectile dysfunction (ED), little was known about the causes and epidemiology, and the few treatments prescribed were largely unsuccessful. Before the availability of commercial prostheses, most physicians believed that impotence was a psychological malady and referred afflicted patients to a psychiatrist. This chapter explores what we have learned from experience with this medical device over the past three decades. An extensive review of the subject occurred in June 2003 at the Second International Consultation on Sexual Medicine held in Paris, France *(3)*.

The semi-rigid or malleable prostheses initially were much more popular than the three-piece implant. The surgery was considerably easier, and there was less need for mechanical correction. Over the years, however, the multicomponent implants were noted for less compromise in both flaccidity and erection, and their mechanical reliability steadily rose. As the three-piece inflatable penile implant passed its 30th birthday, 5-yr survival

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Fig. 1. AMS Ultrex CX and CXR.

Fig. 2. Mentor of Titan and Titan NB.

from mechanical revision exceeded 90% *(4)*, and manufacturers reported that 70% of devices sold in the United States were of the three-piece variety.

TYPES OF PENILE IMPLANTS

There are three classes of penile implants: hydraulic, semi-rigid, and soft silicone. The hydraulic consists of two types: the three-piece inflatable and the two-piece inflatable. Two companies, American Medical Systems (AMS) and Mentor Corporation, manufacture three-piece hydraulic penile implants. Both companies market two widths of cylinders. AMS calls its standard cylinder the CX and its narrow cylinders the CXM and CXR (Fig. 1). Mentor calls its standard cylinder the Titan and its narrow model the Titan NB (Fig. 2). The narrow cylinders are appropriate for the thin penis and for the penis with scar tissue where dilatation to a larger caliber corporal body is not easily accomplished. All

of these cylinders expand in girth but not in length. AMS also manufactures the Ultrex cylinder, which expands in girth and length.

Cylinder construction is quite different between the two manufacturers. AMS cylinders are composed of three layers. The inner layer is silicone, the middle layer is a fabric of woven Dacron and Lycra, and the outer layer is silicone. The CX and CXR have a unidirectional weave to their fabric, allowing only girth expansion, whereas the Ultrex has a bidirectional weave, permitting expansion in both length and girth. In late 1999, AMS added a Paralyne coating to the surfaces of any silicone not in contact with the body tissues. This micropolymer increases the lubricity of the silicone and makes the silicone much more wear-resistant in bench testing by the manufacturer. Although no clinical survival studies have been published, experience during the last 6 yr has confirmed markedly improved cylinder longevity following the introduction of Paralyne. The AMS pump and reservoir are also made from silicone, and Paralyne has not yet been added to their construction.

Mentor cylinders and reservoir are made of Bioflex, a material similar to polyurethane. Silicone is the material used to connect the components of the pump and the tubing. Apparently, it is not possible to make tubing from Bioflex because it is formulated as a dispersion, whereas tubing construction requires extrusion. Bioflex and silicone do not bond to each other chemically, and the process used to bond the components to the silicone tubing is proprietary; Mentor does not disclose information regarding this process. Mentor cylinders in lab testing are more abrasion-resistant than silicone cylinders, and clinical studies before the introduction of Paralyne bore this out, as the recent studies of non-Paralyne AMS devices *(5)* had worse 5-yr freedom from mechanical revision than the Mentor implants. Notably, a very large series of Mentor devices had virtually no failures from Bioflex; most revisions were necessitated by silicone tubing failure adjacent to the pump *(4)*.

Mentor devices are all preconnected between cylinders and pump. The cylinders are available in 2-cm increments, from 10 to 22 cm. Reservoir sizes are 75 and 100 cc. AMS devices are available in preconnected and as separate components. Cylinder length is in 3-cm increments, from 12 to 21 cm for the standard size CX and Ultrex; however, the cylinder length for the downsized CXR is available in 2-cm increments. Reservoir sizes available are 65 and 100 cc. Rear-tip extenders (RTEs) are 1 to 3 cm for the Mentor implants and are stackable, enabling the rear tips to equal 6 cm. RTEs for AMS CX and Ultrex are similar, but a 0.5-cm extender is also available. The CXR has a nonstackable, snap-on RTE that is available in 0.5 to 6 cm.

Infections are the most disastrous complications of any implantable device. Both companies have taken steps to decrease the incidence of these problems by applying coatings to the prosthesis that are designed to retard bacterial growth. In May 2001, AMS introduced InhibiZone, a patented antibiotic surface treatment that impregnates minocycline and rifampin into the external silicone surfaces of all the components, with the exception of the RTE, resulting in a mottled orange appearance. The antibiotics elute into the implant spaces over 7 to 10 d, and all traces are gone by 12 d. Concentrations of the antibiotics represent less than a common oral dose but appear effective in preventing early colonization and the development of a bacterial biofilm layer *(6)*. The mechanism of minocycline (inhibits protein synthesis) and rifampin (inhibits DNA-dependent RNA polymerase) may help reduce the likelihood of developing bacterial resistance to either agent *(7)*. In vitro and in vivo studies have demonstrated that minocycline is effective in retarding the emergence of staphylococcal strains that are resistant to rifampin *(8)*. Short-term follow-up

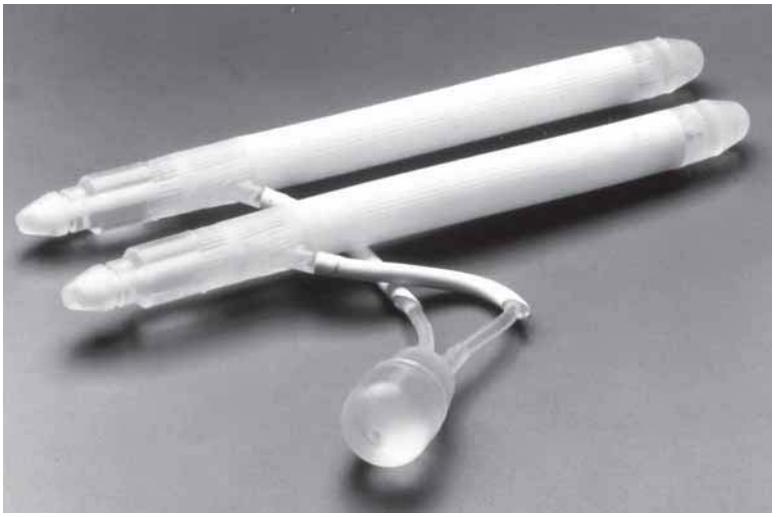


Fig. 3. AMS Ambicor two-piece prosthesis.

for this prosthesis enhancement shows statistical improvement in infection reduction for first-time implant patients in a single surgeon study *(9)* as well as in the manufacturer's databank study *(10)*.

Mentor recently began to coat their Mentor Alpha 1 and Mentor Alpha NB with a hydrophilic coating. Initially, this coating was called Resist, but this title was subsequently eliminated in the United States and the prosthesis was renamed Titan and Titan NB. The hydrophilic coating absorbs 23 times its weight in water, and when a coated implant is soaked in an antibiotic-containing solution, the antibiotics are theorized to adhere to the surface of the device. No clinical studies are available, but a manufacturer databank study has shown a decreased rate of implant infection compared with Mentor's uncoated devices *(11)*. Coincident with the introduction of the new-coated Titan prosthesis, the tips of the cylinders were changed to a more physiological tapered shape, rather than the former blunt appearance.

The only two-piece device available in the United States is the AMS Ambicor (Fig. 3). This device has cylinders similar to the obsolete AMS self-contained implant, the Dynaflex. In this two-piece model, the pump mechanism has been moved from the tip of each cylinder to a separate scrotal pump attached to the two cylinders. Depression of the pump causes fluid to move from a 3- to 5-cc reservoir in the base of the cylinder to a cylinder distensible to a fixed width in the middle of the penile shaft that achieves rigidity. Detumescence is obtained by bending the penis 90 degrees from the horizontal position for 12 s. Flaccidity and erection are compromised with this model compared with the three-piece multicomponent device, mainly because reservoir volume is so severely restricted. The device is not yet available with Paralyne or InhibiZone coatings, but it has a popular following and good short-term mechanical reliability *(12)*.

Mentor previously marketed a two-piece device entitled Mentor Mark II. This device had an egg-shaped pump/reservoir that contained 25 cc but delivered approx 15 to 20 cc to Bioflex standard-sized cylinders. The device was not popular, and Mentor withdrew it from the market. Mentor presently has a similar device called the Excel in clinical trials; it has narrow-based cylinders attached to a smaller (20 cc) combined pump reservoir. This device is currently approved in numerous markets outside the United States.

Fig. 4. Genesis semi-rigid rod penile implant.

There are two types of semi-rigid rod prostheses: the malleable and the mechanical. The Genesis of Mentor Corporation is a malleable prosthesis composed of a braided silver wire surrounded by a silicone hydrophilic coat (Fig. 4). The AMS 650 and 600 implants have a construction similar to silicone surrounding a stainless steel woven core. The Jonas prosthesis, which has been manufactured in Germany for more than 20 yr, also has a silver core and silicone covering *(13)*. The AMS Dura II is a unique semi-rigid rod. This device has articulating segments of polyethylene held together by a central spring. The articulating segments resembling a ball and socket are covered by a polytetrafluoroethylene sleeve and are surrounded by a silicone jacket to prevent in-growth of tissue into the mechanical parts (Fig. 5). Finally, there are soft silicone rods that were originally manufactured in France by Subrini (Fig. 6; ref. *14*). These inexpensive devices are sold under various names in several countries—mostly in Europe and mainland China. This implant has been promoted to aid the partially impotent man who has tumescence but no rigidity. The soft silicone implants are used less often because many men with partial ED now respond to oral medication. There are other rods locally manufactured worldwide, but few of these find their way out of their native countries. Only one semi-rigid rod model, the Mentor Genesis, is available with a coating that retards infection.

The three-piece inflatable penile implants are somewhat complex to insert because they require a reservoir placed in the abdominal cavity. However, they do provide the best rigidity and the best flaccidity because they will fill every part of the corporal bodies, just as an inner tube fills a bicycle tire. Because reservoir capacity is capacious, stretching of pliant tunica and compression of erectile tissue does not cause deterioration of the erection as commonly as (in our experience) self-contained or two-piece devices that have no reserve fluid volume for future needs *(15)*. The three-piece inflatable also provides

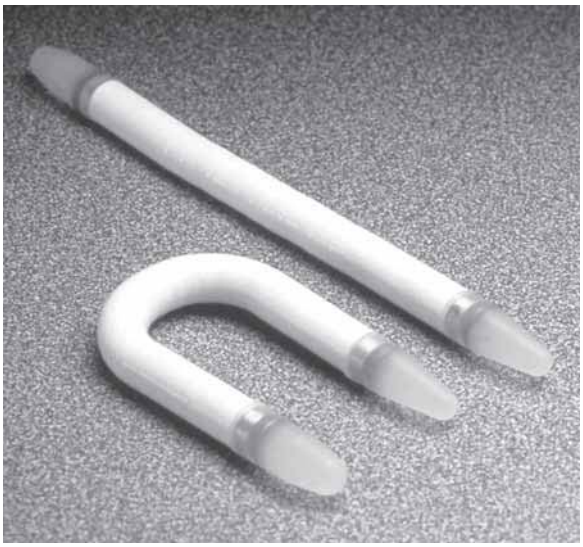


Fig. 5. AMS Dura II mechanical penile implant.

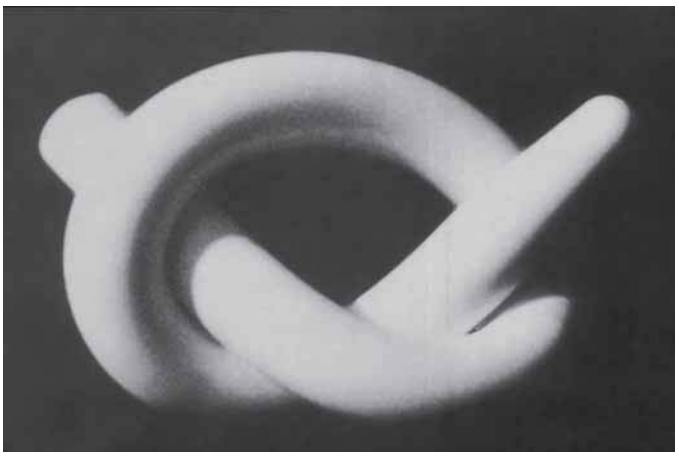


Fig. 6. Soft silicone penile implant developed by Subrini.

the best flaccidity, because all fluid can be drained from the cylinders into the reservoir when a patient desires the nonerect state. The pumping and deflating mechanisms of both the Mentor and AMS require some manual dexterity, and patients who are lacking in this ability may find it difficult to work these devices. The Tactile Pump is a recent improvement to the AMS three-piece (Fig. 7). Compared with the previous pump design, this larger pump delivers more volume per squeeze and has a much larger deflation zone with "ribs and pads" that facilitate grasping, activating, and de-activating the device. Early clinical reports indicated marked reduction in the amount of time spent instructing patients in use of this device *(16)*.

For patients with complex anatomical issues such as kidney transplant or neobladder, the surgeon should consider placing a simpler prosthesis than the three-piece. Another solution might be to place the reservoir outside of its usual location behind the pelvic bone in the space of Retzius. Mentor manufactures a reservoir suited for patients with these circumstances. The reservoir has a lock-out valve that prevents transfer of fluid

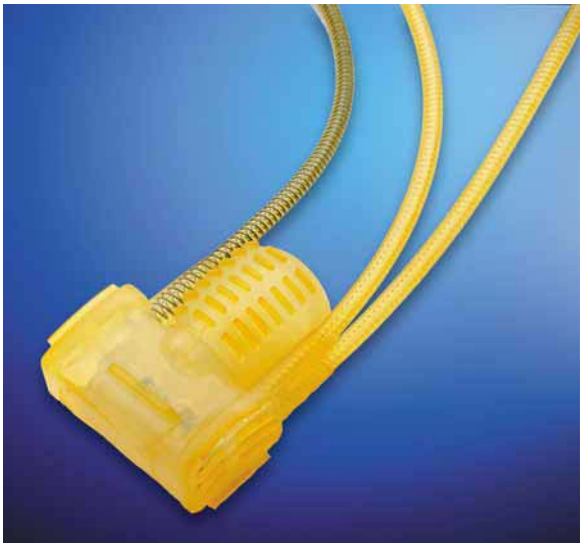


Fig. 7. New AMS Tactile Pump.

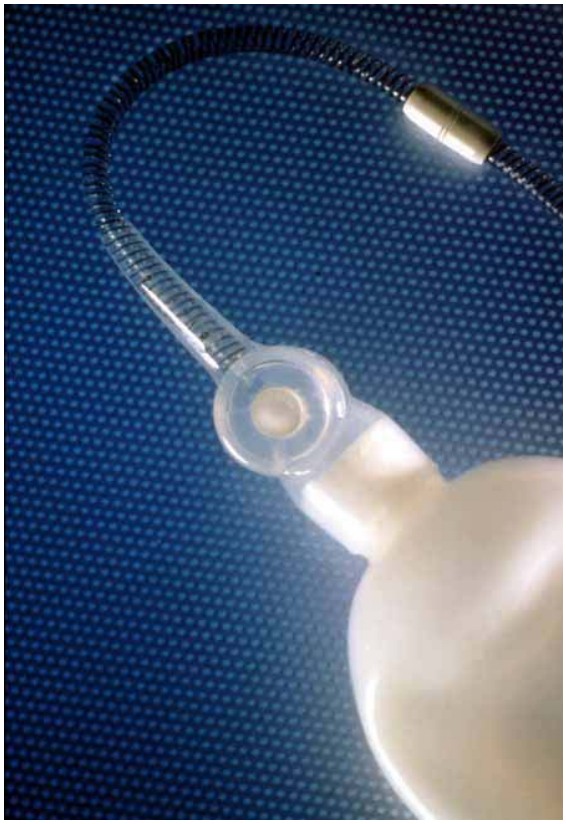


Fig. 8. Mentor Reservoir with Lock-Out Valve.

from the reservoir into the cylinders (Fig. 8). Fluid is only transferred from the reservoir to the cylinders on negative pressure from the pump and is not transferred in response to positive pressure on the reservoir.

The pelvic space of Retzius is chosen for reservoirs without this auto-inflation prevention because it is a capacious potential space. Three months after reservoir implantation, the capsule development around the reservoir usually prevents increased abdominal pressure from milking fluid from reservoir to cylinder. The Mentor reservoir with a lock-out valve allows placement of the reservoir in locations that would be subject to considerable auto-inflation (e.g., anterior to the transversalis fascia but posterior to the abdominal wall muscles) *(17)*.

Many skilled surgeons continue to use the traditional reservoir position, even in anatomically compromised patients; however, others resort to ectopic locations like those mentioned earlier or may place the reservoir in an intraperitoneal location. The tubing caliber for the AMS and Mentor products is identical, thereby permitting the surgeon to mix manufacturer's components in special situations. On several occasions (e.g., in an anatomically compromised patient that had previously been infected), we have combined AMS InhibiZone CXR cylinders, the new AMS Tactile Pump, and a Mentor Lock-Out Valve reservoir. However, mixing components from different vendors voids any warranty.

When selecting a prosthesis for a particular patient, the surgeon should consider the three choices of semi-rigid and a two- or three-piece inflatable. Without considering cost, the three-piece is considered the gold standard. The semi-rigid rod implants are easy to insert and are usually easy to manipulate. The tubes are especially bendable and can easily be maneuvered in the up- or downward position with minimal exertion. The wire devices sometimes have spring back and may not be perfectly positionable for either erection or in a straight downward position *(18)*. Sitting and standing may require surreptitious manipulation of the device to promote concealment. Cystoscopy with a rigid instrument was formerly a problem, but flexible cystoscopy has eliminated this objection to semi-rigid rod implants. Patients with spinal cord injury have been more prone to have erosion of the semi-rigid rod cylinders to the exterior in the region of the glans because of cylinder pressure in the absence of sensation. The patient without sensation may not appreciate that the rods are eroding through the tissues of the penis. Most authorities recommend inflatable implants for patients with spinal cord injury, even if the implant is only used to facilitate condom catheter urinary drainage *(19)*. When considering semi-rigid rods, the mechanical model AMS Dura II is more expensive than the devices with wires but is "the prosthesis of choice for patients with no manual or mental ability to manipulate other devices" *(18)*.

If the surgeon wishes to avoid intra-abdominal reservoir placement, the two-piece prosthesis is advantageous because the functional result is better than a rod implant. The Ambicor can provide good rigidity and fair flaccidity or fair rigidity and good flaccidity, but it rarely provides good rigidity and flaccidity simultaneously. There are other compromises when considering the two-piece prosthesis compared with the three-piece prosthesis. The long proximal segment between the proximal end of the implant and the input tube (5 cm) tends to make this tube palpable on the shaft of the penis in thin patients, resembling what some call "tailpipe penis." Finally, as mentioned earlier, erection deterioration may occur with time.

The three-piece (gold standard) accounts for 70% of implants placed in the United States, whereas Ambicor comprises 20% and semi-rigid rods comprise the remaining 10%. Outside the United States, where reimbursement by third parties is less frequent and the cost of the rods is considerably less, 50% of implants are inflatable prostheses and 50% are rods.

In the decade before the introduction of sildenafil (Viagra) in 1998, sales of penile prostheses were approx 30,000 per year worldwide. Penile implants had the distinction of being the most effective treatment for ED and had a high acceptance rate. With the advent of an effective oral drug for ED in the latter part of 1998 and 1999, sales for implants plummeted 50%. Pfizer's pervasive marketing of the little blue pill caused many more patients to visit physician's offices for treatment of ED, and 65% of them responded to Viagra. Less than 2 yr after the introduction of Viagra, researchers noted that depressed numbers of penile implants remained unchanged but both the complexity of the implant procedure and the severity of the patient's illness had significantly increased *(20)*. In other words, a higher percentage of implants were being provided to patients for replacement and revision than those implants being provided to first-time implant recipients. Additionally, patients who did receive first-time implants experienced more comorbidities than previous patients. Six years later, and after the introduction of two additional phosphodiesterase (PDE) inhibitors, implant sales now exceed the pre-sildenafil era as patients who have made a commitment to restoring potency become refractory to the oral medications and choose an implant rather than the second-line therapies of intracorporal injections, intra-urethral therapy, and vacuum devices. These patients possess knowledge of these "so called" second-line therapies but decide not to try them and prefer to have implant surgery. Indeed, in the era of increased public medical information from the marketing of drugs and the Internet, patients have never been so well informed. After recommending a therapy, physicians commonly hear patients say, "I'll get back to you soon," which translates to "after I research it on the Internet."

It is estimated that the three drug companies that manufacture PDE-5 inhibitors spent $450 million in 2005 to promote their therapies for ED. This huge budget assures that every American who watches television knows that treatment for ED is available. Patients who fail the drugs or in whom medical therapy is contraindicated can easily continue their education via Internet, texts, community health talks, or education from their physician.

Outcome studies published in the medical literature indicate higher satisfaction from implants than pills, injections, or vacuums *(21)*. In 2005, we found that the majority of these well-informed patients elected surgical correction rather than a trial of injections or vacuums. Many individuals continue their research to seek out a urologist with a focus on prosthetic urology. It is imperative that physicians with a focus on prosthetic urology identify themselves to the searching patient.

MARKETING ERECTILE RESTORATION IN THE 21st CENTURY

It is estimated that fewer than 7% of the 7000 American urologists do one or more penile implants per year *(22)*. The other urological surgeons perform none. Fewer than 50 American urologists do as many as four implants per month. In the 21st century, with declining reimbursement for surgical procedures, many urologists are developing subspecialties so they can focus on a particular interest. Therefore, urological subspecialties have been developed (e.g., urological oncology, female pelvic urologists, stone specialists, endourologists, and prosthetic urologists). Because of the media blitz by the drug companies, the restoration of erections has become a publicized subject. When treatments fail and therapies are contraindicated, not desired, or both, the education process must illustrate the benefits of surgical correction. There are tens of thousands of patients who have failed drug treatment who are not being treated. Many of these men do not know where to go

for help, and some are not even aware of further treatments when the most familiar ones do not work. This is where the focused prosthetic urologist must present his story about the ultimate treatment for impotence.

As we cross deeper into the 21st century, the economics of the practice of urology have changed drastically. Urology was formerly a critical care specialty, and in-patient surgical procedures were the largest source of revenue. Our practice is now driven more by outpatient procedures, and reimbursement for surgical procedures has drastically reduced. Urologists historically practiced alone or in small groups. Currently, urologists band together in large single-specialty practices. In some cities, virtually all urologists are in the same economic association. This weight of patient volume allows the group to purchase lithotripters, computed tomography scanners, pathology labs, and so forth. These revenue sources supplement the declining professional "fee for service" income.

Despite the new current trend to subspecialization, many cities in the United States do not have a single urologist with a focus in prosthetic urology. Several years ago, a group of focused prosthetic urologists headed by the authors of this chapter banded together under the banner of the *Institutes of Urologic Excellence* (IUE). This group of physicians was interested in using penile implants and urinary sphincters to cure end organ failure and devoted advanced study to the surgical techniques. A patient handbook and a website were developed to educate the public about the treatment of impotence and incontinence with medical devices, as well as about the IUE physicians who were skilled in the implantation of the prosthetics. One of the device companies helped the IUE physicians fund a national advertising program in the American Airlines and Northwest Airline magazine. The advertisement was specifically targeted to failures of oral therapy. The patient could call or "click" to obtain information about implants or to find a nearby physician who was skilled in prosthetics.

The program was a vast success in attracting several thousands of requests for information. Unfortunately, many large US cities did not have one urologist who performed more than 8 to 10 implants per year. Our experience showed that the patients were willing to drive to a neighboring city for help but drew the line at getting on an airplane to address problems with sexual function. Although thousands of requests for information were generated by the advertising campaign, only a modest number of implants were performed compared with the number of interested parties. Most patients went "back on the couch," because there was not a prosthetic urologist nearby.

The lesson of this airline magazine experience is that (a) more implanting urologists are needed in more locations, and (b) patients are interested in therapy after the pill is ineffective; urologists who perform penile implants must make the public aware of their interests and skills.

This chapter was written 5 yr after the IUE magazine experience. The new trend of urology toward subspecialization is hopefully encouraging more young urologists to take an interest in prosthetic urology, which should improve patient access. Despite more available implanters, patients still need knowledge of the possibility of surgical correction and the location of a qualified prosthetic urologist.

Educating the public about surgical correction as well as a particular physician's interest and training is called marketing. Marketing is not advertising "vasectomies at a discount." Most of us are loath to do this type of promotion. Marketing is simply education to stimulate demand. As the IUE experience indicates, patients who are afflicted with end organ failure seek information and, if convenient, may consider the surgical option. Subspecialization places more prosthetic urologists in each demographic area to satisfy

patient convenience. The current challenge is to educate the public with ethical and economic marketing. The educational process may be private among your own patients or public to stimulate interest in patients who are not presently under your care. These two types of education are known as internal and external marketing.

INTERNAL MARKETING OF PROSTHETIC UROLOGY

Internal marketing of a physician's interest in implants requires nothing more than spending time to overcome patient misconceptions and demonstrating enthusiasm to the afflicted patient. A common scenario is the patient who exclaims, "I'm impotent from my prostatectomy, Viagra doesn't work, but I don't want surgery." The physician not interested in education (marketing) may say, "Fine. I'll see you in a year and recheck your PSA." When faced with this type of patient, a focused physician might put him at ease by saying, "I don't blame you, I understand; if I had the condition, I wouldn't want another operation either." He might then continue, "There are some other therapies we will try, but I don't want you to close your mind to surgery because if nothing else works, I will introduce you to a patient who initially felt exactly like you. He is now so happy, he serves as our patient advocate." In the role of an educator, the physician might add, "Today's surgery is minimal and is performed as an out-patient surgery through a tiny two-inch incision. It is completely invisible and perfectly natural, and Medicare and most insurance plans cover it."

This educational process is not unlike what occurs when a 50-yr-old patient presents with an aggressive prostate cancer and proclaims, "I know I have cancer but I have been reading on the Internet and have decided on a course of watchful waiting." Most physicians would attempt to educate this patient to have curative therapy and would not allow him to go "back on the couch." In our opinion, failure to present a penile implant in a favorable light to a patient with no other options is similar to allowing the patient with aggressive prostate cancer to choose his early demise by not treating the malignancy properly.

In our experience, there are three important points to cover with patients when discussing an implant:

1. The implant is invisible. Many patients assume it is like an erector set on their genitalia. *"You could take a shower at the golf club in front of ten men and not one would know you had a penile implant."*
2. The implant is natural and (unlike the oral drugs) always dependable. The leading patient complaint regarding PDE inhibitors is their unpredictability of response. *"Sex drive and sexual satisfaction are the same with a prosthesis as they were before you became impotent—the implant merely gives you the erection for penetration."*
3. *"Medicare and most insurance programs cover the cost, so there is minimal out-of-pocket expense."* Many patients with ED are retired and/or on fixed incomes and are reluctant to inquire about cost. These patients will not ask because of embarrassment. Knowledge that Medicare covers the surgery is a big relief.

Physicians who are interested in developing a large implant practice should also have one or more patient advocate(s) that discuss or even demonstrate the natural nature of the device. Happy customers are an integral part of a successful marketing program for prosthetic urology. The patient advocates should also be used to help answer questions at the community health talks discussed later. An occasional gift certificate to a local restaurant shows your appreciation to these courageous individuals.

Even in the days of the Worldwide Web, patients remain very interested in what their personal physician thinks. In our experience, if time is spent educating and endorsing the quality-of-life improvement available with a penile implant, many patients will overcome their reluctance to "surgery." Every day, the television bombards the American public with advertising (not marketing) for prescription drugs. The phrase "ask your doctor if this drug is right for you" concludes virtually every advertisement. We are not asking the urologist with an interest in prosthetics to advertise. We are simply saying that if the physician takes the time to educate and validate, many more necessary implantations can occur. In a simple statement, internal marketing acknowledges, "It is okay to recommend an implant."

EXTERNAL MARKETING FOR PROSTHETIC UROLOGY

External marketing consists of providing education outside your personal patient population. External marketing educates other physicians' patients who have the problem but do not know how to get available help. External marketing does not have to be expensive advertising on television, radio, or newspaper. One of the most effective tools of external marketing is the community health talk (CHT). The CHT can be administered on a regular basis to patients in your practice. Letters to the patients with a specific CPT code or a public notice in a prominent location in the reception area can generate interest. Many successful implanters choose to have their nurse and patient advocate run a regular meeting without the presence of the physician. Therein, the meeting can be informal, and the patient can have all his questions answered without intimidation or perceived pressure.

The CHT can also be offered to a civic club, church, country club, or any other planned gathering looking for a speaker. The CHT gives the physician a podium from which to educate the public about the problem of impotence and also conveys the physician's qualification, his interest, and, hopefully, his passion. One of the most dreaded jobs in these civic organizations is to be the program chairman! The chairman spends much time cajoling potential speakers. Your availability as an educator will make the chairman an ally and will increase your visibility. The Chamber of Commerce usually has a list of those organizations searching for speakers.

Serving as a speaker to these organizations is inexpensive and valuable but has the disadvantage that many in the audience have not suffered from the problem you are addressing. A free-standing event that utilizes media advertising will narrow the audience of a CHT to individuals afflicted with a particular malady. For example, a seminar on "Life After Prostate Cancer" will yield a target-rich audience full of wet and impotent survivors of prostate cancer. Additionally, many of these patients will belong to prostate cancer support groups, and marketing your interest to these groups will spread the word to individuals who were treated by urologists that do not perform implants. If a urologist does not offer implants, they are unlikely to educate their patient about their availability at a competitive practice. Often, their patients have been kept in the dark to the extent that on occasion, a respondent to external marketing has exclaimed, "Why didn't my urologist tell me of the availability of these implants?"

Many other forms of external marketing are available, depending on the budget of the urologist. One of the least expensive and most effective are advertorial columns in the newspaper. We use a series of "Ask the Doctor" questions. Each week a question is featured with a 200-word answer in the same place in the newspaper—for example, one column might begin with the question, "Viagra has ceased to be a dependable therapy for my ED, should I try one of the newer pills?" The important thing to remember is that

a single burst of marketing does not achieve desired results. There is a reason that beer and pizza are on the television every night. Keeping education and your interest consistently in front of the public is the key to having patients select your services for a particular problem. In our experience, the average impotent male suffers 18 mo before seeking help. This reluctant patient needs the reassurance of the physician's continuing interest in his embarrassing condition. A constant presence in the media urges him to "get off the couch."

To summarize, marketing is not advertising—it is education. The public needs to know those physicians that will treat their end organ failure and needs a physician that has the passion and skill to improve quality of life. Because so few urologists perform implants, the only way the afflicted individual will find the right physician is through public education—that is, marketing.

PATIENT SELECTION AND INFORMED CONSENT

In 2005, a patient was considered a good candidate for a penile prosthesis if he had failed medical therapy or if medical therapy was contraindicated. Because of pervasive media coverage of ED, the well-informed patient should have knowledge of the second-line therapies (e.g., penile injections, intra-urethral therapy, and vacuum constriction devices). In the era of effective oral therapy, most patients opt not to attempt the cumbersome vacuum constriction device, the expensive and nonspontaneous injections, or intra-urethral agents. Patients who opt for the implant are highly motivated to continue sexual activity. Most are older citizens and the fact that Medicare covers the surgical procedure makes the decision relatively easy.

In most instances, the physician chooses the prosthesis. His or her decision is based on comfort with the surgical implantation and assessment of the body habitus and manual dexterity of the patient. Patients with a larger penis are best served by a three-piece inflatable. These devices provide the best rigidity, especially in the longer phallus. Likewise, patients with shorter penises should receive the three-piece inflatable because the semi-rigid rods and two-piece implant are difficult to conceal in these patients. Patients with limited manual dexterity or those who would have difficulty manipulating the hydraulic devices are encouraged to choose a semi-rigid rod. An exception to this rule is a patient with a motivated partner who could be trained to manipulate the hydraulic prosthesis.

It is important that the patient understand that the size of his penis will likely be shorter than his natural erection at full potency. When the penile implant is in place, a fibrous capsule forms around the cylinders. Unlike the elastic tunica albuginea during natural tumescence, this capsule does not stretch as the device is inflated. In effect, this inner sheath of scar tissue negates the elastic qualities of the tunica. In our pre-operative consultation with the implant candidate, we negate this loss of length to some degree by imparting the knowledge that girth of the penis is frequently better than a natural erection, and girth, rather than length, is responsible for rigidity. To continue this line of reasoning, rigidity is responsible for sexual satisfaction for the female because the area of maximal satisfaction for a woman is just inside the introitus.

Sensitivity of the penis, ejaculatory abilities, and sexual drive are usually unchanged following placement of the prosthesis. The patient should understand that penile implants restore only the ability to penetrate. They do not restore any special sensitivity or sexual drive that may have been present years ago. If the cylinders are removed later, the capsule will remain and the space will partially fill with proliferating scar tissue, which may make it difficult for the patient to respond adequately to other treatments such as medication or

a vacuum device. To summarize, it is important that the patient have a realistic expectation of the result of implantation.

As with any surgical procedure, there are many complications associated with penile prosthesis implantation. The most common complications necessitating re-operation are infection (1–4%; ref. *6*) and mechanical breakage (5–13% in the first 5 yr; refs. *3* and *4*). A pre-operative consultation should include a discussion of the possibility of these relatively common causes of a return to the operating theatre. It is not necessary to list the myriad of other very rare occurrences of curvature, erosion, hematoma, SST, bowel fistula, death by blood clot, and so forth. To meet the standard of care, it is not necessary to categorize every risk of surgery and anesthesia. The patient and his physician should be mutually satisfied that they have covered most risks and rewards of the surgical event, and it should be noted in the clinical record.

PRE-OPERATIVE PREPARATION AND POSTOPERATIVE CARE

Most penile implants are indicated in patients with organic causes of ED who have failed to respond, do not tolerate, or are unwilling to consider more conservative options *(23)*. There is a high risk that oral therapy will fail in patients with severe ED resulting from diabetes mellitus or following radical pelvic surgery. Patients with Peyronie's disease associated with impotence, severe penile fibrosis, or conditions after priapism should also be considered for implantation of a penile prosthesis. In the pre-sildenafil era physicians believed it was important to diagnose the etiology of a patient's problem. Comprehensive blood testing (including cholesterol, glucose, and hormone studies), injection testing, duplex color Doppler ultrasound, and nocturnal penile tumescence studies were obtained. This comprehensive diagnostic evaluation is not believed necessary in the days of effective oral therapy. Indeed, many third-party payers have recognized that some of these diagnostic tests do not influence patient outcome and refuse to reimburse for the test expenses.

Diabetes mellitus is known to be a risk factor for penile prosthesis implantation *(24)*. In 1992, Bishop and associates *(25)* published that patients with diabetes mellitus whose blood sugar was in better control for a period of time pre-operatively (as manifest by a normal hemoglobin A1C) were less prone to develop a penile implant infection than a group whose Hgb A1C was elevated. In a larger series, Wilson and associates *(26)* repeated the study, and no difference was demonstrated in infection rates between patients with normal and elevated Hgb A1C levels. The presence of diabetes in a patient raised the risk of infection from 3 to 8%, but the level of glycosylated hemoglobin, the FBS on the day of surgery, and the insulin dependence of patient were not predictive factors for increased infection.

Our work-up consists of a history and physical, with some focus on sexual desire and enjoyment. Failure of or intolerance to oral drug therapy and knowledge of the availability of penile injections, intra-urethral agents, and vacuum therapy is ascertained in the history. If the history or physical is suggestive, we obtain specific—but not exhaustive—diagnostic testing. If the patient indicates interest, we prescribe conservative therapy of intracorporal injections, intra-urethral pellets, or a vacuum device. For patients with an absence of interest or with a history of unsatisfactory experience with the second-line therapies, we move to an explanation of the surgical benefits of prosthesis implantation. Many high-volume implanters are tertiary referral centers for prosthesis implantation, and patients travel to them from considerable distances. Well-informed patients com-

monly have surgery the day after their first visit to the center. These patients' work-ups consist of history, physical, and assessment of the lower urinary tract.

We believe it is important that the lower urinary tract be evaluated before implantation of a penile prosthesis. The implant surgeon should avoid untoward events such as urinary infection, difficulty inserting the catheter, or urinary retention. We commonly perform a urinalysis, post-void residual, and, if indicated, cystoscopy to rule out correctible conditions before prosthesis implantation. Urinary tract infections are treated and patients who are prone to develop urinary infections, such as those with neurogenic bladders, are placed on prophylactic antibiotics for several days to maintain sterile urine on the day of surgery. If prostate obstruction is detected, it is treated with medication or mechanical or surgical therapy before implantation. Because many of our patients have had postradical prostatectomy, it is common to detect a bladder neck contracture that would restrict Foley catheter placement or postoperative urination. These patients are dilated at cystoscopy or undergo transurethral bladder neck incision coincident with prosthesis implantation. The transurethral procedure is performed in the lithotomy position. The patient is then placed supine, is reprepped and draped, and the prosthesis is inserted. If significant urinary incontinence is anticipated, prosthesis insertion is postponed for 1 mo to determine if artificial urinary sphincter placement is also needed.

It is recommended that the patients bathe the genital area with antibacterial soap the day before surgery. The genital area is shaved in the holding area or operating room to minimize the chance of nicks becoming colonized by bacteria. The genitalia are washed and prepped with antibacterial soap and antiseptic solution.

Antibiotics are usually started prophylactically before the procedure. The surgeon usually decides which antibiotics to use from those antibacterials that are appropriate for treating infections resulting from skin contaminants. The antibiotics may be continued 48 h postoperatively, at which time the wound is sealed. Some surgeons continue the antibiotics for 5 to 7 d, but there have never been any controlled studies demonstrating that postoperative antibiotics decrease the incidence of surgical infections.

If the scrotal incision is utilized, a catheter is inserted to facilitate urethral identification and to empty the bladder before reservoir placement. The catheter may be discontinued when the patient is fully recovered from his anesthesia or may remain until the following morning if a scrotal pressure dressing is used. Some surgeons prefer to use drains at the conclusion of the procedure to reduce the edema and to provide an exit for any corporal bleeding that may occur in the postoperative period. The drain is usually removed the following morning and has been shown to decrease hematoma formation in patients with interrupted corporotomy closure without increasing the incidence of prosthesis infection *(27)*.

Pain following placement of a penile prosthesis is variable depending on the patient's tolerance and the particular disease process. The pain is usually more prolonged than that associated with other operations of the same magnitude not involving prosthetic parts. Scrotal bruising and swelling is common, and scrotal hematoma usually recedes without operative intervention. We have recently noted that high doses of a Cox2 inhibitor started the day before surgery and continued for 7 d postoperatively markedly decreases the swelling and pain that require medication.

Patients are instructed at discharge from the hospital to wear brief-type underwear for the first month and to wear their penis up, pointing cephalad in their shorts. This encourages capsule formation around the cylinders and permits the normal physiological upward deflection of the erect penis. This seems particularly important in patients who receive

a Mentor device with a Lock-Out valve because there is very little transfer of fluid from reservoir to penis, and the patient maybe tempted to wear his flaccid penis down against the scrotal wall.

Patients receiving the AMS devices are warned about the inevitable auto-inflation in the immediate postoperative period. A capsule has not fully formed around the reservoir until 3 mo, and in the early period, any increase in intra-abdominal pressure will cause fluid to bleed from the reservoir into the cylinders, resulting in partial tumescence. The patient does not know how to release the device and must be warned that the semi-inflation will occur and he must tolerate it until he is instructed regarding how to operate the device. The patient should return to the office for deflation before the device instruction session if the auto-inflation becomes a nuisance. At 3 mo the capsule that has formed around the reservoir generally protects the patient from future auto-inflation. A new pump for the AMS three-piece prosthesis that obviates this annoying auto-inflation is planned for release in early 2006.

Patients are instructed to operate their hydraulic devices after 5 or 6 wk. Some surgeons prefer to begin cycling these devices earlier, but in many patients, pain may still be present to the degree that it would make such a maneuver uncomfortable. At 6 mo, most patients have no pain. Pain may persist longer—especially in cases of neuropathy. If prolonged pain occurs, the suspicion of an infection associated with the prosthesis should be entertained.

After patients are instructed regarding the operation of their device, they are advised to cycle it regularly. They are encouraged to inflate the device every week to avoid capsule contracture around the cylinders, which would result in a curved or unsymmetrical appearance to the erect penis. They are advised to deflate the device a couple of times daily for 2 mo (even if it has not been inflated that day) to keep all the system fluid in the reservoir (not in the cylinders) and to avoid scar contracture over the reservoir that would limit its expansion. When the patient leaves the cylinders semi-inflated for prolonged periods of time, a capsule forms over the reservoir in the less-than-full state; the capsule restricts the expansion of the prosthesis in the future and prohibits complete emptying of the cylinders. Many patients who form a capsule complain of auto-inflation if they subsequently attempt to achieve complete flaccidity; after 3 mo, it is no longer possible to influence reservoir capacity within the capsule, and corrective surgery must be performed for auto-inflation, or "failure to deflate" *(28)*.

INCISIONS

The three-piece devices are placed through infrapubic or scrotal incisions. The original description by Scott and associates *(2)* illustrated an infrapubic incision with tubing run through both inguinal canals. Historically, all implants were placed through this incision, although the advent of kink-proof tubing made the circuitous tubing routing unnecessary. In the mid 1980s, interest in the penoscrotal incision blossomed, and vertical and transverse incisions were promoted. The chapter by Montague *(29)* was a driving force, and by the late 1990s, more than half of all penile implants were placed via a scrotal incision. In 2003, after the publication of a new technique in which both the penile implant and urinary sphincter can be performed through the same transverse scrotal incision *(30)*, AMS indicated that in 2004, more than 80% of three-piece penile prostheses were placed through the scrotum, and more than 60% of sphincters were placed through this incision.

An advantage of the infrapubic incision is the secure placement of the reservoir in the midline location. If the midline prepubic area is scarred or a renal transplant is present,

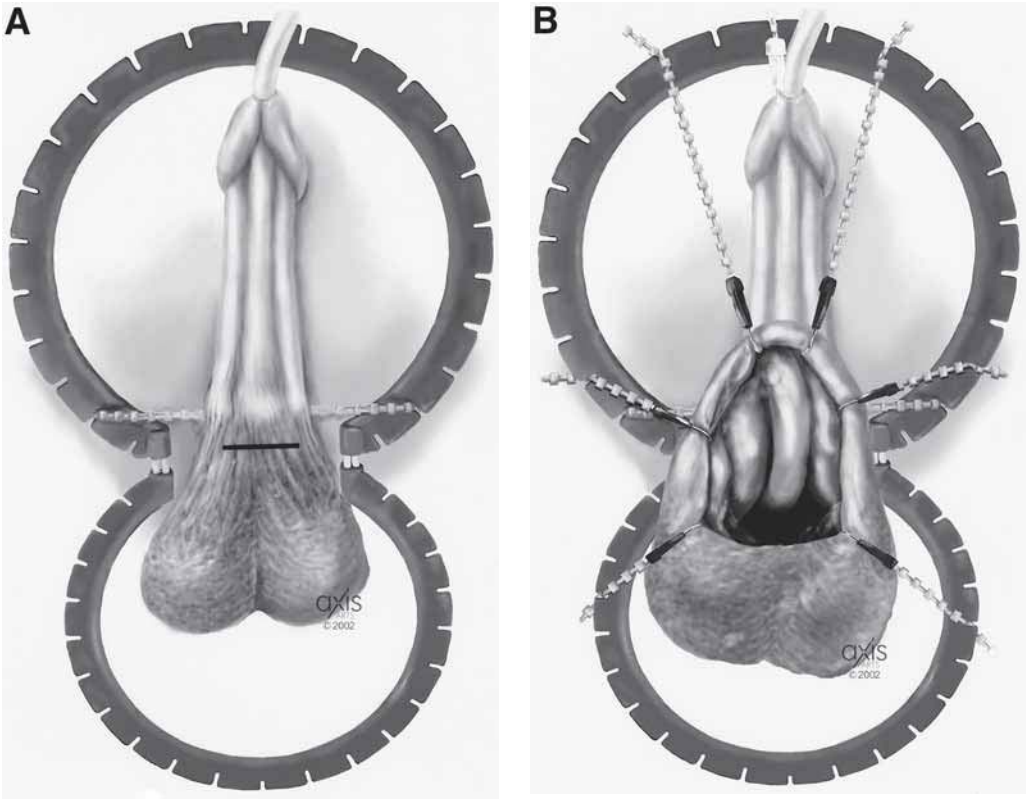


Fig. 9. (A) Transverse scrotal incision. **(B)** Excellent exposure of proximal corpora and bulbar urethra with transverse scrotal incision. (Printed with permission.)

the epigastric or extra- or intraperitoneal placement of the reservoir can be accomplished. If a prosthesis is placed through an infrapubic incision, it is necessary to incise the dorsal surface of the corpora cavernosa to dilate and place the cylinders. Surgeons should exercise care to avoid injuring the neurovascular bundle. If the cross-section of the penis can be considered as the face of a clock, the neurovascular bundle runs between 11 and 1 o'clock on the upper surface of the corporal bodies. Making corporotomies at about 10 or 2 o'clock will avoid damaging this structure. Damage to this structure affects the sensory nerves to the distal shaft and glans penis. Preserving the bundle from injury allows the maintenance of good sensitivity in the distal penis. With the infrapubic approach, the pump tubing is passed around the side of the penis into the scrotum, and the pump is usually not pexed in position. Migration of the pump may occur, and the patient is encouraged to push his pump inferiorly each day of the immediate postoperative period to assure optimal dependent pump position.

Proximal corporal bodies are easier to expose from the scrotal incision than from an infrapubic incision. Surgeons can get so proximal with this incision that it is possible to place a sphincter cuff in approximately the same location as through a perineal incision (Fig. 9). During placement of a hydraulic implant through a vertical or transverse scrotal incision, the reservoir is placed blindly through the inguinal canal. The scrotal incision is displaced over the inguinal area, and the pubic tubercle is palpated. The finger is then passed cephalad into the external inguinal ring. A baby Deaver retractor is used to hook

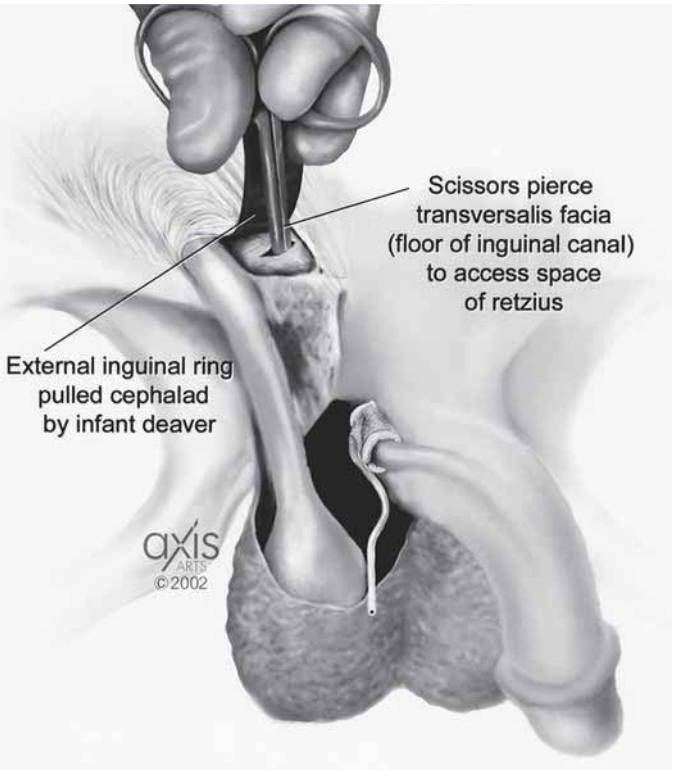


Fig. 10. Reservoir placement using scrotal incision. (Printed with permission.)

the ring and to apply traction cephalad. This flattens the ring and allows palpation of a rim of bone, over which the transversalis fascia is stretched, similar to a drum. The "head of the drum" must then be pierced with a finger, clamp, or scissors to gain access to the space of Retzius, thereby allowing placement of the reservoir behind the pubic bone in the midline (Fig. 10). The surgeon must take care to stay immediately adjacent to the penis with this maneuver. All the trouble (iliac vessels, spermatic cord) is lateral. The only structure in danger is the bladder, and decompression with the Foley catheter protects this viscus.

There are advantages to the scrotal incision in placement of the three-piece implant. There is no possibility of injury to the dorsal nerve, pump placement is more secure, and an abdominal scar is avoided, which produces a more acceptable cosmetic result. The surgical procedure time for frequent scrotal implanters is usually quicker than that of implanters who regularly use the infrapubic approach. There is no difference in infection rates between the infrapubic and scrotal incisions *(24)*.

The Ambicor and Excel prostheses can only be placed via a penoscrotal approach. The preconnected tubing from cylinders to pump will not reach into the scrotum if these devices are placed through an infrapubic incision.

The semi-rigid rods and soft silicone implants are commonly placed through a subcoronal, penoscrotal, or ventral penile incision. A ventral incision is used in the patient who is not circumcised. If a subcoronal incision is used, then simultaneous circumcision is recommended. If the excess foreskin is left following closure, maceration of the suture line or lymphedema may develop. Through the subcoronal approach, there is also less tissue to close over the suture line of the corporotomy.

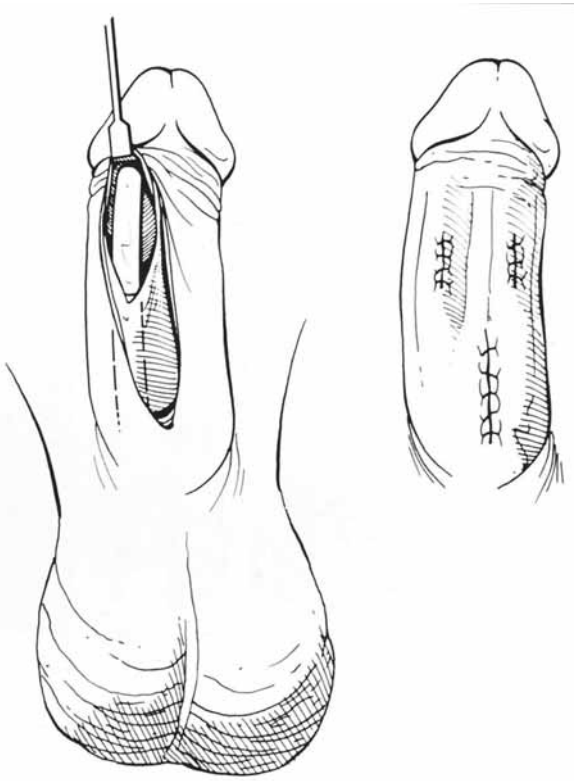


Fig. 11. Ventral penile approach for placing semi-rigid rods in uncircumcised patients.

When the penoscrotal approach is used to place semi-rigid rod implants, it may be difficult to bend the rods to fit under the distal edge of the corporotomy. Under these circumstances, extending the corporotomy may be necessary. In the ventral penile approach, a proximal midline skin incision is made on the ventral surface of the penis *(31)*. This is retracted distally using a vein retractor and relatively distal corporotomies are made (Fig. 11). The distal end of the corporotomy can then be lifted over the end of the rod using a vein retractor, thus avoiding the need to bend the rod. The layered subcutaneous tissue and skin closure can then be performed without overlapping suture lines. The corporotomy closures are lateral, and the skin closure is midline.

ANESTHESIA

Three-piece penile implants can be placed under general or regional anesthesia. A short-acting spinal seems ideal for the procedure. It is difficult to anesthetize for the reservoir placement if a local anesthetic is attempted. On the other hand, semi-rigid rods may be placed with local anesthesia. A penile block with 1% lidocaine is used. A tourniquet is placed around the base of the penis, and approx 25 cc of anesthetic is injected into either corpus cavernosum and is held in place for 1 min with the tourniquet. The tourniquet is then released, allowing the local anesthetic to diffuse into the proximal portion of the corpora. Infiltration of the skin incision site completes the anesthetic block. Some surgeons inject the corpora with a small amount of long-acting anesthetic, such as Marcaine, to keep the patient comfortable in the postoperative period.

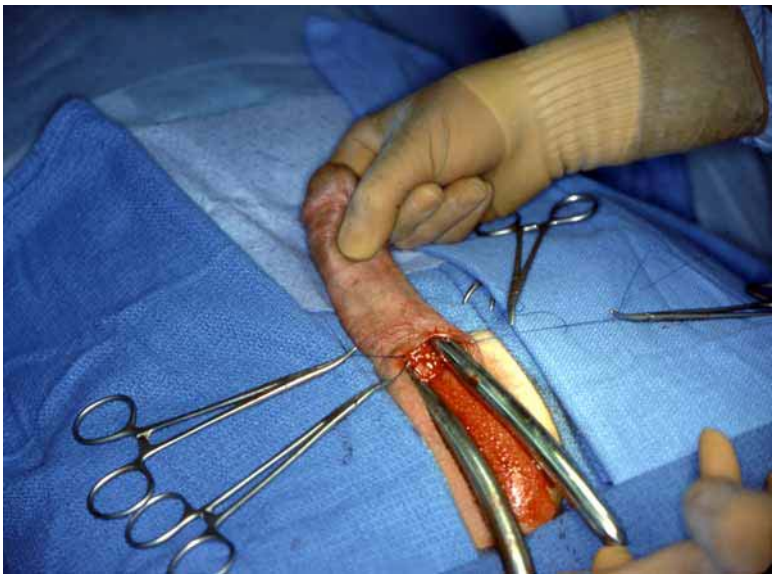


Fig. 12. Determining appropriate width size of cylinders with nonexpanding girth.

OPERATIVE TECHNIQUE

Appropriate cylinder sizing is the critical portion of the surgery. If a cylinder is larger than the corporal body can accommodate, then the patient may experience persistent pain, protrusion of cylinders far into the glans, or curvature of the erect penis. Semi-rigid rods should be sized about 0.5 to 1.0 cm less than the measured length of the corpora. This allows comfortable bending with less tendency to spring back. With most inflatable cylinders, a cylinder of the same size as the measured corporal length (without stretching) should be implanted. Cylinders that expand distally (e.g., AMS Ultrex) should be downsized 2 cm. As the cylinder expands distally during inflation, it will easily make up the difference in length and fill out the distal aspects of the corporal body to provide good support to the glans. Montague *(32)* believes measurements for the Ultrex should be calculated by measuring from the top of the corporotomy for the distal measurement and the bottom of the corporotomy for the proximal measurement. Experience has shown that unless the Ultrex is downsized, the "S"-shaped deformity may result, causing penile curvature and decreased rigidity of the erection *(33)*.

In addition to sizing for length, proper fit for width is critical for optimal support of the erection. All semi-rigid rods and the two-piece inflatables come in variable fixed widths. It is crucial to place as wide a rod as possible because rods appear to act as tissue expanders over time, compressing the corporal tissue. A good fit now may become a floppy penis in a few years, because the critical determinant of axial rigidity is girth. In our practice, we downsize the length but try valiantly to place the largest width for a semi-rigid rod or two-piece inflatable. A technique for appropriate width sizing of such cylinders involves placing two dilators of the proposed size simultaneously into the distal corporal bodies. One then apposes the thumb and index finger between the two dilators. If it is possible to touch the two fingers between the two dilators, the proposed size is too narrow. An ideal fit is achieved if one can obtain a slight or no separation of the dilators as the thumb is apposed to the index finger (Fig. 12; ref. *3*).

Three-piece inflatables also come in two widths. The narrow cylinders are approx 9 mm in diameter, with minimal inflation, and they expand to 14 mm. The standard cylinders are 12 to 13 mm when soft and expand to 18 mm (AMS) or more (Mentor). The optimal width fit of an inflatable cylinder is that which fills the corporal body like a finger in a glove. Because the inflatable cylinder does not exert constant pressure, subsequent loss of axial rigidity is not as large of a problem as with the constant fixed girth of the semi-rigid rods and the two-piece inflatables.

The critical determinant for inflatable cylinder size is the proximal dilatation. Placement of the base of the standard size cylinder for both AMS and Mentor cylinders requires a dilatation to at least 12 mm (optimally to 13 mm). If it is not possible to pass the 12-mm dilator to the ischial tuberosity, the surgeon should choose one of the downsized cylinders. These smaller, expanding cylinders also have significantly smaller bases. The Mentor NB requires dilatation to 10 mm, the AMS CXM requires dilatation to 11 mm, and the AMS CXR requires dilatation to only 9 mm.

Many patients with arterial insufficiency develop fibrosis in the distal corporal body as erectile tissue is converted to scar because of limited blood supply. This fibrosis limits dilatation in the distal penis beneath the glans. Dilatation to 10 mm is sufficient in this area, and the surgeon is not required to dilate higher. A forceful dilatation to a larger diameter might increase the likelihood of inadvertent corporal or urethral perforation. If a 10-mm dilator can be passed distally, the Furlow inserter can maneuver the standard size cylinder into the distal corporal body. Subsequent use of the implant will eventually dilate the distal corpora to the same size as the reminder of the penis.

To summarize, placement of a standard sized cylinder requires dilatation to 10-mm distally and 12-mm proximally. The critical measurement is proximal, because it will not be possible to place the base of a standard cylinder in the proximal corporal body if a size 12-mm dilator cannot be passed.

The inflatable cylinders have input tubing that exits from the cylinder at the base. This tube may run intracorporally and may exit at a convenient location from the corporotomy or may exit directly where the tube is attached to the cylinder. It is important to understand that the diameter of the cylinder at the tubing exit is more than 15 mm. If proximal dilatation is difficult because of extensive scar tissue, the surgeon should use a shorter cylinder and longer RTEs. For example, if the combined measurements were 20 cm and proximal dilatation was difficult, the surgeon should choose a 15-cm prosthesis and build the base with 5 cm of RTEs, rather than the standard choice of 18-cm cylinders with 2 cm of RTEs. If the surgeon runs the tubing along the cylinder in the presence of extensive proximal fibrosis, the input tubing may be compressed, despite its kink-proof construction. Under this circumstance, inflation would be possible, but it would not be possible to deflate the prosthesis. If this situation is noted at surgery, the surgeon should incise the tunica albuginea over the tubing with the electrosurgical cautery until the tubing exits the corporal body as it comes off the cylinder. If the surgeon allows the tubing to exit the corporal body as it comes off the cylinder, it should not be so far distal that it would be sheared during the pressure exerted during intercourse. When fibrosis is met proximally, building the base with RTEs can prevent too proximal of a corporotomy for tubing exit, with the inevitable difficulty of closing the incision because of poor exposure.

The operating surgeon should be aware of the anatomy of the so-called septum between the corporal bodies to prevent the relatively common septal crossover distally. Many times, this structure has areas of thinning or even outright gaps. It is surprisingly easy to be deflected to the opposite corporal compartment during dilatation or cylinder insertion.

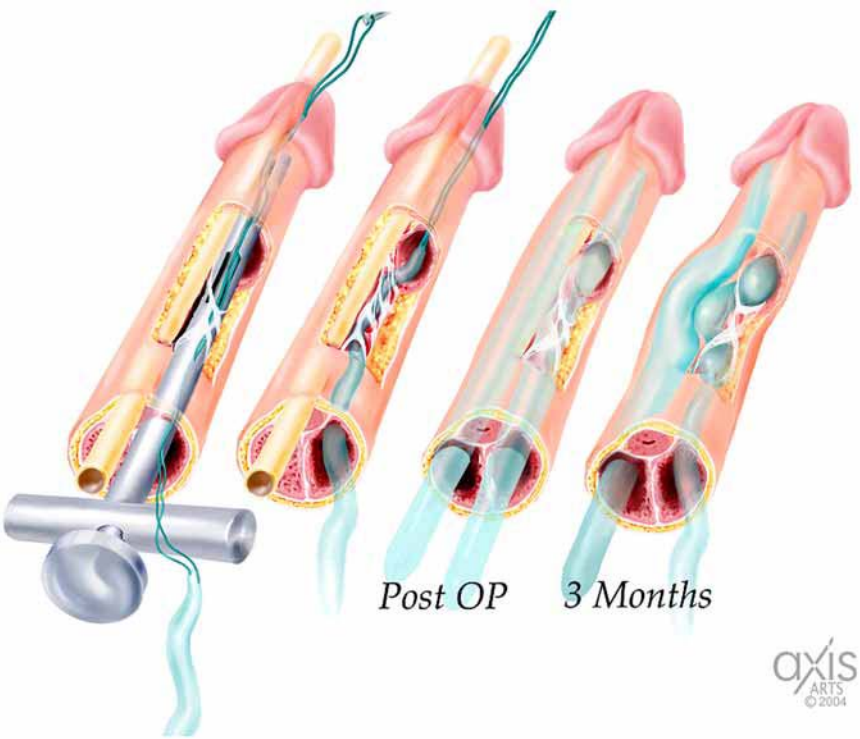


Fig. 13. Cylinder crossover. (Printed with permission.)

In dilating and inserting the Furlow inserter, the surgeon must take care to stay lateral to avoid crossing over and back, thereby setting up a crossed-over cylinder. Cylinder crossover is quite subtle at the time of surgery. Months later, following subsequent unilateral tissue compression, the penis is deformed in the area of crossover, and the cylinders may undergo retraction and/or aneurysmal dilatation (Fig. 13).

Proximal cylinder crossover can also occur. Proximal crossover can be suspected when difficulty is encountered during insertion of the second cylinder base. It can be diagnosed by placing dilators proximally in both corpora at the same time (Fig. 14). Many experienced implanters do this both proximally and distally to routinely check for both septal crossover and crural perforation. The dilators should be the same depth and same angle on each side. Similar to distal crossover, proximal crossover requires only recognition and rerouting of the cylinders into their proper locations. The repair of crossover is simple. The surgeon must place a large dilator in the side where both cylinders were located and then dilate the contralateral side and place the cylinder properly. The presence of the dilator prevents re-occurrence of crossover by keeping the cylinder in its proper side. It is not necessary and is very difficult to try to repair the septum.

Many authorities believe an adequate reservoir cavity should be created at the time of surgery to minimize the chance of auto-inflation. Auto-inflation occurs when the cylinders of a hydraulic penile prosthesis do not stay deflated or the prosthesis inflates without squeezing the pump. The implant patient may have a chronic partial erection and may experience difficulty concealing the penis. The problem is initially caused by abdominal pressure that causes fluid to be transferred passively from the reservoir to the cylinders. All hydraulic implants with abdominal reservoirs without Lock-Out valves initially

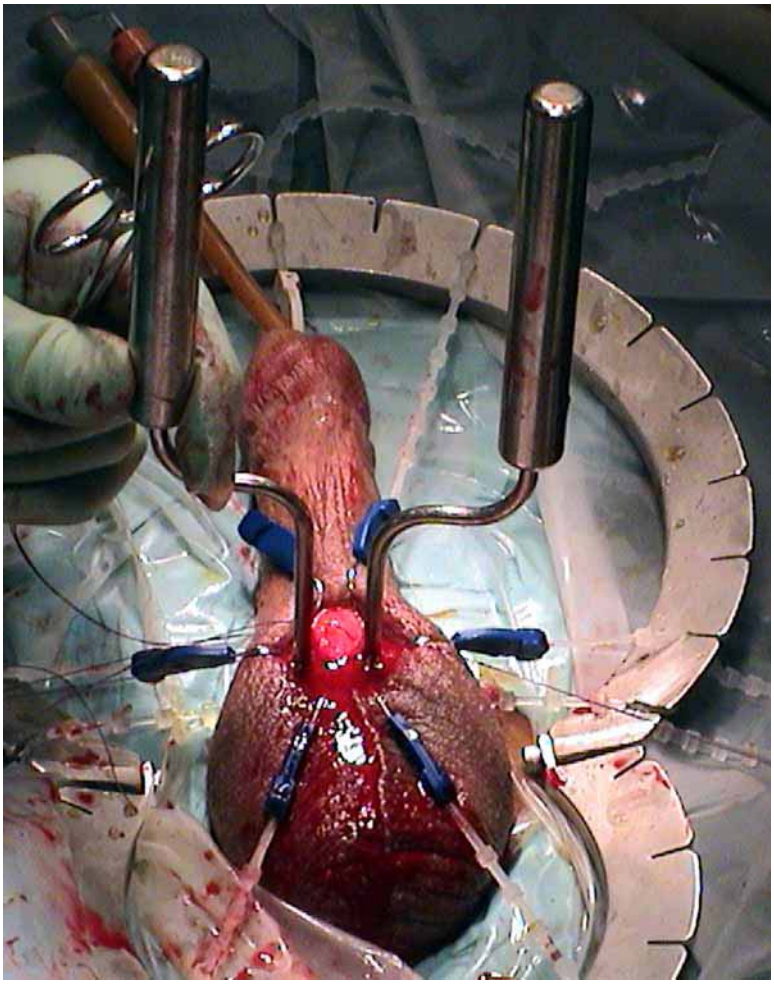


Fig. 14. Dilators placed proximally to check for proximal crossover or corporal perforation.

auto-inflate. The development of a capsule around the reservoir, which protects the reservoir from the intra-abdominal pressure increase, eventually corrects the condition. The initial formation of a large reservoir space does not prevent future auto-inflation. We believe that no matter how large the initial space is at the time of implantation, it has contracted down to the size of the reservoir in a matter of hours. Most importantly, at the teaching visit 5 to 6 wk following implanation, the patient should be instructed to deflate daily. The size of the fibrous capsule surrounding anything implanted in the body can be influenced for up to 3 mo. If the patient keeps most of the prosthesis fluid in his reservoir and keeps his cylinders completely empty for 2 mo after he is instructed regarding use of the device, the problem of auto-inflation vanishes.

If auto-inflation persists beyond 6 mo, the problem is irreversible and must be corrected surgically to expand the reservoir space. One series reported the incidence of annoying auto-inflation in 11% and patients; of these, 2% required correction *(34)*.

Mentor has introduced the Lock-Out valve to minimize the occurrence of auto-inflation. This valve responds only to negative pressure from the pump rather than permitting

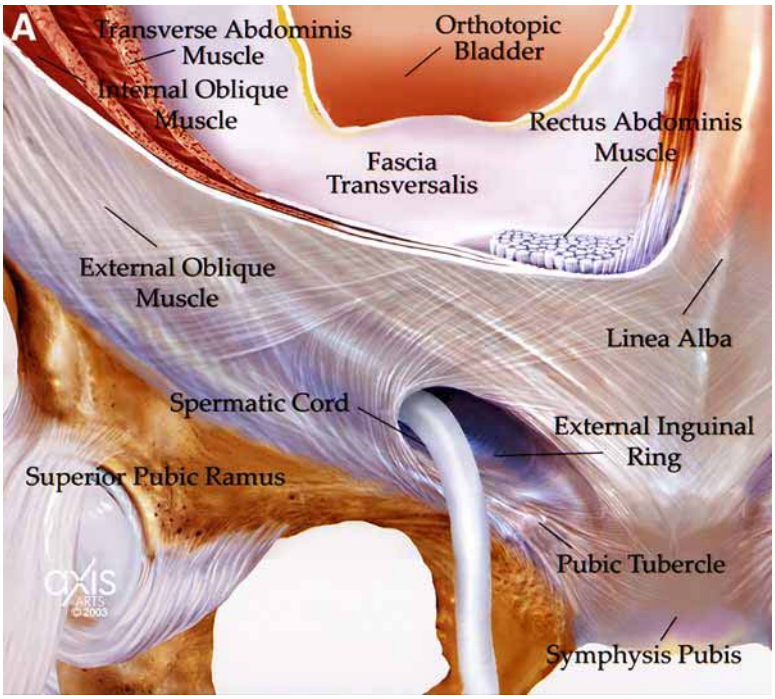


Fig. 15. (A) Anatomy. (Printed with permission.)

positive pressure on the reservoir to transfer fluid to the cylinders. When placing the enhanced Mentor reservoir, the surgeon should take care to avoid placing the valve against a firm structure such as bone or scar tissue. This may indent the valve, causing it to malfunction. The results with this reservoir modification have been excellent *(17)*, and as mentioned earlier, placement of the reservoir is possible in ectopic locations that would otherwise have predisposed to auto-inflation.

The usual location for the reservoir is the prevesical space. If this space is excessively scarred following pelvic surgery or the removal of a bladder, then the reservoir can be placed in an alternative location, even within the peritoneal cavity. German physicians routinely place AMS reservoirs in the peritoneal cavity to preclude the development of auto-inflation. Items placed in the peritoneal cavity do not stimulate capsule formation. The large intraperitoneal space prevents the transmission of intra-abdominal pressure to the reservoir. If intraperitonal placement is considered, then two caveats should be followed. Bowel can readily be intertwined around a reservoir that floats freely within the abdominal cavity, which can result in bowel obstruction. Therefore, the reservoir should be placed against the pelvic wall and should not be allowed to float freely. Additionally, the tubing should not be tight because this might cause erosion into a surrounding viscus *(35)*.

The ectopic placement of the reservoir is performed through the infrapubic incision by staying anterior to the transversalis fascia and finger-dissecting underneath the rectus muscle until a space is created that will hold the filled reservoir. The same space is created via a scrotal incision by displacing the incision over the inguinal area. The pubic tubercle is palpated, and the finger is inserted into the inguinal ring. The finger is then forcibly passed cephalad, piercing the back wall of the inguinal canal. A space anterior to the transversalis fascia and posterior to the muscle layers of the abdomen is created by moving the finger back and forth, with the pad of the finger palpating transversalis fascia (Fig. 15).

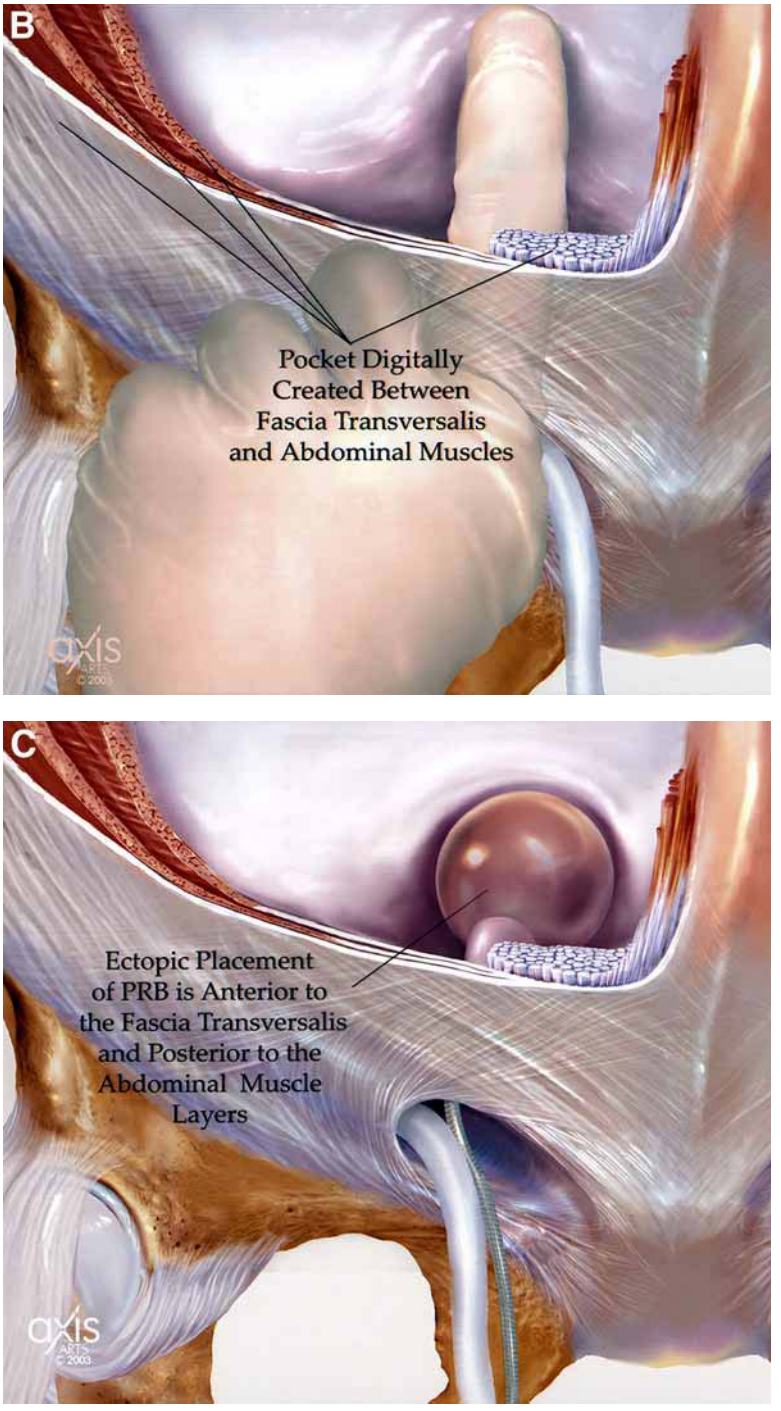


Fig. 15. (B) Pocket formation. **(C)** Ectopic placement of reservoir. (Printed with permission.)

Ideally, the Mentor reservoir with Lock-Out valve should be used. However, we have also used AMS reservoirs and have informed the patient about frequent auto-inflation that occurs during the first 3 mo. In our experience, auto-inflation ceases to be a problem if

the patient keeps his reservoir full with most of the system fluid. One major disadvantage of ectopic reservoir placement is that the reservoir is palpable, and a bulge is frequently visible in thin individuals. Researchers recently described ectopic placement of the pressure-regulating balloon in urinary sphincters *(36)*. Because the balloon is smaller and auto-inflation is not a concern, the ectopic placement of this reservoir is becoming more common.

With the infrapubic approach, the prosthesis pump is placed freely in the scrotum after an adequate subcutaneous pocket has been created. A large Hegar dilator, size 20, has proved helpful in achieving an adequate space for pump placement. The pump should be placed anterior to the testis and as far inferiorly in the scrotum as possible. Patients are encouraged to push down on the pump gently in the first few weeks of the postoperative period to maintain this dependent position. If it migrates to a position adjacent to the shaft of the penis, then it becomes difficult to operate and inconvenient during intercourse.

When the scrotal approach is used, the septum between the testicles is taken down. The pump is placed between and posterior to the testes. The scrotal septum is re-approximated over the pump tubing with a single suture. The pump is not pexed in any fashion. If the pump becomes too anterior, then the patient can reposition it by manually displacing it posteriorly. Unlike the infrapubic placement of the pump, the necessity to reposition the pump during penoscrotal insertion is distinctly unusual. During the placement of a penile prosthesis via either surgical approach, copious irrigations with antibiotic fluid should be stressed. It is not important which antibiotics are used; the effective prophylaxis is believed to be the flooding action that washes away the bacterial contaminants that have dropped in the wound during the surgery. Concurrently, double-gloving the operating surgeon is a good idea. Because prosthesis infections come from bacterial contamination at the time of surgery, double-gloving serves as protection from skin bacteria of the surgeon if his glove becomes punctured. At the conclusion of the procedure, two layers of subcutaneous tissue in the infrapubic technique and two layers of Dartos in the scrotal technique are closed with 00 absorbable suture. Skin closure occurs with interrupted or running absorbable sutures.

RESULTS

Repairs of the early models of inflatable penile prostheses were relatively common. Manufacturers have eliminated or reinforced areas that tended to wear, and the products on the market have reliability rates equal to or greater than any other implantable medical device. Additionally, over the years, surgeons have gained experience in implantation techniques, proper sizing, and placement of parts. Several recent series have been published to attest to this finding.

The Cleveland Clinic group reported a mechanical survival rate of 78% with the Ultrex cylinders *(37)*. Levine et al. *(12)* reported a 93% 3-yr survival rate with an enhanced Ambicor prosthesis. Choi *(38)* reported on the reliability of the AMS 700 CXM prosthesis in Korean men and related that 90% functioned at 5 yr. Carson et al. *(39)* reported a prospective study on the AMS 700 CX that showed an 86% mechanical survival at 5 yr. Wilson et al. *(4)* studied a very large series of Mentor implants and concluded that enhancements made in 1992 improved 5-yr device survival for mechanical revision from 73 to 93%. Govier and coworkers *(40)* studied numerous different devices and reported that 91% of the implants worked well at 3 yr. In 1998, The Wayne State group published a series with a mean follow-up of 5.5 yr. This series from these very experienced implanters showed that Mentor Alpha had a 96% survival and AMS 700 Ultrex and CX had survival rates

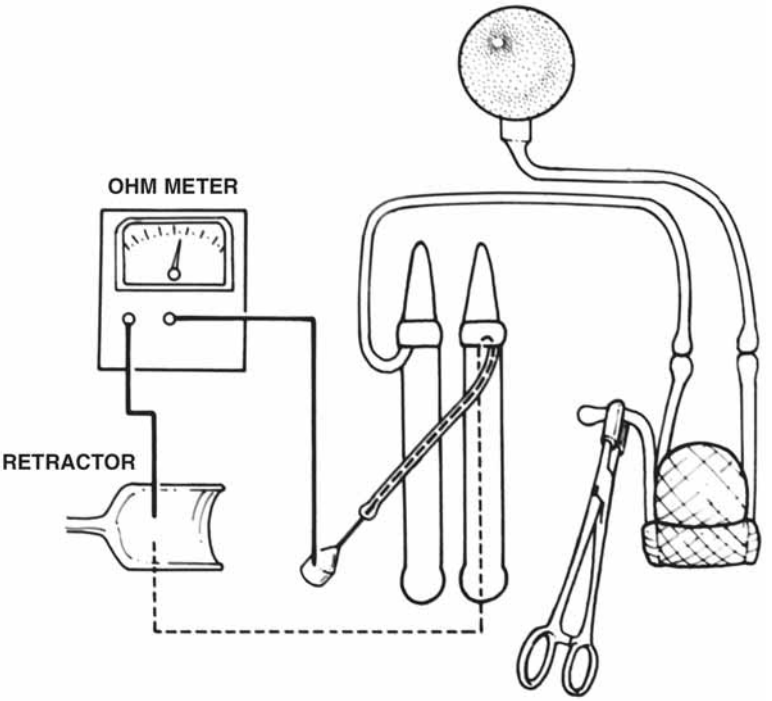


Fig. 16. Ohmmeter used to detect site of fluid leak in a hydraulic penile implant.

of 84% *(41)*. As mentioned earlier, the introduction of Paralyne coating to all the AMS three-piece products in 2000 was expected to further reduce the incidence of revisions and to significantly improve survival from revision for mechanical breakage for the AMS product line.

IMPLANT REPAIR

In the United States, all penile prostheses are sold with a limited lifetime replacement policy. This is indicative of the confidence that manufacturers have in the mechanical reliability of the penile implant after 30 yr of device improvements. The manufacturers constantly upgrade the devices with enhancements designed to improve ease of use and patient outcomes. Until recently, it was widely believed that if the prosthesis developed a malfunction within 2 yr of placement, parts that were not defective might be left in. To diagnose the defective component at the operating table, an ohmmeter can be used to detect leakage of sodium and chloride ions through an opening in the part. Movement of these ions completes the circuit and gives a positive deflection of the ohmmeter needle (Fig. 16). Others filled the implant with contrast in the past to detect extravasation or a tubing kink site with an X-ray. Currently, most physicians fill the system with isotonic saline.

A single-component replacement was considered particularly advisable if the penile cylinders were not responsible for the mechanical failure. Opening the corporal bodies to replace cylinders increases scar tissue that might contract and may shorten the penis. Patients who have had numerous repairs have related that after each change of cylinders, the penis has become noticeably shorter *(3)*.

As we learn more about the etiology of prosthesis infection, current theory regarding revision management is changing from historical dogma. Revision operations have been reported to have an infection rate significantly higher than that of first-time implantation

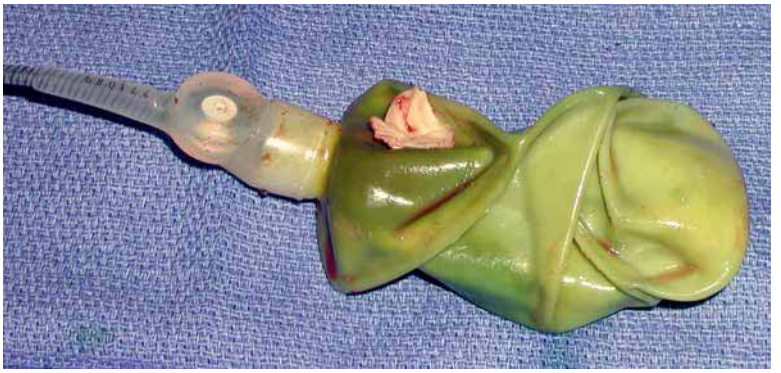


Fig. 17. Bacterial Biofilm on a clinically uninfected reservoir revised for mechanical failure of implant.

(42). In a published series of infected implants (the largest reported to date), revisions carried an infection incidence of 10%, and the risk of infection in revisions of diabetics was even higher *(24)*. To explain this increased risk of infection during revision surgery, a multi-institutional study was conducted that cultured clinically uninfected implants that underwent revision for mechanical reasons. The incidence of positive cultures taken from the wound during revision for mechanical breakage was found to be 70%, despite the fact that there were no clinical signs of infection *(43)*. The bacteria reported were mostly staphylococcal skin organisms such as *Staphylococcus epidermidis* or *S. lugdunesis*. These organisms do not usually cause human infections, with the exception of in the presence of an implant. Needless to say, these are the same bacteria responsible for most of the implant infections in prosthetic hips, knees, heart valves, and so forth.

On the basis of this research, a patient undergoing a revision has bacteria living in symbiosis with the host in his implant spaces. The bacteria exist in a lowered state of metabolism surrounded by a mucopolysaccharide matrix that protects them from antibiotics and the body's defense mechanisms *(44)*. In many instances, we have encountered visible biofilm on implant components during revisions of clinically uninfected implants (Fig. 17). Biopsy and culture of this biofilm typically yields opportunistic staphylococcal organisms. If these bacteria reach a critical mass, they have the potential to cause clinical infection. Something about the revision operation causes this in 10% or more of clinically uninfected revisions.

Therefore, some surgeons *(45)* are now copiously irrigating the wound of revision cases with the antiseptic solutions described by Brant et al. *(46)* as effective in cleansing overtly infected wounds. The incidence of revision operation infection has been reduced from 10 to 3% by sequentially irrigating each of the four implant spaces before placing a new implant. It is not necessary to change the gowns, gloves, and instruments as with a formal salvage, nor is it necessary to use a pressure irrigation as is classically described. The Asepto syringe irrigations (approx 28) add an additional 10 to 15 min to the time of the operation *(47)*. Antiseptic solutions are theorized to cleanse and sterilize the implant spaces of bacteria and their products (biofilm) that have been present since the original surgical procedure.

SCARRED CORPORAL BODIES

Peyronie's disease is a common condition in which scar replaces the natural elastic covering of the corporal bodies. This focal fibrotic replacement of the elastic tunica

albuginea causes curvature of the penis toward the side of the scar because the scarred tunica no longer stretches and expands. ED is commonly associated with Peyronie's disease, regardless of the size of the plaque. Carson et al. *(39)* performed a recent large, multi-institutional study that indicated Peyronie's disease is the second leading implantation etiology following vascular insufficiency. In that series, Peyronie's disease accounted for 16.9% of cases and exceeded diabetes at 12.9%.

Placement of a three-piece inflatable implant without any adjunctive maneuvers adequately straightens the erection in patients with Peyronie's disease in more than 40% of cases (Fig. 18 A,B). When using a three-piece implant for correction of Peyronie's curvature, cylinders should be restricted to the AMS CX, CXR, and CXM and the Mentor standard size Titan cylinders. Use of the AMS Ultrex cylinders in scarred corporal bodies is not recommended because their lengthening capability limits the development of enough axial rigidity to achieve straightening *(48)*. The downsized Mentor Titan NB is not used in patients with Peyronie's disease because aneurysm formation may develop if additional maneuvers (e.g., modeling) are necessary to straighten the penis after implantation.

Scott, an original inventor of the AMS inflatable penile prosthesis, conceived the modeling procedure. He had noted that orthopedic surgeons molded broken bones over metal rods, and he postulated that the concept might be useful in Peyronie's curvature. Unfortunately, during his active clinical years, the AMS cylinder was completely composed of silicone and did not have a fabric insert to limit distention. This limitless distensability did not provide enough rigidity against deformity to act as a fulcrum for disruption of the plaque. Modeling became a possibility with the introduction of the AMS CX and Mentor polyurethane polymer cylinders in the late 1980s. Modeling was initially performed in 1987, and the technique has been used successfully in hundreds of patients. The publication of the original article *(49)* describing modeling was met with some disbelief in the urological community. However, this therapy has achieved widespread acceptance. Ralph and Pryor *(50)* wrote "operative modeling of the penis over a prosthesis may look and sound horrible but gives a good result in any deformity."

After dilatation of the corporal bodies, cylinder size is determined from the intracorporal measurements. RTEs are used as needed. Because Peyronie's disease tends to shorten the penis, corporal measurements may differ by 1 or 2 cm. When there is any confusion about cylinder length, a shorter cylinder should be used, rather than a longer cylinder, and the cylinder and RTEs should be equal in length on each side *(51)*.

After cylinder placement, the corporotomies are closed with interrupted or continuous sutures, and the implant is inflated to the absolute maximum. If hydraulic cylinders are placed and the curvature is more than 20 or 30 degrees on full inflation, modeling can be used to improve straightening. The tubing leading to the cylinders is clamped to protect the pump from excessive pressure. During modeling, it is also advisable to protect the corporotomies from rupture by supporting the area with the fingers and thumb. The penis is then bent in a direction opposite to the curve as hard as possible, and the pressure is held for 90 s (Fig. 18 C,D). Feeling the scar tearing can sometimes be appreciated. Following the first modeling procedure, additional fluid can be added to the cylinders because the pressure has partially dilated the stenotic corpora. If the curvature is still prominent, then an additional modeling session of 1.5 min can be conducted after protecting the pump and corporotomies again. It should be stressed that it is persistent pressure that overcomes the curvature rather than a quick fracture similar to breaking a twig over a knee. There is nothing magic about 90 s. Requiring a predetermined amount of time enforces the discipline that constant pressure during periods of modeling is necessary for successful straightening.

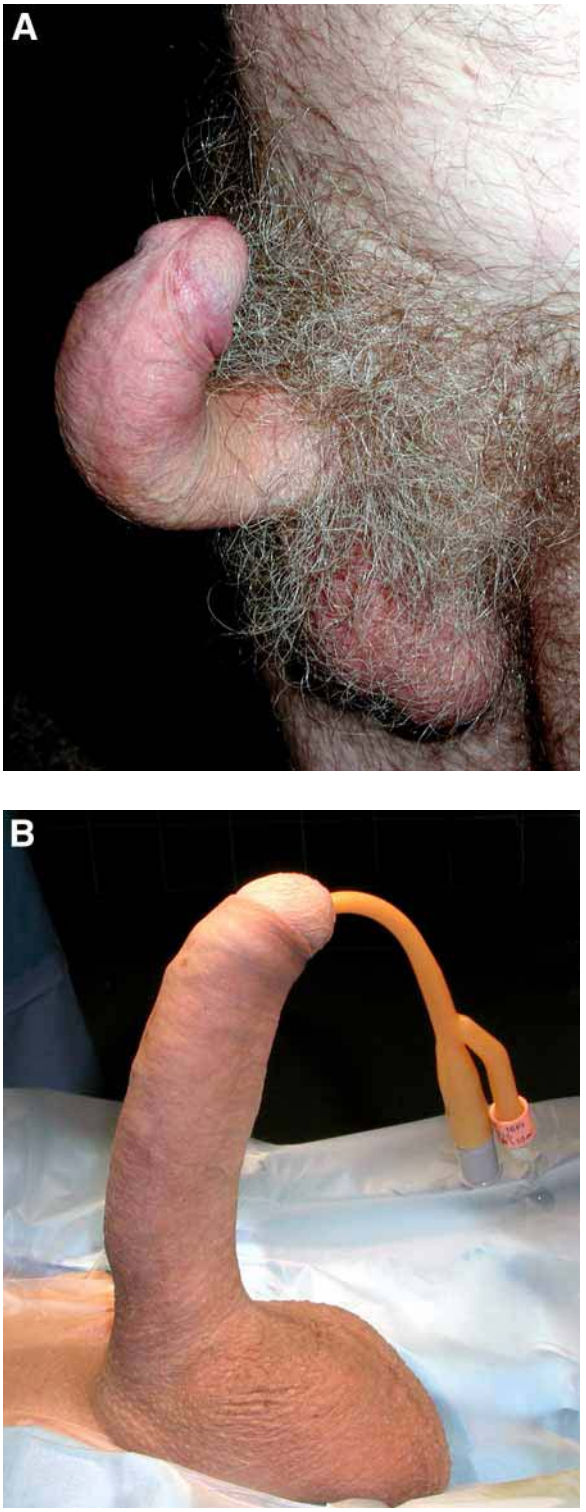


Fig. 18. (A) Peyronie's before implant (injection of PGE1). **(B)** After implant only (modeling not necessary).

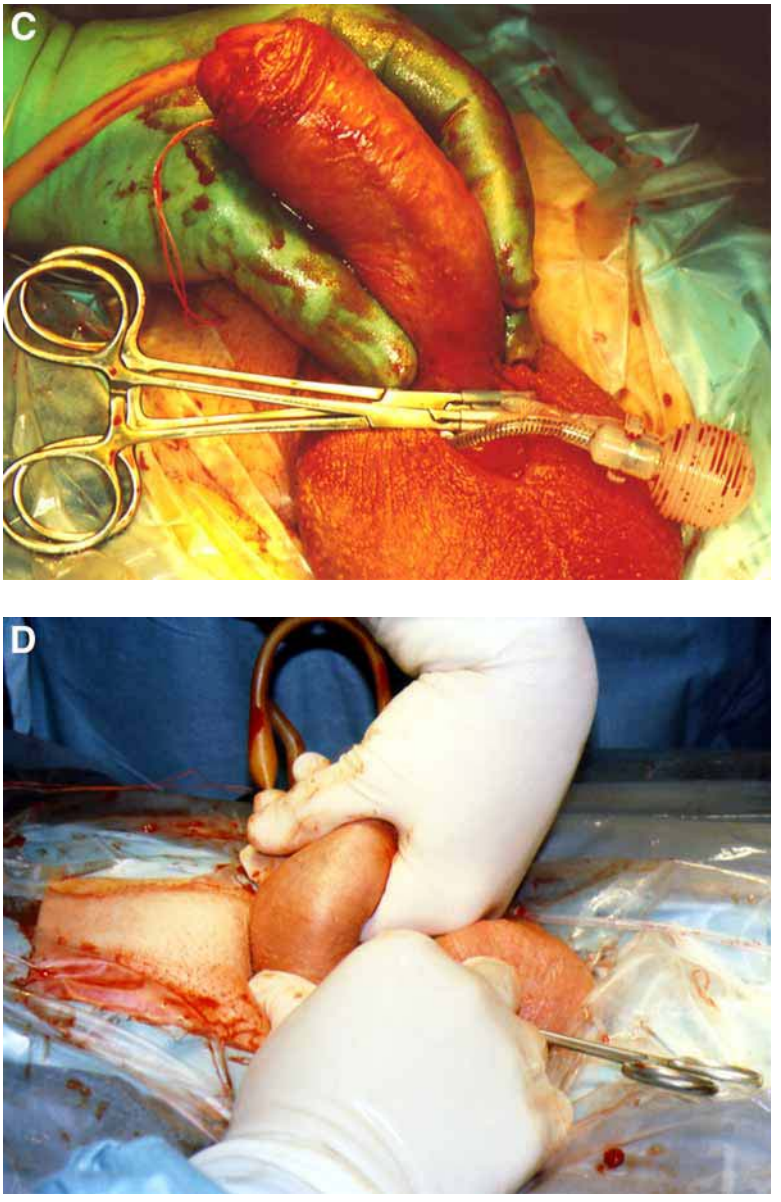


Fig. 18. (C) Protect pump and corporotomies. **(D)** Bend penis and hold for 90 s.

After two modeling sessions, the prosthesis is deflated completely. Complete deflation and subsequent re-inflation to approx 75% allows reseating of the cylinders distally and permits the surgeon to view the result at less than maximum inflation (where the patient will view the results). Maximum inflation is needed for correcting the curvature, but the patient never inflates maximally during sexual intercourse. The cylinders are filled with only enough fluid to achieve a satisfactory erection. It is not necessary to repeat the modeling procedure to achieve an absolutely straight erection. A total of 20 or 30 degrees *(51)* of residual curvature is considered successful straightening, and the patient can be assured of continued improvement with usage. If the surgeon's decision is made at less than max-

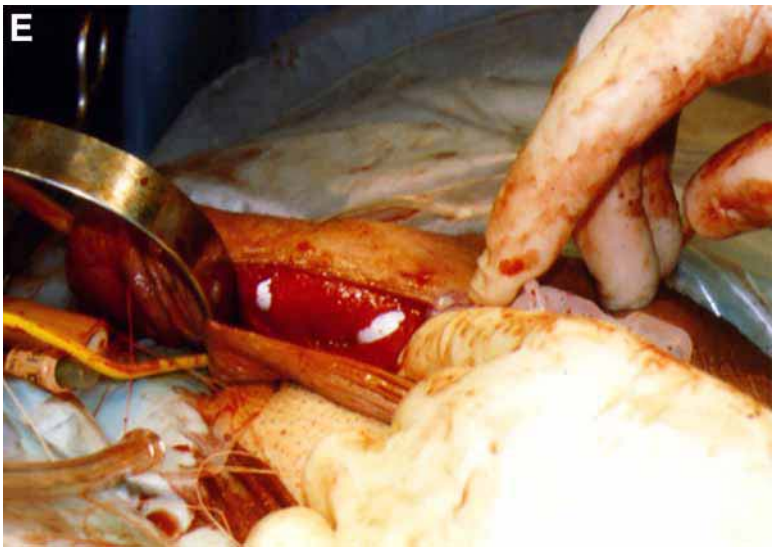


Fig. 18. (E) Relaxing incisions if modeling not sufficient to straighten.

imum inflation, adequate straightening is usually achieved by two modeling sessions. After modeling, it is important to check the corporotomies for rupture and to inspect the urethra for injury. Urethral laceration at the meatus is noted in approx 4% of cases. When this occurs, the offending cylinder should be removed, and the other components can be left in place. The cylinder can be replaced after 2 mo. Some patients seem satisfied with a one-cylinder expansion, particularly if the Mentor cylinder was used.

It was originally reported that despite modeling, 8% of patients required additional corporoplasties. This adjunctive procedure was not needed in a subsequent report *(52)*. Nevertheless, a formal straightening procedure over the inflated cylinder can be performed if modeling fails to adequately straighten the penis. A variation of the Nesbit technique has been reported that removes elliptical wedges of tunica from the convex surface of the curve *(53)*. The cautery device is useful for this purpose and will avoid damage to the prosthesis with a sharp instrument. Others have reported incising on the concave or inner surface of the curve. If the AMS CX cylinder is used and the gaps are small, they may be left open (Fig. 18E). If the gaps created are large and/or the Mentor cylinder is used, the defect is covered with natural materials such as cadaver pericardium or porcine small intestinal submucosa (Fig. 19; refs. *54* and *55*). Columbo and associates *(56)* have reported various grafts to broaden the caliber of the corporal bodies, enhancing girth in association with hydraulic implant placement (Fig. 20). This seems superfluous, but in our experience, inflation of the implant over time acts as a tissue expander, eliminating stenotic corporal areas such as the hourglass deformity.

The most difficult challenge in prosthetic urology is re-insertion of penile implants into corpora scarred from removal of a previously infected implant or an episode of priapism. In these cases, the usually spongy, easy-to-dilate erectile tissue has been replaced by sheets of fibrotic scar tissue. Fibrosis is worse distally in patients who have had priapism and is worse proximally in previously infected patients who have had an implant. Shortening of the penis is particularly noticeable in the patients whose implants have been removed for infection. The fibrosis defies dilatation with conventional instruments such as Hegar

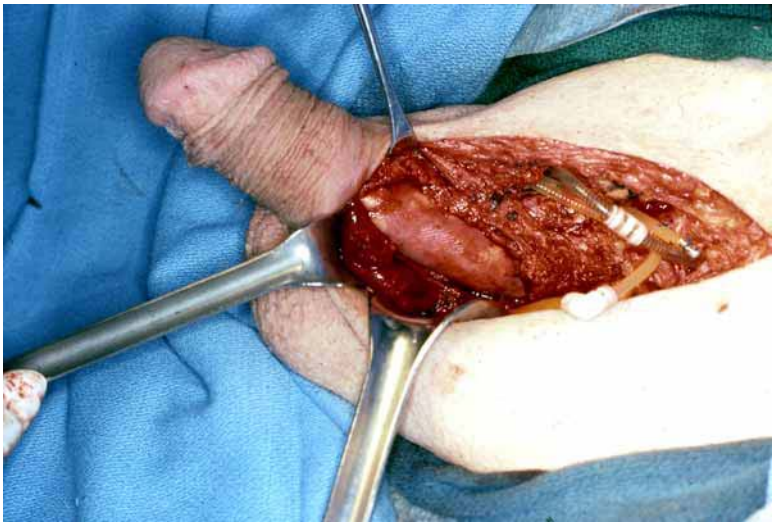


Fig. 19. SIS graft used to replace tunica albuginea of the corpus cavernosum.

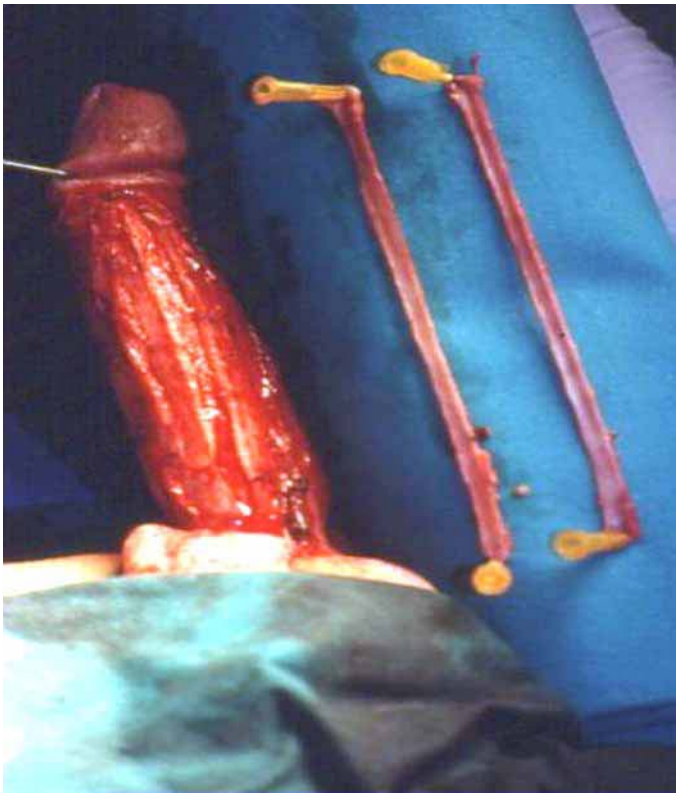


Fig. 20. Longitudinal incisions in tunica albuginea allowing girth enhancement with cylinder inflation.

or Brooks dilators. The standard size AMS or Mentor cylinder requires dilatation to 12 mm proximally to properly seat the base of the cylinder. To create the space necessary for placement of the cylinders, traditional methods involved extensive corporal resection and coverage of defects with synthetic material. Even experienced implanters reported

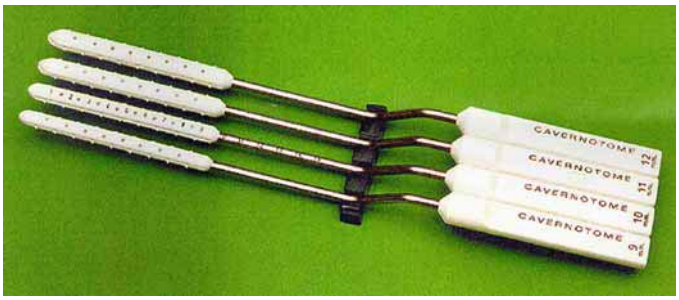


Fig. 21. AMS disposable Carrion-Rossello cavernotomes.

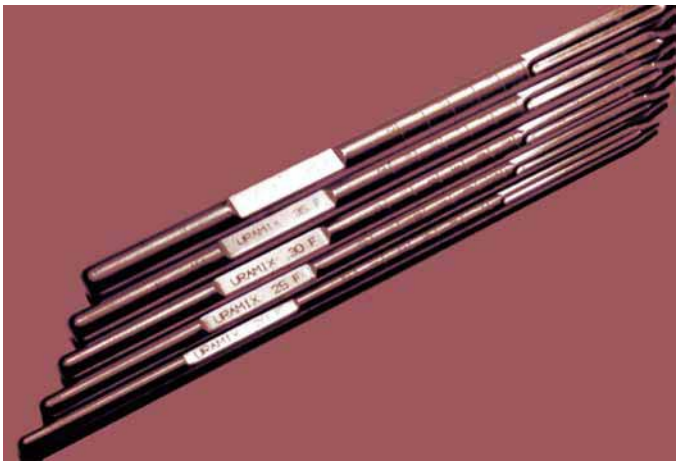


Fig. 22. Uramix cutting cavernotomes.

only 50% 1-yr implant survival *(57)*. Chances of successful re-implantation into these fibrotic corpora were considerably lower in the hands of occasional implanters.

In the late 1990s, two instruments that improved the chances of success in these difficult cases were introduced, including the Carrion–Rossello cavernotomes (Fig. 21; ref. *58*). These were sequentially sized (9–12 mm) metal dilators with a wooden rasp configuration and backward cutting teeth. They were advanced in an oscillating fashion, walking the toothed dilator forward in the scarred corpora. When withdrawn, the backward cutting teeth tore a channel in the scar tissue. The Carrion–Rossello cavernotomes were initially introduced in a metal version, but they have subsequently been supplied in a disposable version with sharper plastic teeth.

In 1999, Mooreville *(59)* reported a new dilator with a recessed knife blade known as the Uramix cavernotomes. These are even smaller: 6 to 13 mm in diameter (Fig. 22). These cavernotomes allow the surgeon to drill a space in the fibrotic corpora with controlled 1-mm cuts, thereby creating a cavity in the scar tissue.

The downsized cylinders have narrower bases and less expansion of the cylinder bladder. The AMS CXM (introduced in 1989) requires dilatation to 11 mm for base insertion. This was an improvement over the standard size cylinder base, but the new downsized implants are even narrower. The Mentor Titan NB requires dilatation to 10 mm, and the AMS CXR base needs a cavity of only 9 mm (Fig. 23). Combining tunnel creation with these specialized cavernotomes and the downsized implants affords experienced sur-

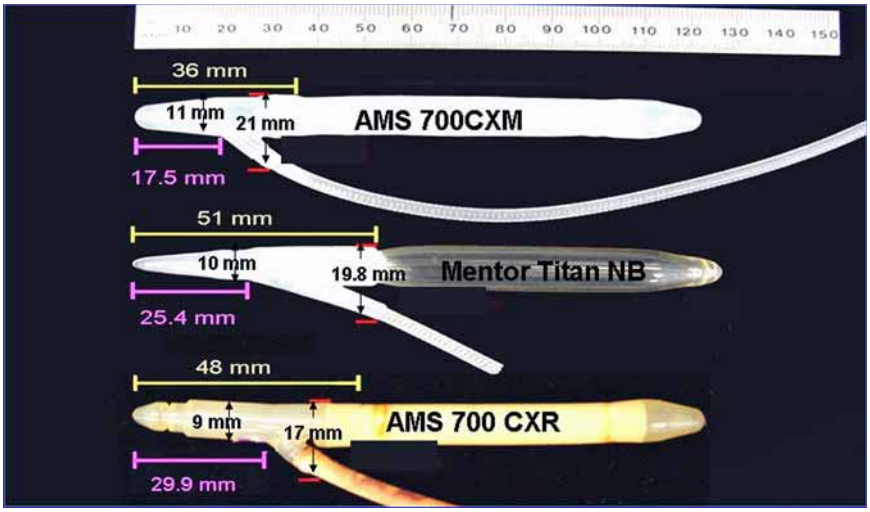


Fig. 23. Measurements of downsized cylinders.

geons a much greater chance of successful re-implantation in these challenging surgical circumstances *(58)*.

Although the surgeon appreciates success in these difficult cases, many patients are disappointed with penile length after re-implantation. Typically the re-implanted cylinder is 4 to 6 cm shorter than the one used at the original implantation—not to mention narrower in girth. Patients may be encouraged by the possibility of being able to accept longer and wider cylinders after a period of use with the downsized cylinders. Like the tissue expansion noted in Peyronie's disease, whereby the hourglass deformity from circumferential scar recedes with use, tissue expansion has been noted following implantation with downsized cylinders in these shortened fibrotic penises *(60)*. Frequently, after 8 to 12 mo, the downsized cylinders can be removed and substituted with standard AMS or Mentor cylinders, despite the fact that during the original surgery it was not possible to create a cavity that would accept the diameter of the standard size cylinder base. Additionally, with time and hydraulic usage, the fibrotic shortened corpora stretches, and a SST-type deformity of the glans penis may be noted because of cylinders that are now too short. During the re-insertion of the standard size cylinders, it is often possible to increase cylinder length 2 to 3 cm. This new, properly sized cylinder supports better and eliminates the hypermobile glans (Fig. 24). In our experience, patients who have had priapism do not exhibit the severe penile shortening observed in patients who have had an implant removed for infection. Intracorporal shortening is less in patients with corporal fibrosis secondary to priapism than in patients with previously infected implants. However, patients who have had priapism do exhibit girth enhancement that permits placement of standard width cylinders.

CORPOROPLASTY: GLANS FIXATION

Protrusion or extrusion of penile prosthesis cylinders is unusual (Fig. 25). Aggressive distal dilatation with small-diameter dilators during placement, oversizing of the cylinders, or excessive pressure against the end of the penis during sexual activity may predispose to protrusion or extrusion. The protrusion can be repaired using a natural tissue

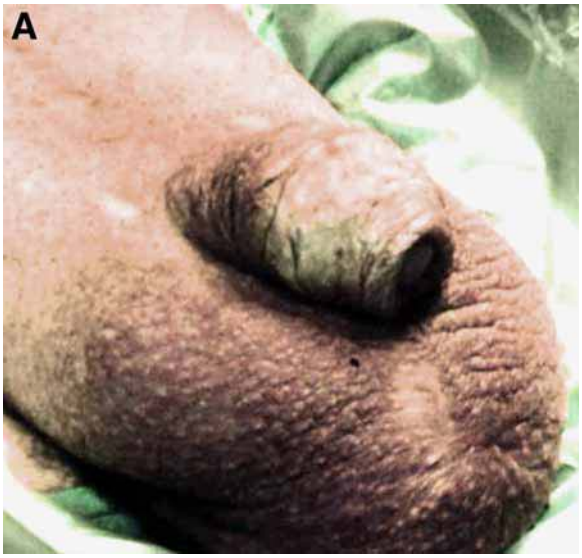


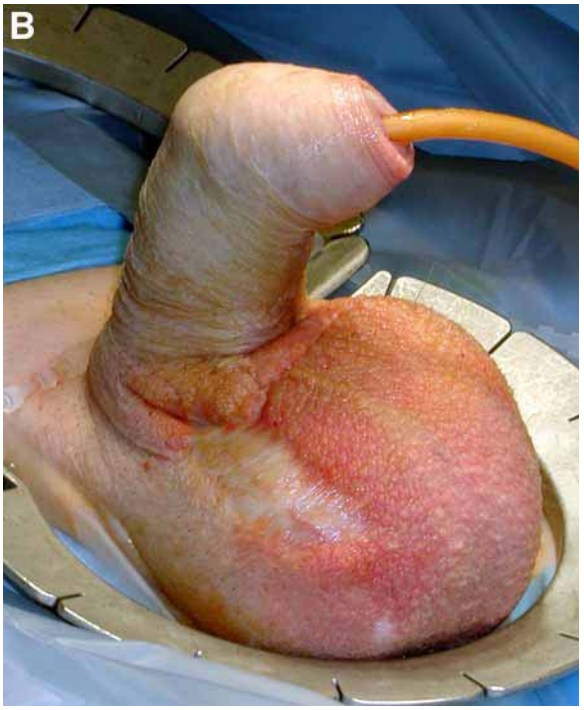
Fig. 24. (A) 19-cm cylinders removed for infection.

method *(61)*. A hemicircumcising incision is made on the side of the extrusion. A longitudinal corporotomy is made over the cylinder, and the cylinder is removed from the cavity. The back wall of the sheath that contained the cylinders is then incised, and a new plane is developed behind this capsule down to the distal end of the corporal body (Fig. 26). This original interior capsule wall will now provide the outer covering of the penile prosthesis cylinder. The guide suture in the cylinder can be replaced by passing a swedged-on suture through the tract previously occupied by the guide suture. A new tract dorsal and medial to the original cylinder cavity is created (Fig. 27). The cylinder is then guided into the newly created cavity by passing a Keith needle through the glans penis using the Furlow inserter. The outer wall of the capsular sheath, as well as the original tunica albuginea is reinforced with absorbable suture (Fig. 28).

An alternative approach is to place a windsock of synthetic material over the end of the prosthesis and to replace it into the corporal body as reinforcement for the distal tunica albuginea *(62)*. This substitutes one foreign body close to the skin surface for another. Carson *(63)* compared natural tissue repair vs windsock and found that the former was more successful.

Hypermobilility of the glans following prosthesis implantation is an unusual complication. It has been called glans bowing, the Concord deformity, and SST; the latter two descriptions reference the supersonic transport airplane's nose. It may be observed when the implant is improperly sized (too short) because of inadequate distal dilatation or when an originally properly sized implant has acted as a tissue expander. Other cases may result from unrecognized proximal corporal perforation that allows migration of the cylinder. Finally the Concord, or SST, deformity may result in cases of correct implantation for unknown reasons and is more commonly seen in uncircumcised patients.

Occasionally, after a routine implantation, the glans appears too mobile. Despite encouragement in the literature to perform immediate glans fixation *(64)*, our experience has been that the subsequent capsule formation around the cylinder tip often corrects the problem. If the glans still appears floppy after healing, it can be easily corrected as a subsequent procedure.



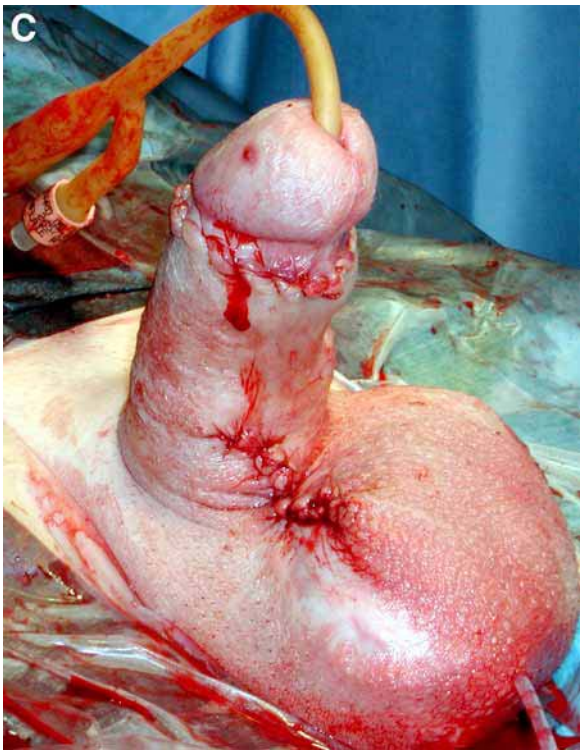


Fig. 24. (B) 14-cm CXR cylinders 1 yr later. SST development. **(C)** 16-cm cylinders substituted with circumcision.

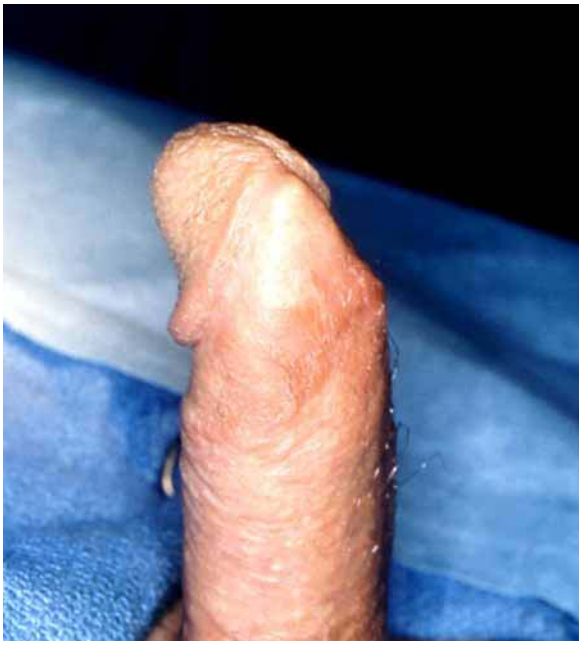


Fig. 25. Extrusion of implant cylinders through end of corporal body into subcutaneous tissue.

Undersizing of cylinders can be corrected by redilatation and addition of RTEs to the implant. If the problem is proximal migration of a unitary implant, the implant may be replaced with a three-piece inflatable, and the RTE may be stabilized by a suture sling of nonabsorbable suture that is firmly attached to the tunica albuginea. If cylinder size and placement are proper, and the problem is truly glans bowing or hypermobility over a properly sized implant, then glans fixation should be performed. Ball *(65)* described the surgical technique in 1980 and the technique remains as the most valid.

A hemicircumcising incision is made proximal to the glans, and dissection is carried down to the tunica albuginea. The tunica is not opened but is used as a guide for distal dissection underneath the glans on either side of the midline. In effect, the SST deformity is increased by the creation of these spaces beneath the glans, and the cylinder tips are visualized in the distal corpora under the tunica. Deep, nonabsorbable sutures are placed from underneath into the glans (Fig. 29). The deflated cylinders are milked in their sheaths proximally, and the sutures are placed in the distal tunica over the cylinder tips without injuring the cylinder. Tying the sutures "hitches" the floppy glans to the distal tunica, thus correcting the problem (Fig. 30). Dimples on the glans may be apparent from the underlying sutures (two on each side), but these recede with time.

INFECTION

Infection associated with a penile prosthesis is considered a catastrophic event that necessitates removal of the device. Although infections of penile implants are rarely life-threatening, they can cause major disfigurement and psychological trauma *(66)*. The rates of infection are low, in the range of 1 to 3% for initially inserted implants in patients without risk factors *(67)*. Commonly cited risk factors are diabetes mellitus (8%), spinal cord injury (9%), and revision surgery (10%) *(24)*. In our opinion, additional risk factors are steroid dependence (with the exception of transplant patients) and complicated implants

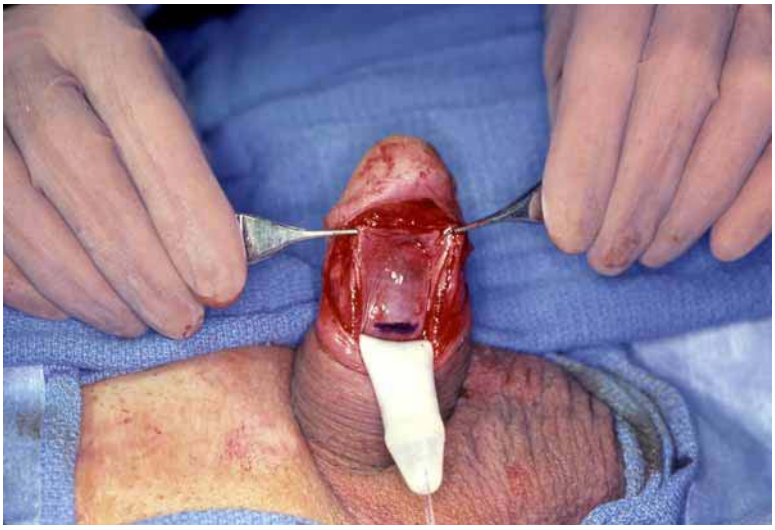


Fig. 26. Incision of back wall of sheath previously containing extruded implant cylinder.

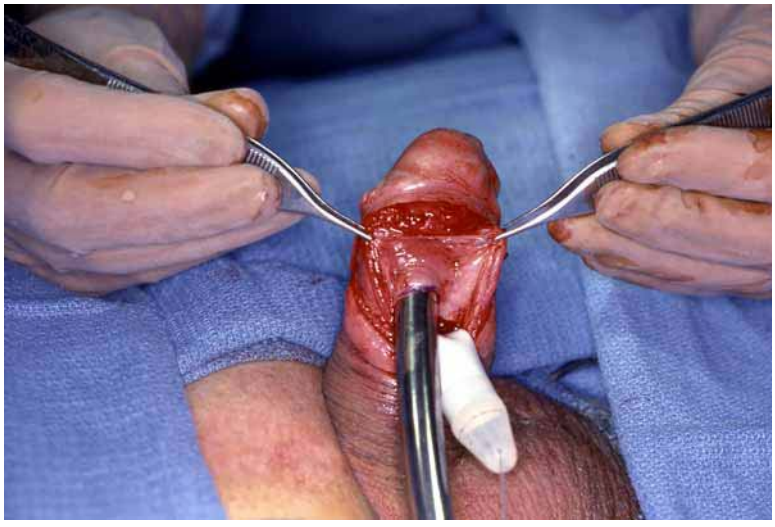


Fig. 27. Dilatation of new cavity for implant cylinder dorsal and medial to original cavity.

requiring synthetic graft materials. Based on our experience, conditions that are not risk factors are obesity, site of incision, concurrent circumcision, and previous radiation.

Current theory states that almost all prosthesis infections are caused by bacterial contamination at the time of surgery. Late hematogenous infections are distinctly rare. Costerton and colleagues *(44)* called it a "race for the surface." The bacteria are attempting to multiply and attach themselves to the prosthesis surface. The patient is simultaneously using peri-operative antibiotics and the body's defense mechanisms to eliminate the bacterial contamination. Unfortunately, recent studies have shown that in up to 70% of cases, the bacteria persist, multiply, and reach enough critical mass to secrete a biofilm. Subsequently, the bacteria may live in the biofilm at a decreased state of metabolism for many years; they live in symbiosis with their human host, causing no clinical symp-

Fig. 28. Placement of implant cylinder in newly created cavity.

toms to suggest their existence. Periodically, the bacteria may break free of the biofilm and swarm in the implant space in a "planktonic shower" *(44)*. These bacteria may produce symptoms and can be eliminated by the body's defense mechanisms or contemporaneous antibiotic administration. However, the reservoir of bacterial infection continues to be protected by the biofilm. That is why chronic administration of antimicrobials to a suspected implant infection is futile.

The biofilm inhibits phagocytosis and provides a barrier to diffusion of antibiotics to the area where the organisms are present. This slime is often visible on clinically uninfected implants *(6)* that are explored for mechanical failure and virtually provides a hiding place for the bacteria. The mechanism of the revision operation that causes the sleeping bacteria to reach a critical mass and cause an implant infection in 10% of uninfected revisions is unknown *(24)*. Therefore, as discussed earlier, some surgeons are removing all components and prophylactically washing out the implant spaces with antiseptic solutions to mitigate the high rate of infection following revision for mechanical failure *(68)*.

Infection associated with prosthesis implantation should be suspected if the patient has persistent pain beyond 2 mo. The presence of fever, erythema, or fixation of the components to the skin would also lead to suspicion of an infection. Purulent drainage occurs from the wound, especially if this is increased with pressure on the components, or any part of the prosthesis eroding through the skin is an indication that infection is present. The use of systemic antibiotics to clear such infection has not been successful, probably because of the biofilm phenomenon discussed earlier. When an infection is convincingly present, it is prudent to explore the wound and remove all the implant components. It is tempting to leave parts that are arduous to remove, such as the reservoir, but the bacteria may wick along the tubing, thus contaminating all the components; components left behind may present with infection months later.

The traditional approach has been to remove all components and any other materials such as graft or suture. A particular effort should be made to ensure the "boots" on the AMS

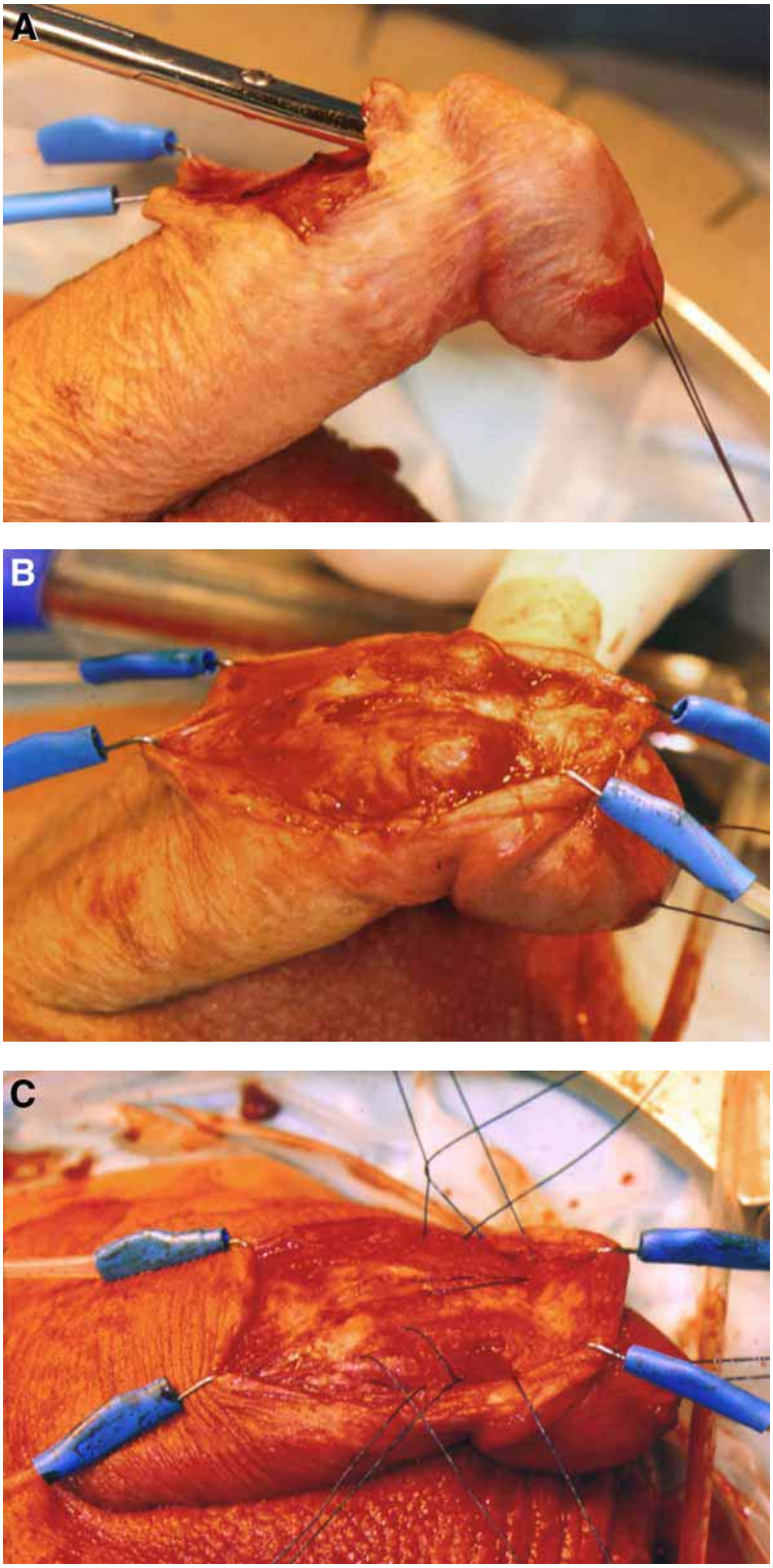


Fig. 29. (A) Dissection underneath glans. **(B)** Dissection complete. **(C)** Hitch sutures are in place.

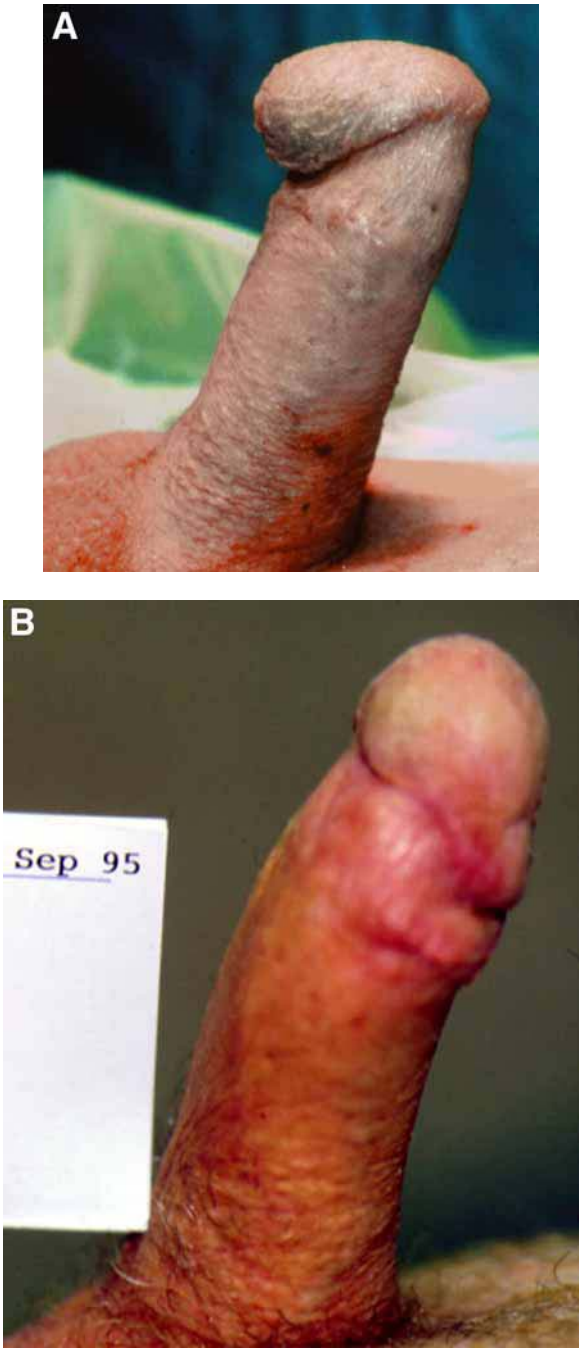


Fig. 30. (A) SST deformity in a patient with properly sized cylinders. **(B)** Correction with Hitch procedure.

cylinder tubing are removed because they are frequently obscured by tissue ingrowth. Likewise, a RTE left behind may continue to harbor symptomatic infection, requiring its removal at a subsequent exploration. If retained components are suspected, the best diagnostic tool is magnetic resonance imaging (Fig. 31; ref. *69*). Removal without imme-

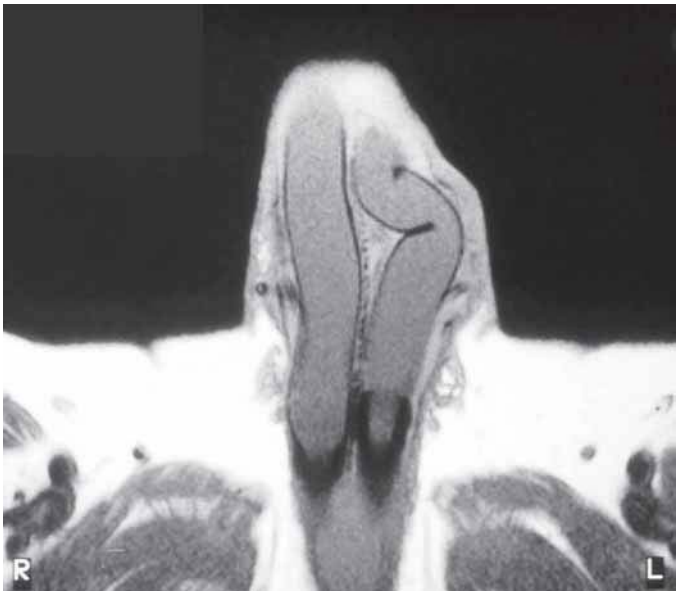


Fig. 31. MRI visualization of implant components.

diate replacement of the cylinders causes the patient to lose as much as 1 to 2 inches of penile length. Replacement of the cylinders at a later date is a daunting surgical challenge because of the development of scar tissue in the penis following removal for infection. These cases are of sufficient difficulty that one should consider referral to reference centers that have experience as well as the requisite cavernotomes. In 1996, Brant et al. *(46)* introduced an alternative method of dealing with the infected implant. This new method is called salvage or rescue and allows preservation of the implanted status, thus avoiding both penile shrinkage and the difficult surgical challenge of re-insertion of a prosthesis into scarred corporal bodies.

This approach entails removal of all the components and foreign material, cleansing the wound with a series of antiseptic solutions and replacing the prosthesis with a new sterile prosthesis at the same procedure (Tables 1 and 2). The salvage procedure is gaining popularity, and long-term follow-up in several studies has shown about an 80 to 90% success rate *(70)*. Low-toxicity opportunistic skin organisms like *S. epidermidis* or *S. lugdunensis* cause most prosthesis infections. These infections present late in the clinical course—at least 6 wk and sometimes years from implantation. The patients are not particularly sick; they may experience chronic pain, a component stuck to the skin, or a sinus tract through which tubing or cylinder tip can be seen. Notably, the scrotum is not swollen, and scrotal rugae are not obliterated by edema. These cases are ideal for salvage.

Occasionally, the prosthesis becomes infected quickly (less than 2 mo after insertion) and the patient is toxic, with immediate scrotal swelling and erythema, purulent drainage, fever, and so forth. The etiology in these infections frequently is a more powerful organism such as *S. aureus*, *Pseudomonas*, *Escherichia coli*, or *Enterococcus*. Salvage is less likely to be successful in these obviously sick patients. These bacteria are capable of tissue penetration outside the implant space. Therefore, the tissue surrounding the implant as well as the implant cavity is infected, and cellulitis is evident in the wound with or without abscess formation. In these circumstances, the use of systemic antibiotics (vancomycin and gentimicin) for 48 to 72 h before the salvage has improved the chances of success.

Table 1
Salvage Protocol For Infected Implants

1. Remove all prosthetic parts and foreign material.
2. Irrigate wound with seven antiseptic solutions.
3. Change gowns, gloves, surgical drapes, and instruments.
4. Insert new prosthesis.
5. Close wound with no drains or catheters.
6. Oral antibiotics for 1 mo.

Table 2
Antiseptic Irrigating Solutions for Infected Implants

1. Antibiotics.
2. Half-strength hydrogen peroxide.
3. Half-strength betadine.
4. Pressure irrigation (water pic) 1 g of vancomycin and 80 mg of gentimicin.
5. Repeat betadine.
6. Repeat hydrogen peroxide.
7. Repeat antibiotics.

An obvious abscess or fluctuance should be drained before salvage attempt. If fluid is available for culture, then the organisms involved can be determined, and more appropriate antibiotics can be substituted systemically for 2 or 3 d before initiating a salvage procedure.

The advantage of the salvage procedure is that most of the length of the penis is maintained. Additionally, it is easier to place the replacement cylinders while the cavities of the corpora cavernosa are patent, rather than returning later to create new cavities in scar tissue. In our enthusiasm to preserve penile length and to avoid the difficult re-insertion, the following caveats about salvage candidates should apply:

1. Diabetics in ketoacidosis and patients with positive blood cultures and tissue necrosis are poor candidates. It is simply too difficult to completely rid their systems of bacterial contamination.
2. It has been reported, and our personal experience has confirmed, that enterococcus is a particularly tenacious organism that is not as likely to be completely removed by the salvage washes. If this bacterium is suspected (usual presentation is a large, tense scrotum filled with clear, nonodiferous yellow fluid) or cultured, then complete removal without rescue may be advisable.
3. If the infection presents with bilateral urethral erosion of a cylinder, removal of the device is the best option. If erosion of a cylinder into the urethra has occurred on one side, then removal of the implant, salvage procedure, and replacement of the implant with only one cylinder on the noneroded side have been successful.

A form of delayed salvage has been advocated. Using this technique, the prosthesis is removed, and drains are placed in the wound, through which antibiotics can be instilled for about 72 h. At that time, the organisms involved in the infection are verified, and, if necessary, more appropriate antibiotics can be substituted before drain removal. After the drainage and antibiotic administration, the patient is returned to the operating room.

Table 3
Washout For Clinically Uninfected Revisions

1. Remove all components.
2. Irrigate one Asepto syringe of each of seven solutions (Table 2) in the four implant spaces.
3. Place new sterile three-piece implant.

Note: new gowns, gloves, instruments, drapes, and water pic not necessary as in formal salvage of infected implants.

Delayed salvage is more costly because of longer hospitalization and two surgical procedures. Additionally, after 3 d of inflammatory process, the wound can be difficult to close. Delayed salvage was initially published with results similar to immediate salvage. Subsequent authors have failed to substantiate early enthusiasm *(24,70)*, and immediate salvage has become the preferred method *(71)*. Furlow and Goldwasser *(72)* have advocated a form of partial salvage. If the wound appeared free of purulence and cellulitis and a part of the implant (e.g., the pump) was exposed, they removed the exposed part and placed a new part in the opposite scrotum without changing other components. Success with this approach was not as great as when all parts of the device were removed.

As mentioned earlier, both AMS and Mentor have introduced infection-retardant coatings to their prosthetic lines. The coatings are only available on the three-piece hydraulic models and the Mentor malleable and Excel. Early results have suggested a clinical benefit of reduced infection for patients implanted with the coated devices versus patients implanted with noncoated devices *(9–11)*. An important caveat is that the introduction of any new microbe-resisting coating should not allow an implanting surgeon to reduce his vigilance, sterile technique, and use of antibiotics to prevent implant infections. Despite the early reports of benefit from these innovations, a larger number of implantations will need to be performed by several different centers and surgeons, followed over time, and analyzed to statistically demonstrate a benefit. Modification of the salvage procedure has been used in clinically uninfected revision cases termed "mini-salvage" with success in reducing the infection rate (Table 3).

VISCUS INJURY

Viscus erosion may present as infection. The reservoir has eroded into bowel or bladder, and the patient develops drainage from his incision of urine or bowel contents. The usual setting is a patient with a scarred pelvis in whom loops of small bowel or the bladder has been fixed by previous surgery. The physician makes the reservoir space under direct vision or with careful finger dissection, and the deflated reservoir is placed. The reservoir is filled with fluid that places unsuspected pressure on adjacent structures that have been rendered immobile by scar tissue. Over approx 1 to 3 d, the inflated reservoir pinches the adjacent viscus, creating a small necrosis and a bladder or bowel fistula.

Management of a bladder injury may be addressed and the implant status preserved *(35)*. The reservoir is removed, the bladder laceration is repaired, and the reservoir is moved to a new location, usually the other side of the pelvis.

Management of bowel injury is more complex. The bowel injury is invariably small intestine, because loops of this bowel have moved into the areas left vacant by bladder removal or other pelvic surgery. The small bowel is fixed in place by adhesions. If the

reservoir traps a segment of bowel and a small area of intestinal wall necrosis ensues, then succus entericus may appear on the evening of surgery or on the dressing several days later. The small bowel content is initially sterile, but the bowel rapidly becomes contaminated. No studies of the proper management of the injury have been published because the injury is exceedingly rare.

Our experience with the treatment of this injury and our observation of patient outcomes of other physicians has been valuable in formulating a treatment approach. Notably, what follows is not an attempt to dictate standard of care, because the complication is so infrequent and presents in different ways. It is merely our idea of what usually works best and minimizes patient morbidity. Based on our anecdotal experience, abdominal exploration should be discouraged. On diagnosis, the implant components should be immediately removed. With a small extension of the incision, staying retroperitoneal, the bowel fistula is usually evident adjacent to the reservoir and frequently can be repaired. The bowel injury is invariably a single area of necrosis. After the viscus is perforated, the drainage stays retroperitoneal and flows to the path of least resistance—around the reservoir and into the wound. If the peritoneum is opened and the so-called "running of the bowel" is conducted, then a retroperitoneal contamination is converted into an intraperitoneal one. The previously sterile abdominal cavity is seeded with bowel contents, predisposing the patient to require future additional surgery for intra-abdominal abscesses or bowel obstruction. If the bowel fistula cannot be found without extensive exploration and opening of the abdominal cavity, then we advise giving the patient a trial of bowel rest and total parenteral nutrition. In our experience, three viscus lacerations have closed within 30 d despite the fistula never having been visualized. In all of these patients, we were able to subsequently re-implant a two- or three-piece prosthesis with ectopic reservoir placement.

SATISFACTION

Of all the currently available treatments of ED, the penile implant has the highest satisfaction rate. It is the most invasive and least often chosen option, but once these devices are placed, patients and partners are gratified with the resulting erection in the vast majority of cases. Levine et al. *(12)* reported that 96% of patients and 91% of partners were satisfied with the results of the Ambicor prosthesis. In a series of 200 patients from a number of Italian institutions, Montorsi *(73)* reported on the AMS 700 penile prosthesis with a 98% patient satisfaction rate and 96% partner gratification. A multi-institutional report from Taiwan used several different prostheses on 331 patients, and 87% of patients were satisfied with the result *(74)*. A study of patients with Peyronie's disease who underwent implantation showed that 79% of the patients were satisfied and 75% of their partners appeared pleased with the results *(75)*. The major reason for dissatisfaction in this study was the shorter size of the erection. Other reasons for dissatisfaction included the fact that it did not feel natural, that the sensitivity and sex drive were not as good as in younger years, and that the partner did not have as great a role in creating the erection as she once did.

Satisfaction with the penile prosthesis is higher than the more conservative therapies. An American study recently compared patients who had used therapies of pills, injections, and vacuum devices and subsequently chose a penile implant. They determined that the penile prosthesis had a much higher rate of satisfaction than the more conservative therapies *(76)*. Penile prostheses have been available for more than 30 yr. They have an important role in the treatment of ED. Although penile implants are the least chosen and most

invasive treatment option, they provide a predictable, reliable, and durable result. Virtually any patient who is motivated and medically suitable to continue with sexual activity can be a candidate for placement of these devices, with the subsequent improvement in quality of life.

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17 Peyronie's Disease

History and Medical Therapy

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SUMMARY

Peyronie's disease is an enigmatic disease characterized by penile curvature, penile pain, and erectile dysfunction. The disease appears to be more prevalent than previously thought as more men seek medical attention for sexual complaints. The lack of a clear pathogenetic mechanism for the disease has led to numerous, diverse treatment options. Inconsistent results from studies evaluating these various treatment options, compounded by a lack of randomized, controlled clinical trials, make it difficult to formulate a clear treatment algorithm for the disease. This chapter reviews the history, pathogenesis, and treatment of Peyronie's disease and attempts to provide a practical framework to guide disease management.

Key Words: Peyronie's disease; induratio penis plastica; tunica albuginea; treatment.

INTRODUCTION

Peyronie's disease (PD), also known as induratio penis plastica, is a disorder characterized by plaque formation in the tunica albuginea of the penis. The disease is named after Francois Gigot de la Peyronie (1678–1747), a Frenchman who served as royal surgeon to King Louis XV and who made significant contributions to intestinal surgical techniques. de la Peyronie was also instrumental in effecting the transition of surgery from a trade into a professional guild in France *(1,2)*. In 1743, de la Peyronie described PD in a treatise on ejaculatory dysfunction, reporting a patient with "rosary beads" of scar tissue extending along the dorsum of the penis, which was associated with upward penile curvature during erection *(3)*. de la Peyronie suggested that the best treatment was bathing in the baths of Berege in southern France.

However, de la Peyronie was not the first to describe the condition bearing his name. In 1561, Fallopius and Vesalius corresponded about a patient with Peyronie's disease, and several earlier references exist, although the vague descriptions make it less clear whether these truly refer to the same clinical entity *(1)*.

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CLINICAL CHARACTERISTICS AND EPIDEMIOLOGY

PD involves the formation of fibrotic plaques in the tunica albuginea. Plaques are typically unifocal (78–84% of cases) and located on the dorsum of the penis, although they may be located in any region of the tunica albuginea *(4)*. In one series, dorsal (46%), lateral (29%), and ventral (9%) curvature were the most common abnormalities, and the remaining abnormalities were intermediate *(5)*. Plaques cause curvature with erection, and the curvature is directed toward the site of the plaque. The plaques can also cause penile shortening and other deformities, such as "hourglass" and "swan-neck" deformities. Penile deformity may develop in an acute manner, in which patients report development of deformity essentially overnight, whereas others have a more insidious onset over weeks to months *(5)*.

The extent of curvature can make intercourse challenging from a mechanical perspective and can cause discomfort for a patient's partner. Curvature can exceed 90 degrees; in one cohort, approx 20% of patients had curvature greater than 60 degrees *(5)*. Additionally, many patients experience pain during the early, acute phase of the disease that is often associated with penile tumescence and/or intercourse, although some patients experience pain while flaccid. This pain is believed to result from active inflammation; biopsy of 12 painful plaques found inflammatory infiltrates in two-thirds of cases *(4)*. In most cases, pain resolves with chronicity, and pain resolution is believed to reflect stabilization of the disease. The acute inflammatory phase typically lasts between 6 and 18 mo *(6)*. The subsequent chronic phase is characterized by little pain, stable penile deformity, and stable plaque size.

Erectile dysfunction (ED) is noted in 20 to 40% of patients with PD, with either generalized lack of tumescence or flaccidity distal to the plaque *(7,8)*. PD also affects quality of life, and 77% of afflicted men report psychological effects, of whom two-thirds report frequent concern regarding the condition *(9,10)*. Spontaneous disease regression has been noted in 5 to 40% of cases, with one large series demonstrating a rate of 13% *(2,6,7,10)*.

PD predominantly affects middle-aged and older men, with prevalence between 0.38 and 3.7% of men age 40 to 70 yr *(6)*. However, age at diagnosis can vary widely, with reported cases ranging from age 18 to 80 yr *(4,5)*. The true prevalence may be higher than currently believed because of hesitance of patients to report this sensitive condition *(11)*. This is supported by an autopsy series of 100 men without history of PD that found pathological derangements similar to those seen in PD in 23% of cases *(12)*. The lowest prevalence of a large series, which is likely an underestimate, was a prevalence of 0.38% noted in a retrospective review of medical records of residents of Rochester, Minnesota, between 1950 and 1984 *(13)*. The prevalence of PD noted in contemporary prostate-cancer-screening populations has been 3.7 to 8.9% *(6,9)*. The prostate-cancer-screening model has the potential advantage that patients are not presenting with any particular urological complaint and diagnosis is defined by a physician palpating a plaque on examination *(9)*. A large German study that assessed for the presence of PD with a questionnaire about the presence of a palpable plaque found a prevalence of 3.2% *(14)*. Notably, approx 10% of men with ED also have PD *(15)*.

HISTOLOGICAL CHARACTERISTICS

The tunica albuginea is a connective tissue structure composed of inner circular and outer longitudinal layers encompassing the corpora cavernosa *(16)*. Normal tunica albu-

ginea is composed of collagen bundles undulating among elastic fibers in an irregular, latticed pattern *(17)*. The tunica albuginea of PD plaques is characterized by dysregulated extracellular matrix, with excessive amounts of collagen in a disorganized pattern, loss and fragmentation of elastic fibers, and fibrin deposition *(17,18)*. Plaques contain an increased ratio of type III to type I collagen, and collagen fibers are tightly packed with loss of normal intervening ground substance *(19)*. In addition to decreased elastic fiber density in plaques compared with controls, patients suffering from PD as well as ED have fewer elastic fibers compared with those with PD who have normal erections *(19,20)*. Additionally, plaque-adjacent "normal" tunica albuginea has been found to contain excess type III collagen and decreased elastin, indicating that the pathological disease process is not solely limited to the clinically evident plaque *(20,21)*.

Peyronie's plaques usually contain an increased density of fibroblasts. Additionally, myofibroblasts, which produce tractional forces in wound organization and are normally cleared by apoptosis after wound healing, can persist in plaques *(22,23)*. A perivascular lymphocytic and plasmacytic infiltrate is noted in some plaques, either within the tunica itself or in surrounding tissues *(18)*. This inflammatory infiltrate is characteristic of lesions of short duration, suggesting that inflammation is an early, inciting event in pathogenesis. Chronic lesions typically have little inflammation, although inflammatory infiltrates have been noted in chronic plaques *(24–26)*. Calcification and ectopic ossification have been noted in up to one-third of plaques, typically in those of longer duration *(18,25,27)*. Additionally, the connective tissue derangements can extend beyond the tunica albuginea into the corporal tissue *(18,21,25)*.

The abnormal extracellular matrix makes plaques inflexible compared with surrounding normal tunica albuginea. Collagen has great tensile strength but poor compliance, whereas elastin can stretch up to 150% of its length *(16)*. Therefore, with erection, plaques do not expand like normal tunica albuginea and cause curvature or deformity by tethering the tunica albuginea *(27)*. Additionally, the abnormal mechanical properties of tunical plaques could contribute to dysfunction of erectile hemodynamics; for example, derangement of the normal compression of subtunical venules during tumescence can lead to veno-occlusive incompetence or venous leakage *(28)*.

ETIOLOGY

Since its earliest descriptions, authors have speculated about the cause of PD. The Byzantine historian Zonar chronicled the case of Emperor Heraclius, who developed penile deformity that caused him to "urinate into his face," an affliction believed to be punishment for an incestuous relationship with his niece *(1,2)*. In the 19th and early 20th centuries, PD was purported to be caused by penetrative trauma from having sex with a nonenthusiastic or bored partner. Indeed, it was believed that intercourse with a facilitating partner could reverse the condition. Infections such as syphilis and gonorrhea have been cited as causative, and medical conditions such as gout and diabetes have been implicated. It has even been suggested that the disease reflects an evolutionary regressive phenomenon because some other mammals, such as canines and some primates, have an osseous penis *(1)*.

However, it has become clear that most cases are idiopathic and are not associated with other disease states, and the cause of PD remains unclear. The current leading theory is that blunt trauma to the tunica albuginea during intercourse causes microhemorrhage, fibrin

extravasation, cellular infiltration, and inflammatory response, thereby inducing deposition of abnormal extracellular matrix *(27,29)*. The inflammatory response may be a self-perpetuating process, with accumulated cytokines and reactive oxygen species inducing more cellular infiltration that subsequently leads to further cytokine production *(27,30)*.

It is also believed that patients with PD might have a genetic predisposition to abnormal wound healing or may be affected by auto-immune, connective tissue, or vasculogenic aberrations *(31)*. Reasons for this theory include a family history of PD in 2 to 4% of patients and an association with Dupuytren's contracture in 20% of patients. Dupuytren's contracture, or aponeurotic palmar fibrosis, is a heritable, autosomal dominant disease with a population prevalence of 4 to 6% *(31–33)*. Identical twins have been reported to have PD. Additionally, in a study of patients with Paget's disease of bone (a condition characterized by abnormal bone turnover), 14 to 31% of patients had PD, whereas 23% had Dupuytren's contracture *(32)*. Studies of human leukocyte antigen (HLA) linkage have found that PD is associated with the HLA-B7 and HLA-B27, although results have varied and the largest study found no association between PD and HLAs *(6,34,35)*. Immunological studies in patients with PD have found at least one abnormal immunological test in 76%, altered cell-mediated immunity in 49%, and markers of autoimmunity in 38% *(36)*. Patients with PD have also been found to demonstrate elevated levels of anti-elastin antibodies, further suggesting auto-immune mechanisms *(37)*.

Age is a clear risk factor; in one large survey, prevalence rates of 1.5% in men age 30 to 39 yr increased to 6.5% in men older than age 70 yr *(14)*. Older men are speculated to be more susceptible to tunical injury because they have less rigid erections that are more likely to buckle during intercourse. Genital trauma has also been reported as a cause of PD; one study showed a threefold increased risk of PD in patients with prior genital or perineal trauma *(33,38)*. An association has also been reported with invasive penile procedures (i.e., cystoscopy) *(33)*. However, a review of 193 patients with surgically corrected penile fracture and 150 patients with a history of taqaandan (the cultural habit of forceful bending of the erect penis to achieve detumescence) found only one case of PD *(39)*. This finding brings to question the role of trauma or suggests that trauma only in association with predisposing factors (e.g., auto-immunity) results in PD. Association with hypertension, diabetes, and other risk factors for systemic vascular disease have been found in some studies, but not in others *(5,9,40)*. Although infection has been speculated as a cause of PD, a sensitive molecular analysis found no evidence of bacteria in plaques *(41)*.

Transforming growth factor (TGF)-β is believed to play a causative role in fibrotic diseases and is implicated as central in the pathogenesis of PD. TGF-β is elevated in the tunica albuginea of patients with PD *(6)*. Injection of cytomodulin, a synthetic peptide similar to TGF-β, into rodent penile tissue produces an intense fibrotic reaction in the tunica albuginea *(42)*. TGF-β promotes expression of other fibrotic cytokines, such as connective tissue growth factor and monocyte chemoattractant protein 1 *(42)*. Several other fibrotic genes are overexpressed in plaques, including basic fibroblast growth factor *(43,44)*. An interesting theory regarding pathogenesis involves the observation that plasminogen activator inhibitor type 1, an inhibitor of both fibrin and collagen degradation, is overexpressed in plaques *(29)*. The inciting traumatic event in PD is theorized to cause extravasation of fibrin into the tunica albuginea, and some believe this extravasated fibrin is the primary trigger to plaque development. Support for this includes the detection of fibrin in plaques that are many years old and the induction of plaque-like histological changes by injection of fibrin into the tunica albuginea of rodents *(29)*. Osteoblast-stimulating

factor 1 is also increased in plaques, potentially explaining the high incidence of calcification in Peyronie's plaques *(27)*. Additionally, genes that are involved in tissue remodeling have been found to be downregulated in plaques *(44)*.

Cell cycle dysregulation may play a role in PD. Aberrant p53 function has been found in association with PD, with increased levels of the protein gene product in plaque fibroblasts compared with normal fibroblasts. This promotes cellular proliferation, allowing damaged cells to inappropriately continue through the cell cycle *(42,43)*. Chromosomal instability, including microsatellite alterations and loss of heterozygosity, has been associated with PD and Dupuytren's contracture *(6,42)*.

The cause of ED in patients with PD is also controversial. Although penile deformity, pain, and psychological factors may be the cause of ED in some patients, it has been shown that penile vascular derangements are etiological in 61 to 88% of patients with both PD and ED *(15)*. The tunica albuginea plays a key role in the veno-occlusive mechanism of erection, and loss of its normal mechanical properties could contribute to malfunction of the erectile mechanism *(1,45)*. However, data are conflicting, and some believe that ED associated with PD results from venous leak, whereas others believe arterial insufficiency is to blame *(46)*. Veno-occlusive dysfunction has been found in 30 to 86% of patients with both PD and ED, and arterial dysfunction has been demonstrated in 44 to 52% *(8,15)*. A study using color Doppler ultrasonography to evaluate vascular function in patients suffering from PD with and without ED suggested that arterial insufficiency, either alone or in combination with venous dysfunction, was the most important factor in the ED of PD *(15)*.

Another study using ultrasonography compared patients with PD to those with a presenting complaint of ED alone. There was no difference in rates of veno-occlusive dysfunction between patients with PD and associated ED and the group with ED alone *(46)*. Interestingly, patients with ED alone had significantly higher rates of normal vascular function (24%) compared with those with PD and ED (4%) *(46)*. Conversely, in a similar study, Lopez and Jarow *(8,46)* found that venous leakage was significantly higher in patients with PD and ED (59%) compared with those with ED alone (16%). Because both veno-occlusive and arterial dysfunction are common, determining the exact etiological factor for ED in every case can be difficult. Moreover, the baseline incidence of ED and the presence of vascular disease risk factors in the age group affected by PD further clouds a clear etiological theory.

DIAGNOSIS

Diagnosis is based on history and palpating a plaque in the tunica albuginea. Most plaques are easily palpable and are typically larger than 1.5 cm *(2)*. Presenting symptoms, duration of symptoms, and stability of the lesion should be assessed. Patients should be questioned about potentially associated conditions such as Dupuytren's contracture, Loederhosen's disease, family history, diabetes, Paget's disease of bone, systemic vascular disease, and prior genitourinary trauma or instrumentation. The physician should question a patient regarding erectile function, paying attention to characteristics of dysfunction: poor tumescence distal to the plaque, generalized lack of tumescence, physical inability for intromission resulting from the degree of curvature, anxiety, and psychological impact. Questioning the partner if possible, or asking about the partner's experience is also important because dyspareunia experienced by the partner may be relevant. Although it is somewhat imprecise, plaque size should be measured.

Numerous imaging modalities have been used to characterize plaques, including ultrasonography, X-ray in mammography technique, computed tomography, and nuclear magnetic resonance imaging (MRI). High-frequency ultrasonography is the only modality that reliably identifies plaque calcification and thickness of the tunica albuginea *(47)*. Ultrasound also provides reliable plaque size and is used by some to follow treatment effects *(31)*. Color Doppler duplex ultrasonography can also be used to evaluate penile vascular function. MRI with gadolinium visualizes inflammation and may provide a method for monitoring plaque inflammation. However, inflammation is associated with pain, and history can provide the basic information garnered from MRI. Therefore, use of this costly imaging modality cannot be justified on a routine basis *(31,47)*.

A practical protocol is to limit imaging to the evaluation of ED associated with PD via penile color Doppler ultrasonography after induction of erection with an intracavernosal injectible vasoactive agent. This is the most cost-effective method to evaluate the vascular erectile mechanism in these patients *(15)*. Evaluation of erectile function is important when planning operative intervention, because patients with preserved erectile function are candidates for straightening procedures alone, whereas those with deranged function likely require prosthesis implantation.

Patients are injected with a vasoactive agent (e.g., 10–20 μg of alprostadil) and are asked to self-stimulate in private, without ejaculation, for 5 to 10 min to obtain penile tumescence equal to or better than obtained at home. Ultrasound is then used to inspect for sufficient arterial flow and for venous leakage. Peak systolic velocity reflects arterial inflow (normal: >35 cm/s), and color Doppler ultrasonography has a sensitivity of 100% and specificity of 95% for diagnosis of arterial insufficiency compared with pudendal arteriography *(15)*. Dynamic infusion cavernosometry and cavernosography are gold standards for detecting veno-occlusive dysfunction, and in PD, cavernosography typically demonstrates a focal area of venous leakage in the region of the plaque *(15,48)*. End diastolic velocity and related measures (e.g., resistive index) derived from ultrasonography provide information regarding veno-occlusive dysfunction. An end diastolic velocity greater than 5 cm/s has a sensitivity of 90% and a specificity of 56% for detecting venous leakage compared with cavernosography. Additionally, a resistive index less than 75% by ultrasonography is associated with venous leak in 95% of patients compared with cavernosography *(15)*. Documenting the degree of curvature during erection with photographs allows for future comparison and patient counseling as treatment is undertaken.

TREATMENT

Due to lack of a definitive pathogenesis for PD, therapies are often directed at symptoms or speculated mechanisms. The phenomenon of spontaneous disease resolution and the divergent natural history of PD put a premium on double-blind, placebo-controlled trials and mandate caution when interpreting studies *(2)*. Unfortunately, placebo-controlled trials are lacking, thereby providing little clarity regarding the effectiveness of most therapies. Nonsurgical management is appropriate during the early phase of the disease with progressive, unstable plaques and/or painful erections. Such clinical management is usually recommended for at least the first 12 mo. However, if a patient presents with a longer duration plaque with significant symptoms, conservative management is likely to be ineffective *(6)*. Because symptoms do not resolve spontaneously in the great majority of patients, clinical therapies are usually administered. Therapies that are currently clinically relevant are reviewed here.

ORAL THERAPY

Numerous drugs have been used to treat PD, often with only tangential rationale. Oral therapies have included mineral water, sulfur, mercury, milk, iodides, disodium phosphate, acetyl-L-carnitine, estrogen, procarbazine, vitamin E, para-aminobenzoic acid (Potaba), tamoxifen, colchicine, and others *(1,49,50)*. Some favor oral therapy over local, intraplaque drug delivery because of pathological findings that suggest a generalized derangement of the tunica albuginea not simply limited to the plaque *(20,51)*. One unanswered issue regarding oral therapy questions the bio-availability of systemically delivered drug at the level of the tunica albuginea *(52)*. Oral therapy is appropriate in the acute disease phase, although once stable, nonpainful deformity is established, oral treatment is likely to have limited benefit *(53)*.

Vitamin E has been used to treat PD since the 1940s because of its anti-oxidant properties. Typical dosing is 400 mg administered twice daily. Noncontrolled studies have found improvements in pain in 82 to 100% of patients, decreased plaque size in 20 to 91%, and improved deformity in 33 to 78% *(53–56)*. However, in a questionnaire survey, Gelbard et al. *(10)* found no differences in changes in disease parameters between patients treated with vitamin E and those who received no treatment. Additionally, a controlled study by Pryor et al. *(50,53,57)* found pain improved in only 35% of patients, deformity improved in only 10%, and there was minimal decrease in plaque size; these findings were comparable to controls. With the available data, the effect of vitamin E on PD, if any, remains unclear. Because of its low cost and lack of side effects, vitamin E continues to be widely used, either alone or with other therapies *(58)*. Current controversy regarding the cardiovascular effects of vitamin E add to the debate regarding the use of vitamin E in the treatment of PD.

Potassium para-aminobenzoate (tradename Potaba; Glenwood, LLC, Englewood, NJ), has anti-inflammatory and antifibrotic properties *(59)*. In vitro, Potaba inhibits secretion of glycosaminoglycans and mucopolyssacharides by fibroblasts. It has been used clinically to treat inflammatory, fibrotic disorders such as scleroderma, dermatomyositis, and pulmonary fibrosis, and it was first used for treatment of PD in 1959 *(50,52,53)*. Typical dosing is 12 g per day, usually in three or four divided doses. Uncontrolled studies have noted improvements in pain in 44 to 100% of patients, plaque size in 11 to 100%, and angulation in 58 to 82% *(53,60,61)*. A placebo-controlled, double-blind study of 41 patients found trends toward symptomatic improvement in the treatment group, but there were no statistically significant differences *(62)*. Weidner et al. *(52)* conducted a prospective, randomized, placebo-controlled trial of Potaba (3 g of powder four times each day for 12 mo) in 75 patients with onset of disease less than 12 mo, noncalcified plaques, and no prior treatment. Therapeutic response was defined as regression in plaque-size and/or reduction in penile curvature of at least 30%. Overall response rates were 74 and 50% for the intervention and placebo arms, respectively. Plaque size decreased significantly in the Potaba arm compared with placebo, and there were no differences in improvement in pain or erectile function between the two groups. A protective effect on the development of new or worsening penile curvature was observed, with degree of curvature remaining stable in the treatment arm; however, it worsened in 33% of the placebo arm. In fact, 0 of 13 patients with a straight penis at presentation developed curvature on Potaba, whereas 6 of 8 developed curvature on placebo *(52)*.

Factors limiting use of Potaba include high cost, frequent dosing, and potential for severe gastro-intestinal symptoms *(53)*. In the study by Weidner et al. *(52)*, 13.7% of

patients in the treatment arm and 7.7% in the placebo arm dropped out secondary to side effects; however, the percentage of patients who dropped out secondary to gastro-intestinal side effects was the same in the two groups. The authors also speculated that the high rate of noncompliance (16%) in their study was related to patients' dislike of powder form of the drug, frequent dosing, amount of drug consumed, and poor taste *(52)*.

Colchicine binds cellular microtubules, with resulting antimitotic, antifibrotic, and anti-inflammatory effects *(53)*. It interferes with intracellular collagen synthesis by fibroblasts and promotes collagenase activity *(51,53,63)*. It has also been shown to inhibit proliferation of plaque-derived fibroblasts in cell culture *(64)*. Pathological clinical case studies of colchicine treatment in other fibromatoses (desmoid tumor and Dupuytren's contracture) have found decreases in abnormal intracellular collagen fibrils and myofibrils *(65)*. Colchicine's anti-inflammatory actions are related to its inhibitory effects on leukocyte motility and phagocytic activity, secretion of inflammatory cytokines, and the lipoxygenase pathway *(51)*. An in vivo rodent study evaluated colchicine's effect in inhibiting plaque-like derangements after injection of TGF-β into the tunica albuginea. Colchicine-treated rats exhibited less tunical collagen deposition, less elastic fiber fragmentation, a more normal extracellular architecture, and significant downregulation of TGF-β expression. Treatment effects were markedly more impressive when treatment was initiated immediately vs at 6 wk after TGF-β injection *(66)*.

Colchicine was first used to treat PD in 1994in a pilot study. Noncontrolled studies have found improved pain in 71 to 95% of patients, decreased plaque size in 47 to 50%, and improved deformity in 30 to 55% *(51,53,67,68)*. Interestingly, one study found that response was improved in patients with short disease duration (<6 mo), no ED, and degree of curvature less than 30 degrees *(51)*. Dosing has varied among studies. Patients are started at a low dose (0.6–1.2 mg daily for 1 wk), and the dose is gradually increased according to patient tolerance to a maximum of around 2.4 mg daily (given in divided, twice-daily dosing). Treatment has typically been for 3 to 6 mo.

Controlled studies of colchicine have produced conflicting results. In a single-blinded study of early PD (duration <6 mo, no ED, curvature of less than 30 degrees, pain present), Prieto Castro et al. *(58)* randomized 45 patients to vitamin E (600 mg/d) with colchicine (1 mg every 12 h) vs ibuprofen (400 mg/d) for 6 mo. They found statistically significant objective improvements in plaque size and curvature in the vitamin E/colchicine group compared with the ibuprofen group. Alhough not statistically significant, pain improved in 91% of the colchicine/vitamin E group compared with 68% of the ibuprofen group *(58)*. Safarinejad *(69)* performed a randomized, double-blind, placebo-controlled trial of colchicine (0.5–2.5 mg/d for 4 mo), and 78 patients completed the study. He found no differences in pain resolution, decrease in deformity, or decrease in plaque size compared with placebo. The average disease duration was longer in the study by Safarinejad than in the other study (e.g., disease duration <6 mo was an inclusion criteria in the study by Prieto Castro et al.). However, subgroup analyses found no differences between drug and placebo when evaluated by severity of disease or disease duration (<1 yr vs ⊕1 yr) *(69)*.

Another consideration regarding the use of colchicine is that side effects (often gastro-intestinal upset or diarrhea) are not uncommon, and this is the rationale for dosage escalation schemes. One series reported gastro-intestinal side effects in 33% of patients, and 17% discontinued therapy *(67)*. Conversely, the study by Prieto Castro et al. found that 16% of patients treated with colchicine experienced diarrhea that resolved after temporary dose reduction, and none of the patients dropped out of the study *(58)*. Hematological derangements (e.g., bone marrow suppression) can occur, and complete blood-count

monitoring is prudent while patients are on treatment *(51)*. One advantage of colchicine is that it is relatively inexpensive.

Tamoxifen, an anti-estrogen, has been studied because of its suppressive effects on TGF-β production by fibroblasts in vitro *(70)*. An uncontrolled study found that patients treated with tamoxifen had positive clinical response, and greatest improvements were noted in patients with disease duration less than 4 mo. Additionally, in a subset of patients with pretreatment tunical biopsy, 75% of patients with inflammatory infiltrates vs none without evidence of inflammation showed clinical improvement with treatment *(70)*. However, a subsequent randomized, placebo-controlled trial of tamoxifen (20 mg twice daily for 3 mo) found no differences in pain resolution or in changes in plaque size or curvature (as determined subjectively and objectively between tamoxifen and placebo) *(71)*. A criticism of the latter study is that disease duration was longer (mean: 20 mo) compared with the initial study (mean: 8 mo) *(50)*. Interestingly, the significance of the placebo effect in PD was clearly demonstrated in the placebo-controlled trial, with subjective improvements in pain (75%), curvature (42%), and plaque size (25%) in patients treated with placebo *(71)*. Side effects have been noted in up to 25% of patients and include decreased libido, facial flushing, reduced ejaculate volume, and gastrointestinal upset *(49,70)*. Because of the lack of supportive data and the potential for side effects, tamoxifen is not recommended for routine use at this time.

Research suggests a role for the nitric oxide (NO)–cyclic guanosine monophosphate system in PD pathogenesis. Inducible nitric oxide synthase (iNOS) and NO synthesis are upregulated in plaques. Specific inhibition of iNOS in the TGF-β rat model of PD worsens fibrosis, suggesting that NO production by iNOS may have an antifibrotic role in Peyronie's plaques *(22)*. An in vitro study of human and rodent tunica albuginea and derived cell cultures and an in vivo rodent study by Valente et al. *(22)* have found that stimulation of the NO–cyclic guanosine monophosphate system might counteract the fibrosis typical of PD. The most interesting finding was that rats fed substances in their drinking water that stimulated this system (including the phosphodiesterase inhibitor sildenafil) had an 80 to 95% reduction in both plaque size and the collagen-to-fibroblast ratio compared with controls as well as increased fibroblast apoptosis in the tunica albuginea *(22)*. In a follow-up study, this group performed gene transfer of iNOS into rodent TGF-β-induced PD-like plaques, with resulting decrease in plaque size, decreased expression of profibrotic mediators (e.g., TGF-β), and increased levels of factors that oppose oxidative damage *(72)*. This preliminary research awaits clinical evaluation before further conclusions can be drawn.

LOCAL DRUG THERAPY: INTRALESIONAL AND IONTOPHORESIS

Similar to oral therapies, numerous agents have been used for intralesional therapy of PD *(69)*. Intralesional therapy has the theoretical concern of disrupting tissue planes, causing additional scarring, and making subsequent surgery more difficult. This clinically has been noted with intralesional corticosteroid therapy (e.g., making dissection of the neurovascular bundles from the tunica albuginea quite difficult) *(73)*.

Use of verapamil, a calcium channel antagonist, is based on its ability to modulate extracellular matrix metabolism. An in vitro study showed that exocytosis of extracellular matrix molecules depended on intracellular calcium ions *(74,75)*. Verapamil alters fibroblast function, resulting in decreased collagen and extracellular matrix synthesis and secretion. Verapamil also increases extracellular collagenase activity, with one in vitro

study noting a 20-fold increase *(74,76,77)*. One in vitro study found that verapamil inhibited the proliferation of plaque-derived fibroblasts and modulated the effects of inflammatory and fibrotic cytokines *(64,74,78)*. The concentration of verapamil needed to induce these effects on in vitro fibroblasts was noted as more than 500 times therapeutic serum ranges observed with the use of verapamil for medical conditions such as hypertension, thus indicating the need to directly deliver the drug into plaques and other fibrotic lesions *(74,79)*. Animal studies have found improved wound healing with verapamil, and in humans, direct injection of verapamil has resulted in improved scar size *(77,80)*.

Multiple noncontrolled series have found improvements in objective and subjective parameters of PD with intralesional verapamil treatment *(74,81–85)*. An Italian study of 39 men found that pain improved in 91%, plaque size did not change, and curvature improved in 50% with disease duration less than 1 yr. However, curvature improved in only 10% of those with disease longer than 1 yr *(86)*. Levine et al. *(82)* reported the largest series to date: a noncontrolled, prospective study of 156 men. In their series, 60% had an objective decrease in curvature, and mean plaque volume was 4.2 cc before and 2.7 cc after treatment. Subjective improvements were noted in curvature, girth, rigidity distal to the plaque, sexual function, and pain in 62, 83, 80, 71, and 84% of subjects, respectively. There were no differences in response to verapamil based on disease duration or severity, and with mean follow-up of 2.5 yr, no patient who experienced improvement in penile deformity reported recurrence of deformity *(82)*. A small, controlled study of intralesional verapamil vs saline injections ($n = 14$) found that penile curvature improved in 29% of the verapamil-treated patients, whereas there no improvement was noted in the controls; however, this was not statistically significant. Plaque volume decreased in 57% of the treatment vs 28% of the control group, whereas subjective ED improved in 43% of the verapamil group vs none of the controls *(77)*. A controlled study of perilesional, subcutaneous injection of verapamil found no advantage of verapamil over placebo, indicating the need to deliver the drug into the lesion *(74,87)*.

Intralesional verapamil has minor side effects. Many men experience mild ecchymosis at the injection site. In the series by Levine et al. *(74)*, only 6 of 156 (4%) reported any side effects; 3 experienced pain at the injection site lasting longer than 1 but less than 7 d, and 3 had transient nausea or lightheadedness without hypotension or dysrhythmia. In their experience, Levine et al. *(74)* noted use of intralesional verapamil has not made subsequent corrective surgery more difficult. In fact, they use verapamil in men who are intended surgical intervention if those men continue to have active, unstable disease or deformity greater than 90 degrees. They find this hastens stabilization of the plaque; they wait to perform surgery until the deformity is stable for at least 6 mo *(74)*.

A standard regimen for intralesional verapamil is to use 10 mg of verapamil diluted to 10 mL total volume with saline or local anesthetic agent. After induction of penile block, the verapamil solution is distributed throughout the plaque by passing a 25-gage needle in and out of the plaque numerous times. Skin is punctured only once, and the needle is directed into different regions of the plaque without drawing the needle out of the skin. The needle should typically be inserted in the dorsolateral or lateral region of the penis, depending on the plaque location, to avoid injury to the dorsal penile neurovascular bed *(74,77)*. Injections are delivered at 2-wk intervals for a total of 12 treatments. Injections more frequent than every 2 wk have been found to induce increased inflammatory response *(74)*.

Other modes of verapamil delivery have been attempted. Dermal application of verapamil to the penis resulted in a low level of systemic verapamil, but no drug was identified

in tunica albuginea tissue samples *(88)*. Electromotive transdermal delivery (iontophoresis) of verapamil into plaques has also been used. This method has the benefit of being noninvasive and pain-free and does not cause tissue trauma from injections. Moreover, it iontophoresis is suggested to provide a more homogenous drug delivery to the plaque *(89)*. A study of this method found detectable verapamil in 72% of tunica albuginea specimens, although drug concentration varied widely. The exact implication of this in the clinical setting remains unclear *(90)*. Both uncontrolled and placebo-controlled studies of electromotive delivery of verapamil combined with dexamethasone provided positive results *(89,91–94)*.

An example of one dosing regimen is 5 mg of verapamil (+ steroid and ± lidocaine) delivered via a 2.4-mA electric current applied for 20 min with four sessions per week for 6 wk *(92)*. This regimen is intensive, and 24% of patients withdrew before completing the full course of therapy. Others use a less frequent treatment regimen *(89)*. Unfortunately, these studies all combine verapamil with corticosteroid and, sometimes, with lidocaine, making the determination of each drug's independent effect impossible. Based on the purported biological mechanism of verapamil, however, electromotive delivery should have similar effects as injection of the drug. The effect of electromotively delivered corticosteroid is unclear. Supportive evidence for corticosteroid injections in PD includes uncontrolled case series, whereas a placebo-controlled study found no benefit *(92,95,96)*. Another issue discusses whether corticosteroid delivered by iontophoresis produces sclerosis, which can hinder future surgery as has been noted with steroid injection therapy *(73)*.

Interferons are a group of naturally occurring proteins with numerous biological properties, including immunomodulatory, antitumorigenic, growth regulating, and cellular differentiation effects, which form the rationale for their use in PD *(97)*. An in vitro study of plaque-derived fibroblasts showed that interferon-α-2b inhibited fibroblast proliferation and collagen synthesis and increased collagenase synthesis *(97,98)*. Moreover, interferon-α-2b has been used successfully in the treatment of keloid scars and in scleroderma *(97)*. Uncontrolled studies have demonstrated mixed results, with some showing marked improvements and others finding no benefit *(99–107)*. With use of interferon, there is also concern for systemic toxicity, which can produce flu-like side effects. In one series, such symptoms (fatigue, myalgia, fever >38°C) occurred after only 2% of injections and were resolved within 24 h; in a different study, 74 of 90 injections produced fever greater than 38°C, side effects were significant, and 8 d of work were lost *(101,103)*. A placebo-controlled study found statistically significant improvement in curvature, pain, plaque size, and penile vascular derangements in the interferon-α-2b group compared with the saline injection control group *(108)*. Because of the side effect profile and high cost, the use of interferon in PD will likely remain limited until further supportive data are available *(50)*.

Intralesional collagenase has been investigated as a treatment option. Case series and a randomized, placebo-controlled, double-blind study reported positive results with collagenase *(109,110)*. However, the controlled study provided little detail regarding the clinical improvements and noted that the absolute change in deformity was small *(109)*. Additionally, treatment with collagenase induced a humoral immune response, with elevated IgG in 88% of treated patients and IgE in 1 of the 44 patients. The authors speculated that future intralesional treatment with collagenase would not be significantly inhibited by preformed IgG antibody because of the relative avascular nature of tunica albuginea, although they did note that the potential for severe allergic reaction existed with IgE antibody sensitization *(111)*. Because of these concerns and the relative lack of significant, supportive data, collagenase is not a current standard therapy. Other drugs

such as orgotein and parathyroid hormone, which have been used for intralesional delivery, currently lack sufficient data to draw conclusions regarding effectiveness or to support their usage *(112–115)*.

EXTRACORPOREAL SHOCK-WAVE THERAPY AND OTHER FORMS OF ENERGY DELIVERY

Modes of energy delivery that have been used to treat PD include radiation, ultrasound, laser therapy, extracorporeal shock-wave therapy (ESWT), and diathermy *(69)*. ESWT delivers directed ultrasound energy to the plaque. The exact mechanistic rationale for a beneficial effect is unclear. Interestingly, the presumed pathogenesis of PD is trauma to the tunica albuginea, and this therapeutic intervention is traumatic *(116)*. Side effects are usually minor and include local pain, bruising, and urethral bleeding with macroscopic hematuria (7% in one large series) *(116)*. No study has reported any serious side effect, although there is the theoretical concern for urethral stricture because of the occurrence of urethral trauma *(116)*. Uncontrolled studies of ESWT have provided conflicting results. Results of various studies include decreased plaque size in 0 to 58%, reduced curvature in 0 to 74%, decreased pain in 56 to 100%, and improved sexual function in 12 to 75% *(116–124)*.

The study most resembling a placebo-controlled study was one in which patients who had previously failed oral therapy were treated with EWST and were compared with age-matched patients without previous therapy who were given oral placebo drug. Although the study design makes interpretation of the results unclear, they found no difference in decrease in pain, subjective improvement, or improvement in sexual function. Curvature showed a greater decrease in the ESWT group compared with the placebo group, but this was not statistically significant *(125)*. An exploratory meta-analysis of outcomes from 17 study groups found no clear effect on plaque size or penile deformity, but it did suggest that ESWT might promote faster resolution of pain compared with the natural course of the disease and may also promote improved sexual function *(126)*. It has been theorized that the mechanism behind pain relief with ESWT is direct disturbance of pain receptors or hyperstimulation-induced analgesia *(116)*. However, the natural history of PD is that of pain relief with time for most patients, raising the issue of whether the treatment of pain alone should be a primary treatment goal *(116)*. At a minimum, further study with appropriately conducted, placebo-controlled trials is needed before generalized implementation of this expensive technology can be recommended.

Radiation therapy has also been used to treat PD. Randomized, placebo-controlled studies are lacking and results of noncontrolled studies are inconclusive, although most have found a reduction in pain *(38,43,127–132)*. One large retrospective, noncontrolled review of 106 patients treated with radiation therapy found that at an average of 9 yr after therapy, 69% with pain before radiation therapy reported improved (decreased) pain; 29% reported decreased curvature; and 13% with preintervention ED had improved erections *(38)*. However, 54% of patients reported not having erections rigid enough for sexual intercourse; this compares to pretreatment rate of 18% with ED *(38)*. Causes for this decrement in erectile function are unclear, but they could be related to increased patient age (mean: 9 yr between the two assessments), effects of PD itself, and possible damaging effects on the neurovascular erectile mechanism by irradiation. Cases have been reported of extensive corporal fibrosis following penile irradiation *(133)*. Interestingly, an in vitro study of plaque-derived fibroblasts found that irradiation significantly increased the expression of profibrotic cytokines *(133)*.

TREATMENT OF ERECTILE DYSFUNCTION IN MEN WITH PEYRONIE'S DISEASE

Treatment of ED associated with PD can be challenging *(134)*. In one series of 56 men with PD and complete loss of erectile function, 51 were unresponsive to intracavernosal prostaglandin E_1 *(8)*. In another group of patients with less severe baseline ED, 36 of 38 experienced good response to intracavernous injection therapy (papaverine + phentolamine + prostaglandin E_1) *(135)*. Levine et al. evaluated the use of sildenafil citrate in a retrospective review of patients with PD and ED characterized by having lack of rigidity sufficient for vaginal penetration and maintenance throughout sexual intercourse *(81)*. Of responders, 71% were satisfied or very satisfied with the effect of sildenafil, 10% were neutral, and 19% were dissatisfied or very dissatisfied *(81)*. In subgroup analysis, 90% of their patients with venous leakage were satisfied with sildenafil, whereas only 52% with arterial insufficiency were satisfied. This suggests that patients with more severe arterial dysfunction and those with comorbid vascular risk factors such as diabetes or hypertension may respond more poorly to the phosphodiesterase inhibitors. However, because this class of drugs is generally safe and an effective first-line therapy for ED, it is still practical to perform a trial of this therapy, even if evidence exists to suggest arterial or vascular disease *(81)*. Vacuum erection devices are another option for patients, although the constriction ring has been implicated in the etiology of PD *(136)*.

SURGERY

The surgical management of PD is reviewed in Chapter 18. Therefore, only a few general points are covered here. Because of the potential for spontaneous regression, conservative management is appropriate in the acute stage of the disease. Surgery should be performed only after an interval of 6 to 12 mo of stable disease. This strategy helps ensure that the surgical correction is not endangered by continued disease progression *(2)*. Surgery should be reserved for those with severe deformities causing significant sexual dysfunction. Ultimately, approx 10% of patients with PD will require surgery—a percentage that reflects surgical intervention for straightening alone as well as those who require operations for ED *(8)*. Options for penile straightening include plication of the tunica albuginea at a point contralateral to the plaque. This is an option for patients with less severe curvature (less than 60 degrees), although it has the intrinsic problem of producing penile shortening. Notably, although penile shortening is an intrinsic component of the disease process itself, many patients do not appreciate this at the time of presentation. It is worthwhile to point out that shortening has already occurred before patients undergo surgery *(4)*. Plaque incision and excision with grafting are other options; these methods are often used for high-grade curvature and in those in whom loss of penile length would be problematic. These methods still produce penile shortening but less so than with simple contralateral plication techniques.

In patients with concomitant ED, conservative measures such as oral or injectible vasoactive agents are first-line therapy. If these are unsuccessful, penile prosthesis implantation is often performed, with straightening of the penis performed either by modeling the penis over an inflated prosthesis or by plaque incision or excision with grafting *(2,137)*.

CONCLUSION AND PRACTICAL DISEASE MANAGEMENT

PD appears to be more prevalent than previously believed, and its prevalence is likely to increase as our population ages and more men seek treatment for ED. The disease

remains enigmatic and incurable, with only limited evidence and speculation as to its pathogenesis. Many medical treatment options have been attempted, and conclusions regarding the various therapies are limited because of the paucity of randomized, controlled clinical trials. Moreover, the natural history of the disease contributes to the difficulty in interpreting the effectiveness of therapeutic interventions.

A practical treatment algorithm is to manage the patient initially and during the acute phase of the disease expectantly. If the patient is relatively asymptomatic, clinical follow-up may be all that is necessary, at least initially. If the patient has progressive or symptomatic disease, clinical therapy is indicated. The choice between the different treatment options depends on the physician's clinical experience and interpretation of the available data and on the patient's comfort with different forms of therapy. Treatment of concomitant ED involves either oral or injectible erection-promoting agents or a vacuum erection device. Surgical intervention for penile straightening should be reserved for those with severe penile deformity that precludes sexual intercourse, and penile prosthesis implantation is used in impotent patients who fail clinical therapy. Surgical intervention should be performed only after the disease has been stable for 6 to 12 mo.

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18 Peyronie's Disease

Surgical Therapy

Gerald H. Jordan, MD

SUMMARY

Among patients with Peyronie's disease, only a few require corrective surgery. The surgical candidate should have stable and mature disease (as defined by resolution of pain and stabilization of the curvature or other deformity) and a deformity that precludes intercourse or is associated with erectile dysfunction that precludes intercourse.

Several surgical procedures have been successfully used to straighten the deformity associated with Peyronie's disease. Because there no single-best surgical approach, counseling allows individual patients to understand treatment options and allows the clinician to match each patient with the optimal treatment to meet his needs. I have an almost completely referral practice, and because most patients have been told that a prosthesis or a plication technique are the only procedures they can undergo, among the surgical techniques, plaque incision followed by placement of a graft to fill the corporotomy defect is my preference for most patients. However, I feel that plication and corporoplasty techniques are clearly superior for patients with Peyronie's disease that is complicated by an element of erectile dysfunction in whom graft procedures have the potential to cause further deterioration of erectile function. It is important to recognize that for such patients, this approach appears to be associated with a decreased potential to interfere with erectile function compared to graft procedures. Various grafts have been used successfully in selected patients, including temporalis fascia, tunica vaginalis, vein, dermal, and nonautologous grafts. This chapter describes a modified technique of plaque incision that involves a sliding H incision and excision of a strip of tunica albuginea and reviews indications, placement, and choice of penile prosthesis.

Key Words: Peyronie's disease; acquired curvatures of the penis; vascular testing for erectile dysfunction; graft techniques useful in Peyronie's patients; penile prosthesis.

INTRODUCTION

Although it was first reported by Fallopius in 1561, credit for the first description of Peyronie's disease has been attributed to Francois Gigot de la Peyronie in 1743 . Peyronie's disease is also known as induratio plastica of the penis, and fortunately, only

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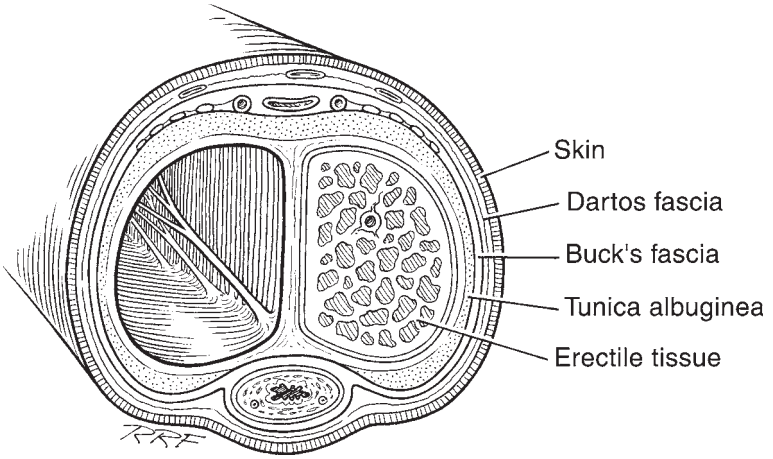

Fig. 1. Diagram of the penis. Fibers of the septum are attached to the inner layer of the tunica albuginea of the corpora cavernosa along the dorsal and ventral midlines. Peyronie's disease plaques occur in the tunica albuginea at the site of septal fiber attachment.

a minority of affected patients have a deformity that precludes them from sharing in intercourse. Furthermore, in most patients, reassurance is sufficient treatment; however, medical therapy is useful for others, with a few requiring corrective surgery.

ANATOMY OF THE CORPORA CAVERNOSA

Knowledge of the anatomy of the corpora cavernosa is essential to understanding the etiology of Peyronie's disease (Fig. 1). Composed of an outer longitudinal layer and an inner circular layer, the tunica albuginea is bilaminar throughout most of its circumference. In the pendulous portion of the penis, the corpora are separated by an incompetent septum, and intracavernous supporting fibers anchor the inner layer at the 2 o'clock and 6 o'clock positions. The tunica albuginea varies in thickness from 1.5 to 3 mm, depending on the position on the circumference, and becomes monolaminar at the point in the ventral midline where the outer longitudinal layer attenuates. The outer longitudinal layer is thickest on the ventrum adjacent to the corpus spongiosum and dorsum and is thinnest on the lateral aspects. Most patients with Peyronie's disease have dorsal lesions, and because the tunica albuginea is bilaminar on the dorsum, these layers might delaminate with buckling trauma. Absence of the longitudinal layer on the ventrum may also contribute to an increased potential for dorsal buckling *(2–6)*.

ETIOLOGY OF PEYRONIE'S DISEASE

Studies have indicated that Peyronie's disease likely begins with buckling trauma that causes injury to the septal insertion of the tunica albuginea and leads to intravasation of blood (Fig. 2; ref. *7*). The body responds to the effects of trauma by initiating the inflammatory cascade, as indicated by activation of fibrinogen and migration of macrophages, neutrophils, and mast cells to the area. Platelets (which are present because of the intravasation of blood), neutrophils, and mast cells secrete cytokines, autocoids, and vasoactive factors that become involved in the creation of fibrosis. Platelets release serotonin and platelet-derived growth factors as well as transforming growth factors. The formation

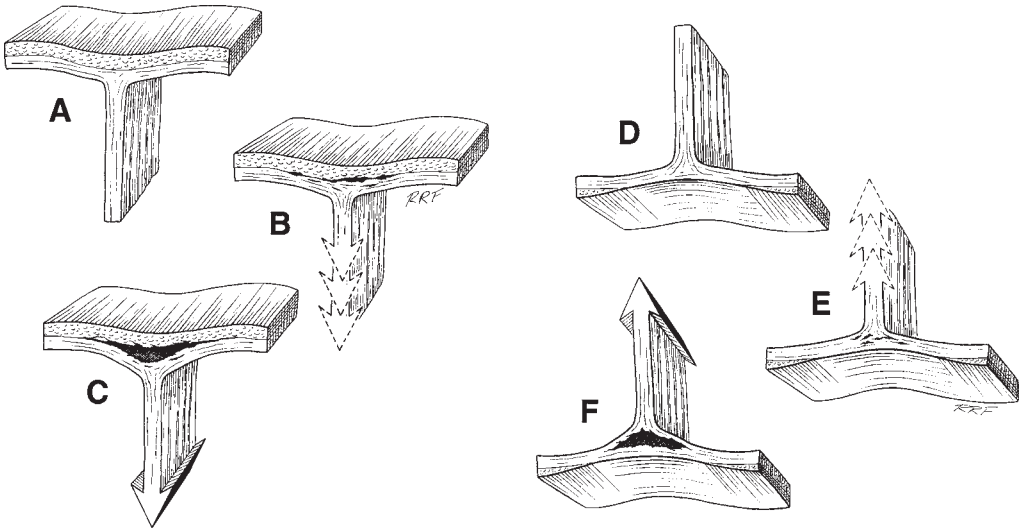

Fig. 2. Mechanism of injury during buckling injuries to the penis. **(A)** Fibers of the septal strands dorsally fan out and are interwoven with the inner circular lamina fibers of the tunica albuginea; outer lamina fibers are longitudinal. **(B)** In the chronic presentation of Peyronie's disease, less turgid erections allow flexion of the penis during intercourse, which produces elastic tissue fatigue and further reduces elasticity of the tissue, leading to multiple small ruptures of the fibers of the tunica with smaller collections of blood and ensuing scar formation. **(C)** Acute presentation of Peyronie's disease bending the erect penis out of column produces tension on the strands of the septum, delaminating layers of the tunica albuginea. Bleeding results in clot formation, and the scar generated by the tissue response becomes the Peyronie's disease plaque. **(D)** Illustration of the condition on the ventrum of the penis, where the midline is monolaminar and the bilaminar arrangement of the tunica albuginea becomes thinned. Fibers of the septal strands fan out and are interwoven with the inner circular layer, and there is no outer circular layer. **(E)** In the chronic presentation of Peyronie's disease, less turgid erections allow for buckling of the penis as per **C**. **(F)** In the acute presentation of Peyronie's disease, buckling of the erect penis out of column produces tension of the strands of the septum, causing the septal fibers to tear.

of thrombus leads to the deposition of fibronectin, which binds numerous growth factors, keeping them localized to the area of injury; fibrinogen leakage leads to the deposition and incarceration of fibrin in the healing process (Fig. 3). It has been further proposed that the avascular nature of the tunica albuginea may impede clearance of many of these growth factors; the transforming growth factors, particularly transforming growth factor-β, are capable of auto-inducement.

There are two phases in all cases of Peyronie's disease, and many patients present with an active phase (commonly associated with painful erections and changing deformity of the penis), followed by a quiescent secondary phase (characterized by stabilizing of the deformity, disappearance of painful erections, and general stability of the process). Alternatively, up to one-third of patients present with the sudden development of a painless deformity; however, although these patients seem to have a relatively quiescent active phase, it appears that changes have been occurring at the cellular level during that time.

Additionally, it has been reported that Peyronie's disease completely resolves in some patients; however, this is probably a misstatement. Among patients who traumatize their penis and develop curvature secondary to the inflammatory process that is associated

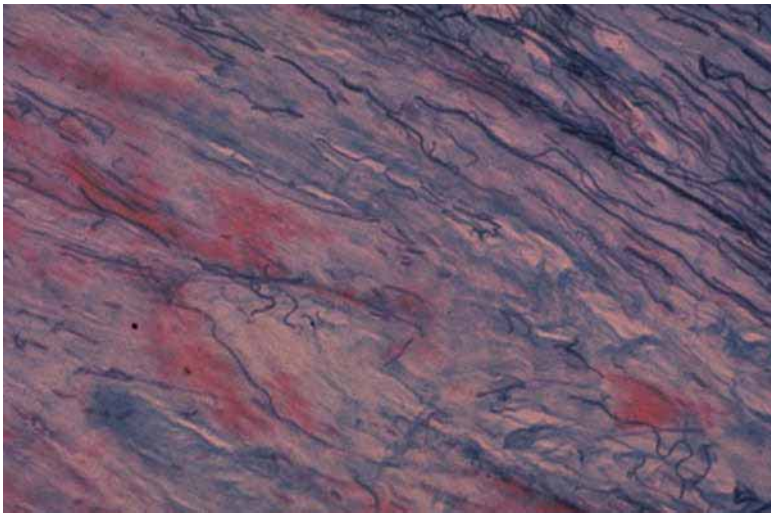

Fig. 3. Photo micrograph of a Peyronie's disease plaque demonstrating entrapped fibrin. The fibrin stains pink and the collagen fibers stain Prussian blue.

with loss of compliance, there are some whose inflammation apparently resolves without entering the phase of chronic inflammation that ends in disordered healing and scar formation. However, these patients probably cannot be said to have resolved Peyronie's disease; rather, the trauma can be viewed as resolved without the development of Peyronie's disease. Furthermore, spontaneous resolution of the symptoms of Peyronie's disease has been shown to be an infrequent occurrence, as illustrated in a recently published study of men who were diagnosed promptly after developing symptoms of Peyronie's disease and who elected to avoid all therapy; of these men, few demonstrated much improvement in curvature during a 12-m follow-up *(8)*.

ASSESSMENT OF PEYRONIE'S DISEASE

Understanding the lifestyle of the patient, as well as the lifestyle of the couple, is an essential element in both the diagnosis and treatment of Peyronie's disease. Peyronie's disease has been described as a disease of aging tissue in a patient with a youthful libido. Compared with age-matched adult couples, it has been stated that those couples in which the male has Peyronie's disease appear to engage in more frequent and vigorous intercourse, often using positions that are potentially traumatic to the penis; in fact, these couples seem to relate through intercourse *(9–11)*.

Patient Selection

Surgery for Peyronie's disease should be viewed as palliation for the mechanical effects of Peyronie's disease or associated erectile dysfunction (ED). For a patient to be a surgical candidate, he must have stable and mature disease (as defined by resolution of pain and stabilization of the curvature or other deformity) and a deformity that precludes intercourse and/or concurrent ED that precludes intercourse. Although an experienced examiner recognizes a mature plaque on palpitation, most investigators arbitrarily impose a 12- to 18-mo period from disease onset, comprising at least 6 mo of disease stability.

Among the existing protocols and algorithms for assessment and management of Peyronie's disease, the original classification system proposed by Kelami *(12)* sought to include all categories of importance when evaluating the Peyronie's patient and included all the important categories, with the exception of ED. In 1993, Gelbard *(13)* proposed a modification of the Kelami classification as part of the original Collagenase Intralesional Injection Protocol. Since then, several other treatment algorithms have been proposed *(14–17)*; however, it is important that these serve only as guidelines, with the findings from the assessment of each individual patient considered of primary importance when making treatment decisions.

Vascular Testing

The place of vascular testing has not been clearly defined, and its use varies among centers. Whereas some centers perform duplex Doppler testing on all patients with Peyronie's disease, others do not perform vascular testing at all, despite routine surgeries for Peyronie's disease and, in some cases, prosthesis placement as the primary treatment option *(18–20)*.

At the Devine Center for Genitourinary Reconstruction Surgery, all patients who desire a surgical treatment option undergo vascular testing. These patients are first examined with color Doppler ultrasound, and if the peak systolic and end diastolic velocities and resistive index are normal, they require no further testing. However, if the end diastolic velocity and resistive indices are abnormal, they are tested with dynamic infusion cavernosometry cavernosography. Because studies from the center have demonstrated a linear association between pre-operative erectile function and postoperative results in most patients *(21)*, we rely on these results when discussing potential options for surgical management. An exception occurs in patients with ventral Peyronie's disease, who have been shown to have the greatest likelihood of cavernous veno-occlusive dysfunction and, therefore, do not experience good outcomes with procedures involving grafting *(18,21,22)*.

SURGICAL TREATMENT OF PEYRONIE'S DISEASE

Several surgical procedures have been successfully used to straighten the deformity associated with Peyronie's disease.

Tunical Excision With Plication

In 1979, Pryor and Fitzpatrick *(23)* described a procedure involving excision of the tunica albuginea with a plicating closure on the opposite aspect, which served to counteract the effects of the lesion by shortening the more compliant aspect of the corpora cavernosa. In the correction later described by Lue *(24,25)*, excision of the tunica albuginea was omitted, and he merely plicated the aspect of the corpora cavernosa opposite the lesion, emphasizing the use of permanent "loosely tied" sutures to correct the deformity. Others have also described modifications of the plication technique. Although these techniques have not historically yielded durable results in patients with congenital curvature, they may be more effective in patients with Peyronie's disease who have lower accumulated intracavernosal pressures. However, although these techniques are valid in some patients with Peyronie's disease, many patients are already concerned by shortening of their penis resulting from the disease and find surgery with the potential to further shorten their penis unacceptable. Additionally, Lue's use of permanent suture is not well-accepted by some patients.

Corporoplasty

The corporoplasty procedure described by Yachia *(26)* (a Heineke–Mikolicz procedure strategically placed at the convex point of maximal curvature) works well in patients with Peyronie's disease as well as in those with congenital curvature. Plication and corporoplasty techniques can be especially useful for patients with Peyronie's disease complicated by ED in whom graft procedures have the potential to cause further deterioration of erectile function. I rely on this procedure as well as excision with plicating closure for patients with ventral curvature and have found that the perceived shortening of the penis associated with these procedures reported in numerous studies is not clinically significant in properly selected patients *(25,27–38)*.

Plaque Excision and Graft

Temporalis Fascia Graft

In 1989, Gelbard *(39)* reported on a series of patients in whom incisions were made in the Peyronie's disease plaque and whose defects were filled with grafts of temporalis fascia. His technique was based on the theory that expansion of the scar by creation of several incisions and then filling them with compliant material would result in a smoother correction of the curvature. He has reported good results with this procedure.

Tunica Vaginalis Graft

In 1982, Das and Amar *(40)* described a procedure involving plaque excision followed by filling the resultant corporotomy defect with a tunica vaginalis graft, which they believed was an easy donor site for the urologist that yielded results similar to a dermal graft. Our experience has been that tunica vaginalis is a suitable substitute in selected patients with small, well-defined lesions; however, we have not had favorable outcomes with the use of tunica vaginalis in patients with large corporotomy defects. In a recent observational report, acceptable results were achieved with tunica vaginalis double-folded to compensate for the problem with larger corporotomy defects *(41)*.

Vein Graft

Lue and El-Sakka *(42)* also described a procedure involving incisions, but the corporotomy defects were filled with vein grafts. They initially reported that the deep dorsal vein provided an adequate donor site for these vein grafts; over time, however, they found that this donor site did not provide an adequate quantity of donor tissue and later harvested saphenous vein to create vein graft patches. Because the intracorporeal space represents a large vessel, Lue suggested that a vessel wall patch represents a physiological procedure, and good results have been reported with this procedure.

In a series of 50 men treated for Peyronie's disease by Montorsi et al. with plaque incision and vein grafting, postoperative evaluation with color duplex Doppler and rigiscan revealed either complete or adequate straightening in 94% of patients as well as maintenance of penile rigidity at pre-operative levels in 94% of patients *(43)*. Additionally, power Doppler showed vascular impairment in 10% of patients, and rigiscan revealed a significant decrease in nightly erections in 10% of patients. Therefore, the investigators concluded that plaque incision with vein grafting can provide satisfactory results in most patients with severe and stable Peyronie's disease who have intact pre-operative penile rigidity.

These results were supported by a report by Akkus et al. of a series of 58 patients who underwent excision and vein grafting for Peyronie's disease who were evaluated postopera-

tively with duplex Doppler ultrasound *(44)*. In this series, complete or adequate straightening occurred in 95% of patients, and preservation of pre-operative erectile function occurred in 93%. Therefore, the investigators have concluded that plaque incision with venous patch grafting is a satisfactory surgical technique for treatment of the curvature associated with Peyronie's disease.

Nonautologous Grafts

Hellstrom *(45)* reported the use of numerous nonautogolous grafts, and Hellstrom and Reddy *(46)* recently reported the use of cadaver pericardium in a small series. In a comparison of the results of plaque incision or excision and grafting with either dermal or cadaver pericardial graft techniques, the minimal pre-operative preparation and decreased patient morbidity with cadaveric pericardium was suggested to be a more effective and appropriate graft compared to dermis; however, superior clinical results compared to dermis were not reported *(47)*. In a retrospective evaluation of 40 men treated with human cadaveric pericardial grafts for the surgical correction of Peyronie's disease, all patients reported sufficient rigid erection for coitus following the procedure; however, many required treatment with intracorporeal papaverine injection *(14)*. Although penile straightening was reported in 98% of patients and successful intercourse was reported in 95%, only 70% of patients in this series had unaided full erections, with 30% requiring pharmacological assistance.

Others *(48,49)* have also enthusiastically used the pericardial allograft for correction of deformity associated with Peyronie's disease. One theory states that the pericardial graft serves as an inert collagen matrix or scaffold for the adjoining tunica albuginea, and the graft is enzymatically dissolved as it is overgrown with newly vascularized tissues *(50)*. In a series of 33 patients who were treated using a technique involving plaque incision with bovine pericardial graft, a good correction of deformity was achieved in 88% of cases, and adequate correction occurred in the remaining patients; all patients were reported to have recovered their ability to "penetrate with no difficulty." These investigators concluded the procedure was very effective; however, their report was unclear regarding how pre-operative erectile function was stratified *(49)*.

Two series have reported on porcine small intestinal submucosal graft (SIS®; Cook Biotech, West Lafayette, IN, 765-497-3355) for surgical management of Peyronie's disease *(51,52)*. In an initial report of a series of 12 patients, the majority had adequate straightening and preservation of erectile function *(51)*. In a later series of 97 patients with curvatures of at least 60 degrees secondary to Peyronie's disease, successful correction of curvature was achieved in 90% of patients after a mean follow-up of 20 mo *(52)*. Although the author reported that the technique offers an excellent alternative, it was not clearly stated whether erectile function was preserved. In our experience, "grafts" composed of foreign material (e.g., Silastic, Gore-Tex, and Dacron) in the absence of concomitant prosthetic implantation generally yield poor results.

Dermal Graft

In 1974, Devine and Horton *(53)* described a procedure for correction of deformity of Peyronie's disease in which the plaque is excised and replaced with a dermal graft; since that time, dermal grafts for corporoplasty have been variously applied. In one report of a large a series ($n = 418$), 17% required further surgery for curvature, and 20% had troublesome postoperative ED *(54)*. However, in this series, the surgery involved an aggressive dissection of the penis that involved disassembling the glans from the tip of the corporal

bodies in many patients; therefore, these results may not be a fair representation of the Peyronie's plaque excision with dermal graft procedure. The World Health Organization 2004 consensus reported that the surgical technique of excision of Peyronie's plaque with dermal graft was regarded as outdated *(55)*. Although I agree that there are several suitable alternatives, we continue to use the procedure for selected patients in our center, with good outcomes.

Plaque Incision With Graft

A large series of patients has also been treated in our center with incisions through the plaque followed by patching of the corporotomy defects with dermis, and now SIS. This has become our preferred technique for treating patients, with the exception of those who have severely calcified plaques. Our early results have indicated that the technique of plaque incision is at least as successful as plaque excision; however, it has not yet been determined whether preservation of erectile function or limitation of the occurrence of graft-induced veno-occlusive dysfunction differs between techniques. Currently, porcine intestinal submucosal graft SIS is substituted for the dermal graft, and the advantage of an off-the-shelf graft cannot be overemphasized.

SURGICAL TECHNIQUE

Incision

The initial skin incision depends on the location of the lesion or of the proposed intervention. Patients who will have ventral plication can be approached through a midline incision of the ventral aspect of the penis. The majority can be most effectively approached using a circumferential incision through the old circumcision scar (if present) or by making an appropriate circumcision incision (Fig. 4A). Although the circumcision scar is displaced far down on the shaft of the penis in many patients, we have not encountered problems with re-approaching the penis through the circumcising incision.

The shaft of the penis is then degloved to its base, which provides good exposure of midshaft and distal lesions. A second peripenile periscrotal incision is created in patients who have relatively redundant foreskin and in those with proximal plaques. After degloving the shaft of the penis, it is delivered into the periscrotal incision. The shaft skin is laid aside and covered with a warm sponge to protect it from trauma until the end of the procedure, when it is returned to the shaft. A counterincision at the penoscrotal junction in the scrotal raphe is optional. Both incisions facilitate exposure for very proximal plaques; however, with the almost exclusive use of plaque incision, very proximal dissection is rarely required.

Elevation of Buck's Fascia and Neurovascular Bundle

Several techniques can be used to elevate the dorsal neurovascular bundle in concert with Buck's fascia. Incisions made just lateral to the corpus spongiosum allow Buck's fascia and the dorsal neurovascular bundle to be dissected off the lateral and dorsal aspects of the corpora cavernosa. Alternatively, dorsal plaques can be approached by dissecting sharply through the bed of the deep dorsal vein to perform a modified vein dissection, an approach we initially used to investigate the potential effect of a modified vein dissection on graft-induced veno-occlusive dysfunction (Fig. 4B–D). Although the beneficial effects of this approach have not been proven, it appears to be a technically superior approach for dorsal plaques.

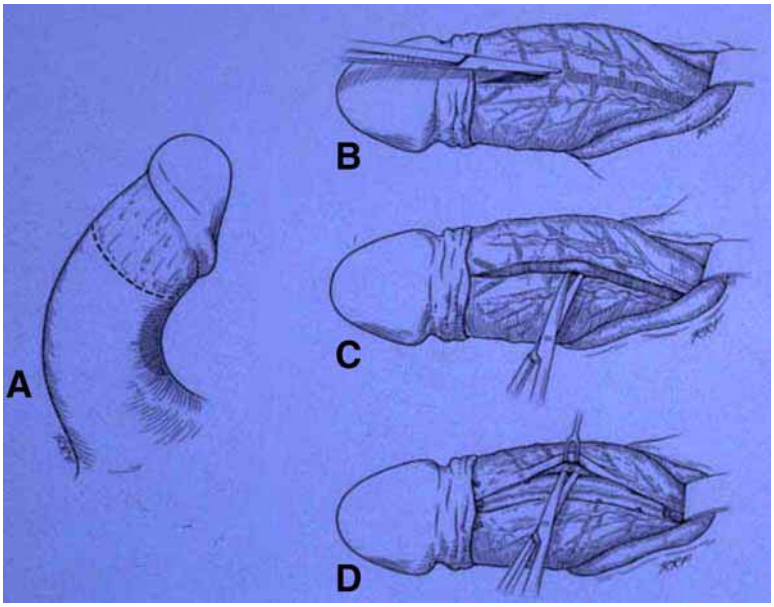

Fig. 4. Elevation of Buck's fascia and neurovascular bundle. **(A)** Diagram of erection demonstrating curvature caused by Peyronie's disease. An erection demonstrates the dorsal curvature of the penis caused by the inelastic scar tissue in a dorsal plaque of Peyronie's disease. A mark indicates the position of the planned incision in the scar of the previous circumcision. **(B)** Degloved penis. The skin has been degloved to the base of the penis by dissecting in the layer immediately superficial to Buck's fascia, and an incision in the dorsal midline of Buck's fascia exposes the deep dorsal vein, demonstrating the coiled dorsal arteries and circumflex veins. **(C)** Mobilization of the deep dorsal vein. **(D)** Elevation of Buck's fascia**.** Buck's fascia is elevated from the Peyronie's disease plaque and the area of dissection is outlined by the dashed line, continuing far enough proximally, distally, and laterally to allow exposure of the plaque without distraction or stretching the nerves in Buck's fascia.

The classical approach was to proceed with a formal vein dissection, ligation, and excision when pre-operative testing suggested veno-occlusive dysfunction; however, vein dissection has not been shown to offer durable results in patients with Peyronie's disease, and it is now believed that patients who demonstrate severe veno-occlusive dysfunction are better treated using either a surgical approach or modeling to straighten the penis with prosthetic implantation for their ED *(56)*. Some patients might benefit from a plication or corporoplasty technique, followed by postoperative pharmacological management of ED.

Plaque Incisions or Excision and Graft Placement

The inelasticity of the plaque will be evident and its extent delineated by feeling the surface of the tunica albuginea after dorsal exposure of the tunica (Fig. 4D). The curvature can be accurately defined by inducing an artificial erection, and incisions are planned for incision (or excision of the plaque, in an occasional case). Prolene stay sutures are placed in the midline (proximal and distal to the plaque) and the planned incisions marked. Because tourniquets can conceal proximal curvatures, we do not favor use of a tourniquet for control of bleeding or induction of an artificial erection.

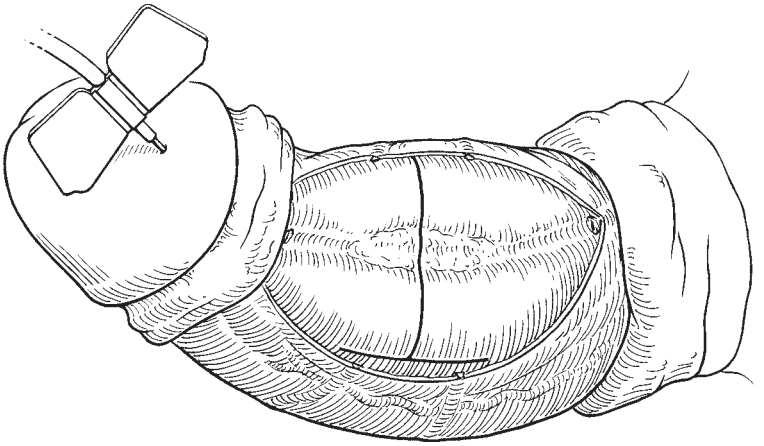

Fig. 5. "Sliding H" technique of incision. The dorsal tunica and plaque are exposed as described, and an H-shaped incision is marked at the site of maximal curvature.

After plaque excision or creation of an incision, the defect is measured by stretching the penis to ensure accurate coverage, and the graft is outlined on the donor site. When a dermal graft is used, we prefer the skin of the abdomen just above the iliac crest and lateral to the hairline as the donor site. The donor site is closed per primam with subcuticular sutures using either a pull-out or the newer absorbable long-acting monofilament suture.

When a dermal graft is used, it is carefully tailored to measure approx 30% larger in all dimensions than the corporotomy defect before placement into either the incisional or the excisional defects. The increased size is necessary because the graft contracts about 30% when released from the inherent tissue tension at the donor site, which should not be confused with graft contraction that occurs later during "take." After completing the graft inlay using a PDS suture, another artificial erection is induced to demonstrate watertight suture lines and penile straightening. Any leaks present are oversewn. Furthermore, if the penis is not straight during surgery, it will not be straight postoperatively; therefore, additional modification using incisions and grafting or "touch-up" plications are necessary if curvature persists.

In 1998, we began to further modify our technique of plaque incision in suitable patients using a technique first described by Lue *(42)*. In this technique, after the plaque is exposed and an artificial erection is used to identify the curvature and point of maximal curvature (as discussed and illustrated earlier), an H-shaped incision is created to elevate flaps so that they are allowed to slide, and these are sutured to leave an approximately square defect (Figs. 5–7).

A modification of the sliding H incision involves excision of a small strip of tunica albuginea at the point of maximal curvature (which is identified during artificial erection) to create a slightly larger corporotomy defect. However, because the corporotomy defect remains approximately square, the graft inlay can be placed without difficulty. If there is lateral indentation after the H-incision is created or the sliding flaps are sutured, the flaps are darted to permit expansion, and a graft is then sutured into the defect. Since 2003, we have preferentially used the SIS graft, and it is our impression that it is at least as effective—if not superior to—alternatives; however, dermis or vein grafts can also be used (Figs. 8 and 9).

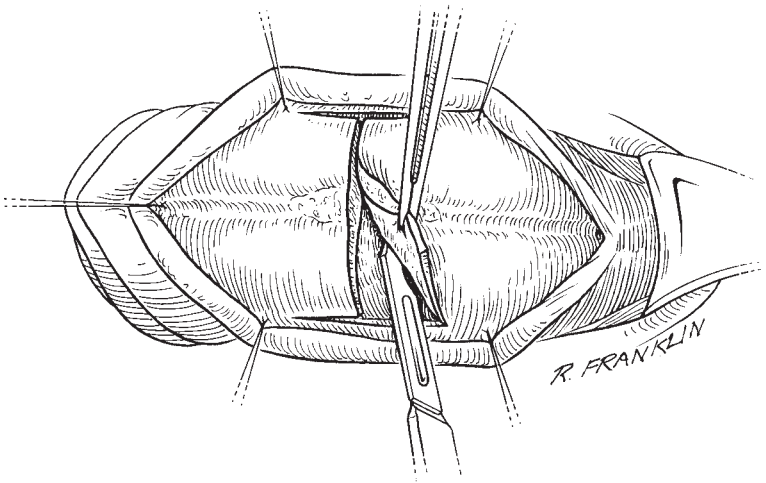

Fig. 6. Incision and elevation of H flaps. The flaps of the H are incised and elevated from the underlying erectile tissue, and the septal fibers are divided and detached back to the point of normal tunica albuginea both proximally and distally—an extremely important maneuver in achieving straightening with this technique.

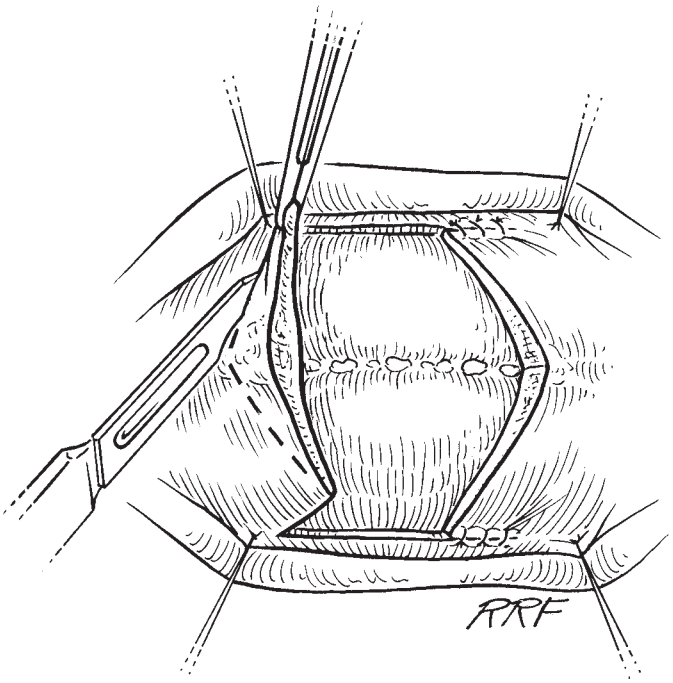

Fig. 7. H flap elevation. The flaps are elevated, and darting incisions are marked to allow circumferential expansion of the defect. Note the flap sutured in place.

Our experience with excision of a strip of scarred tunica at the point of maximal curvature has been that the penis can be effectively straightened with this incision and graft technique alone in approx 90% of patients, with only about 5 to 10% requiring touch-up plication, generally for persistent tilt of the glans (Figs. 10–12). However, although the H technique limits graft size, it is still unknown whether this technique is more reliable or effective regarding preservation of erectile function.

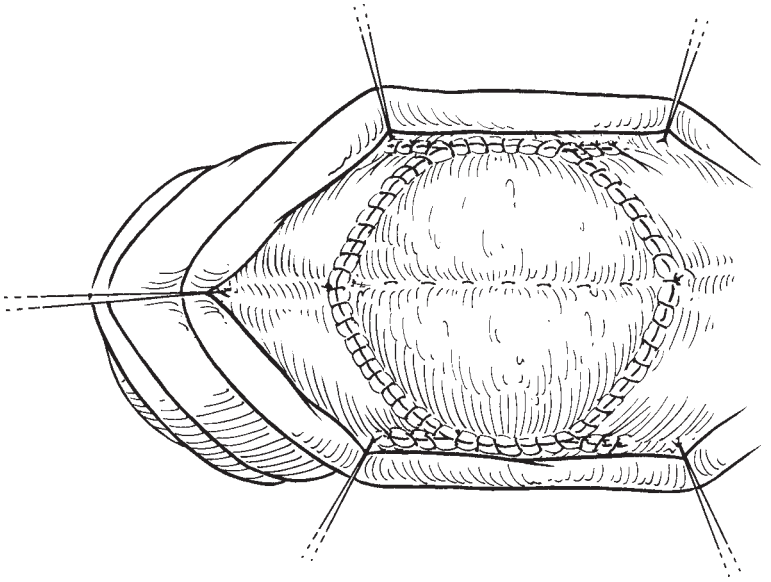

Fig. 8. Corporotomy defect filled with graft. A dermal graft, SIS® graft, or a pericardial graft can be used to fill the corporotomy defect.

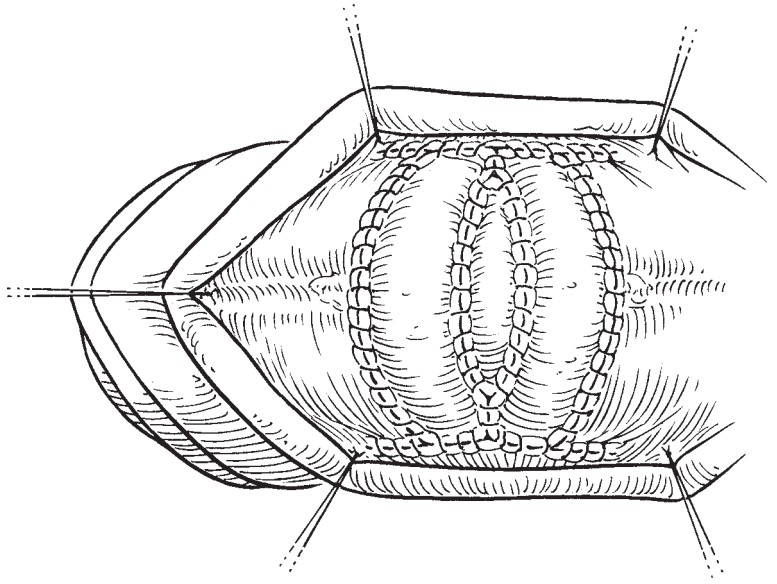

Fig. 9. Corporotomy defect filled with a vein graft. Note that the vein graft is oriented so that the circumferential distensibility allows for long axial lengthening.

Closure

The penis is closed after completing the graft inlay. Buck's fascia is re-apposed using PDS suture, and small suction drains are placed superficial to Buck's fascia but deep to the dartos layer. The skin incisions are then co-apted using either chromic or small Vicryl sutures. If a ventral midline incision was created that crosses the penoscrotal junction, a Z-plasty should be used to prevent penoscrotal tethering.

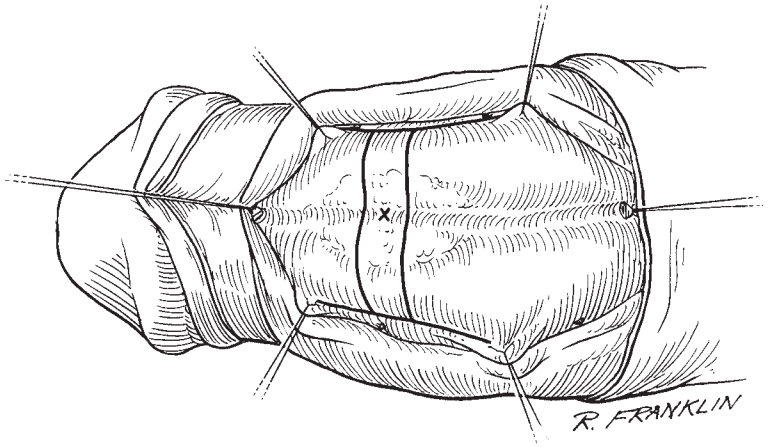

Fig. 10. Modification of the sliding H technique. A small strip is excised at the point of maximal curvature marked by a stitch at that point.

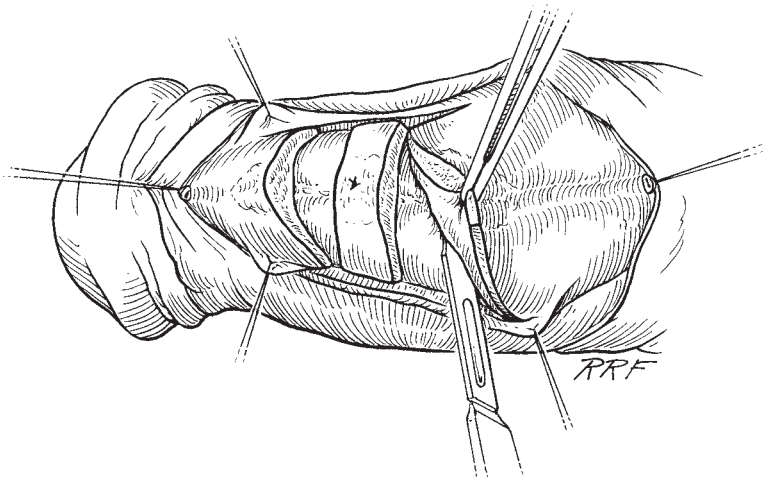

Fig. 11. Modified H-flap elevation. The incisions are created, and the H flaps are extensively elevated, as described in Figs. 10 and 11. Note the expansion of the corporotomy defect.

The penis is dressed with a loosely applied Bioclusive (Johnson & Johnson, Irvine, CA, 888-783-7723) dressing, extending from the base of the penis to the level of the mid glans. A mildly compressive Kling dressing is wrapped over the Bioclusive dressing to limit edema and improve collapse of the surgical spaces around the suction drains. The Kling dressing is left in place for 4 h, and the glans is checked every 30 min for the duration. A 14-Fr Foley catheter is left in place until the patient is ambulatory. On the first postoperative day, the suction drains and Foley catheter are removed, and the patient is generally discharged. Erections are suppressed with diazepam and amyl nitrite for about 5 to 7 d postoperatively; following that, erections are not suppressed and are later encouraged.

Postoperative Care

Early graft maturation is attributed to imbibition of tissue fluids, with inosculation from adjacent blood vessels. Remodeling occurs during the late phase of maturation,

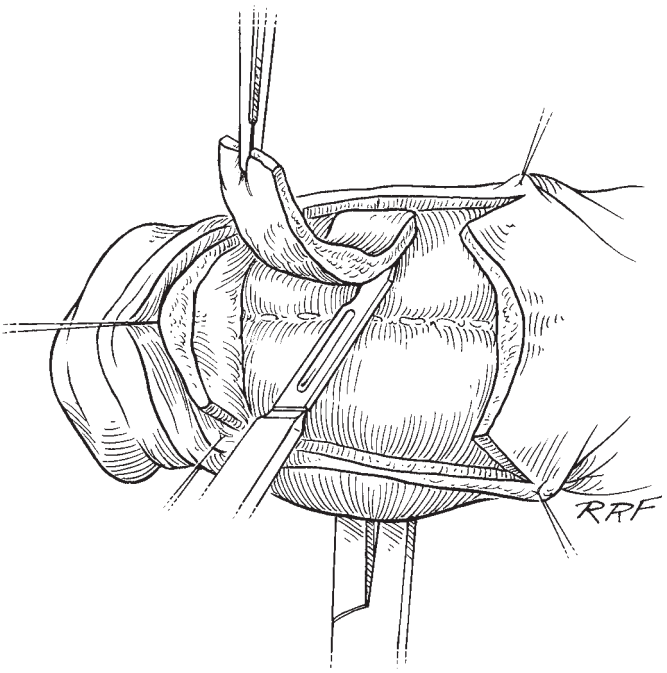

Fig. 12. Modified H flap suturing. The transverse strip is excised, and the H flaps are then sutured as described in Fig. 8; flap can be darted if lateral expansion is required.

with the graft first contracting and then becoming compliant. Although the graft may contact enough to recreate some of the curvature during the first 3 mo, straightening occurs as the graft softens. This occurs less in patients who have had incisions vs excisions and is less often and severe with vein and SIS compared with dermal grafts. However, to prevent undue anxiety, all patients should be forewarned of this sequence of events.

Because erections stretch the graft and aid in the maturation phases of graft take, after the initial 2 wk, patients are encouraged to have erections but are discouraged from intercourse. During this time, it is also desirable for the penis to be manipulated so that the skin does not adhere to the deeper layers of the penis; in some patients, we encourage the use of a vacuum erection device without the constriction ring to aid in graft distention and stretching.

PENILE PROSTHESIS IN PEYRONIE'S DISEASE

The Committee on Peyronie's Disease at the World Health Organization 2nd International Consultation on Sexual Dysfunctions recommended penile prosthesis as a reliable option for older men with vascular impairment, ED, and acquired deformity of the penis *(55)*. Therefore, penile prosthesis placement is a prudent treatment in patients with Peyronie's disease associated with significant ED.

Before 1994, correction of the curvature of Peyronie's disease at the time of prosthesis placement was accomplished by degloving the penis and incising the tunica albuginea in the area of curvature; however, since Wilson and Delk *(56)* reported the modeling procedure in 1994, it has proven to be an excellent technique for straightening the penis in the majority of patients. When a patient is a candidate for modeling, it is important to explain that the procedure can cause urethral injury. This can result from either an extension of the

modeling into the urethra at the point of maximal curvature or the tips of the prosthesis being forced into the urethra through the tip of the corporal bodies. If modeling is not effective, then incision with or without grafts, as previously described, can be used.

Semi-rigid devices have been used in the past, but improvement in three-piece hydraulic devices has made them preferable *(57,58)*. In a study by Montorsi *(59)*, the dissatisfaction rate with semi-rigid devices was shown to be higher than that of hydraulic devices. Furthermore, a comparative study of the AMS CX® cylinders vs. the AMS Ultrex® cylinders in patients with Peyronie's disease demonstrated the superiority of the controlled expansion cylinder *(60)*; therefore, the AMS700CX® (American Medical Systems, Minnetonke, MN, 800-328-3881) or Mentor Alpha I/Titan® system (Mentor Corporation, Santa Barbara, CA, 800-525-0245) are preferred *(56)*. Other publications have also demonstrated superiority of antibiotic- or hydrophilic-coated prostheses in decreasing infection rate *(61,62)*.

In a recent report of a consecutive series of 77 patients who received an Ambicor prosthesis, 32 were primary implants; among these, 20 had bothersome Peyronie's disease *(63)*. The remaining 34 were replacement devices for a malfunctioning AMS700 prosthesis, and many of these patients were patients with Peyronie's disease. Among the patients with Peyronie's disease, 100% had satisfactory straightening without further adjunctive procedure, and there were no infections reported in the series. These investigators have concluded that the Ambicor two-piece inflatable prosthesis provides good patient satisfaction, even when implanted for Peyronie's disease and in patients who have had previous three-piece devices.

CONCLUSION

Peyronie's disease is not the terminal or no-hope diagnosis many patients believe it is. Patients with Peyronie's disease as well as their partners must be educated about their disease and the potential long-term outcomes, emphasizing that in the majority of cases, treatment can adequately restore the sexual relationship. Because there is no single-best operative approach, counseling allows the individual to consider the benefits and disadvantages of each option and to choose the best approach for him, allowing the clinician to optimally manage each patient to achieve satisfactory outcomes based on his needs. Fortunately, the majority of patients with Peyronie's disease never require surgery.

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19 Vascular Surgery for Erectile Dysfunction

William O. Brant, MD, Anthony J. Bella, MD, Maurice M. Garcia, MD, and Tom F. Lue, MD

Summary

Erectile dysfunction (ED) is common and potentially devastating. Men often complain that although the various modalities of treatment are potentially effective, they are not "natural" because they require assistance from a pill, injection, or device and do not allow for the same level of spontaneity that was previously enjoyed. Rather than symptom management, men desire a cure. With the exception of reversible endocrinopathies, no other available treatments address this fundamental desire. Because ED often has a vascular component, it is reasonable that practitioners have tried to develop surgical methods to re-establish penile vascular integrity. This chapter reviews penile vascular anatomy and arteriogenic and venogenic causes of ED. It then reviews various means of evaluation as well as surgical approaches and their associated outcomes and complications.

Key Words: Arteriography; cavernosometry; impotence surgery; erectile dysfunction; penile revascularization; venous leakage; crural ligation.

INTRODUCTION

Although symptom management is often highly successful, at this time correction of most underlying causes of erectile dysfunction (ED) is generally not feasible. However, in highly selected patients, surgery to correct "inflow" or "outflow" pathology may be offered to address the underlying cause, rather than only the symptom of ED. Various diagnostic modalities may be used to delineate the pathology and assess the suitability of intervention. Both arterial and venous surgeries have the greatest chance of success in young, otherwise healthy patients with discrete vascular lesions.

PENILE VASCULAR ANATOMY (FIG. 1)

The main source of blood supply to the penis is usually through the internal pudendal artery, a branch of the internal iliac artery. In many instances, however, accessory arteries

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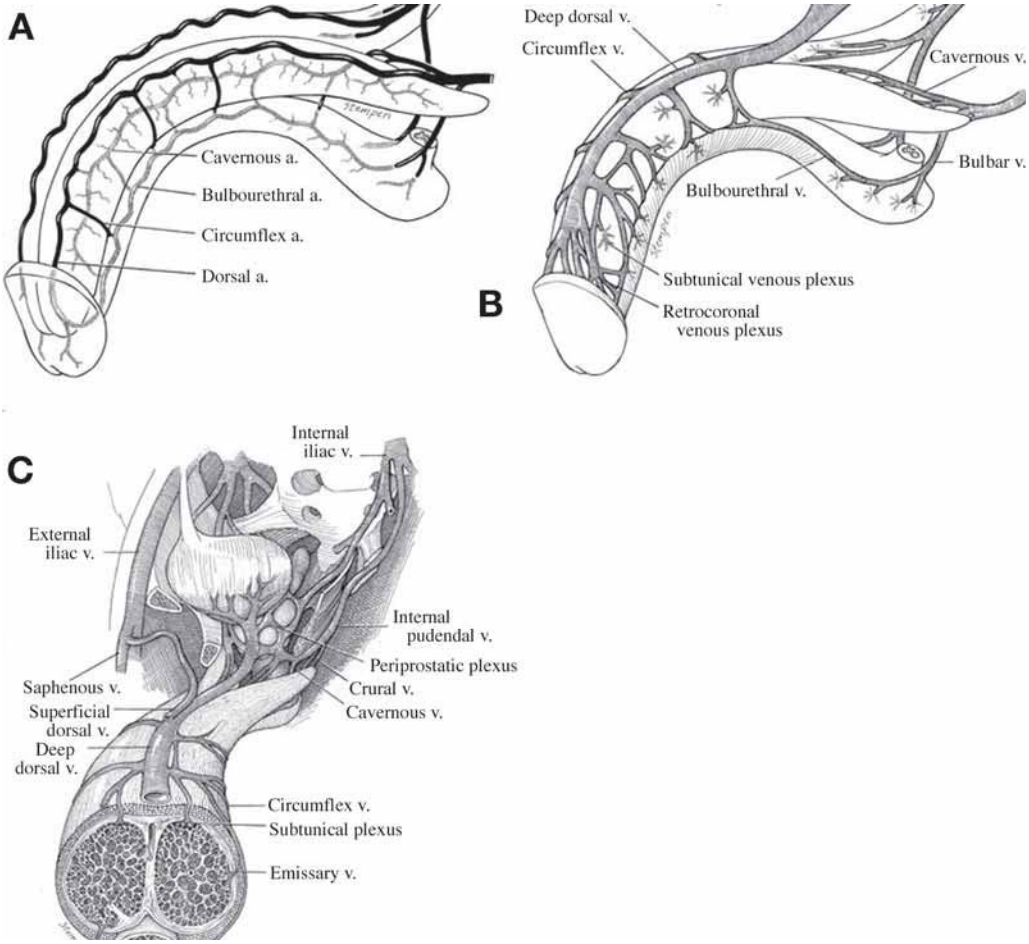

Fig. 1. Penile arterial and venous anatomy. **(A)** Arterial supply. **(B)** Venous drainage. **(C)** Cross-sectional and pelvic venous drainage.

arise from the external iliac, obturator, vesical, and/or femoral arteries and may occasionally become the dominant or only arterial supply to the corpus cavernosum *(1)*. Damage to these accessory arteries during radical prostatectomy or cystectomy may result in vasculogenic ED after surgery *(2,3)*. After giving off a branch to the perineum, the internal pudendal artery becomes the common penile artery. The three branches of the penile artery are the dorsal, bulbourethral, and cavernous arteries. The cavernous artery is responsible for tumescence of the corpus cavernosum, and the dorsal artery is responsible for engorgement of the glans penis during erection. The bulbourethral artery supplies the bulb and corpus spongiosum. The cavernous artery enters the corpus cavernosum at the hilum of the penis, where the two crura merge. Distally, the three branches join to form a vascular ring near the glans. Along its course, the cavernous artery emits many helicine arteries, which supply the trabecular erectile tissue and the sinusoids. These helicine arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection.

The venous drainage from the three corpora originates in tiny venules leading from the peripheral sinusoids immediately beneath the tunica albuginea. These venules travel

in the trabeculae between the tunica and the peripheral sinusoids to form the subtunical venular plexus, before exiting as the emissary veins. Outside the tunica albuginea, the venous drainage consists of the following:

1. The skin and subcutaneous tissue drain through multiple superficial veins that run subcutaneously and unite near the root of the penis to form a single (or paired) superficial dorsal vein, which, in turn, drains into the saphenous veins. Occasionally, the superficial dorsal vein also may drain a portion of the corpora cavernosa.
2. In the pendulous penis, emissary veins from the corpus cavernosum and spongiosum drain dorsally to the deep dorsal, laterally to the circumflex, and ventrally to the peri-urethral veins. Beginning at the coronal sulcus, the prominent deep dorsal vein is the main venous drainage of the glans penis, corpus spongiosum, and distal two-thirds of the corpora cavernosa. Usually, a single vein—but sometimes more than one deep dorsal vein—runs upward behind the symphysis pubis to join the periprostatic venous plexus.
3. Emissary veins from the infrapubic penis drain the proximal corpora cavernosa and join to form cavernous and crural veins. These veins join the peri-urethral veins from the urethral bulb to form the internal pudendal veins.

EVALUATION OF PENILE VASCULAR PHYSIOLOGY AND ANATOMY

Very few patients require formal evaluation of penile physiology or anatomy before first-line treatments. However, there are several indications for formal testing. The indication that is most germane to this chapter is that testing is required when it changes disease management, especially regarding planned invasive procedures. Other indications include young patients with primary ED, patients who have undergone significant trauma to the pelvis or perineum, patients with Peyronies disease, and patients involved in litigation or other proceedings requiring specific evaluation. In patients with small-vessel disease, the connective tissues of the corpora cavernosa eventually undergo histopathological changes that compromise the normal compliance and vaso-occlusive processes. If there is diffuse disease and lack of tissue compliance, then surgical repair of either inflow or outflow can be unsuccessful. Many patients who present with ED are older, use tobacco, or have systemic vascular disease or other chronic conditions that result in small-vessel disease. These patients do not require formal penile vascular evaluation, because they are not candidates for vascular reconstruction or venous surgery.

Although arteriography represents the "gold standard" examination of penile arterial anatomy, it is invasive and should be reserved for patients who have been investigated with less invasive techniques. The first procedure we perform in clinic on appropriate patients is a combined intracavernosal injection (ICI) and stimulation test. This consists of injection of one to three vasodilatory agents, followed by self-genital stimulation and assessment of the resultant erection *(4)*. We typically inject 9 mg of papavarine and 15 μg of phentolamine, with or without 3 μg of prostaglandin E_1. Primarily, this test bypasses neurological and hormonal influences and directly assesses the vascular status, although patients with severe psychogenic ED may not respond fully.

The pharmacological test—especially combined with self-genital stimulation or audiovisual sexual stimuation *(4,5)*—yields important information regarding penile vascular status. A positive response (normal erectile rigidity of sustained duration) presumably excludes significant venous or arterial pathology. More contemporary studies have suggested that normal response rules out the possibility of venous leakage, although some

patients (about 20%) with arterial insufficiency also achieve a rigid erection *(6)*. Generally, a normal office pharmacotest with ICI and stimulation suggests that neurogenic, psychogenic, or hormonal factors may be primarily responsible for ED, although pharmacotesting is unable to distinguish among them. Regardless, further evaluation for veno-occlusive dysfunction is thereby rendered unnecessary. Correlation with both Doppler ultrasound and cavernosometry/cavernosography confirms that a positive pharmacotest is consistent with normal veno-occlusion (flow to maintain erection values of 0.5–3 mL/min) but may occur with borderline arterial function, when normal is defined as a peak systolic velocity (PSV) more than 35 cm/s and borderline is defined as 25 to 35 cm/s *(7)*. Despite its lack of specificity, office pharmacotesting is cost-effective and clinically helpful.

An abnormal pharmacological test result suggests penile vascular disease (arterial, venous, or mixed vascular) and warrants further evaluation, although it may not always be indicative *(8–10)*. To investigate abnormal responses to the combined pharmacological/stimulation test, we next perform color duplex ultrasound of the penile arteries. This test combines pharmacological testing with the ability to visualize arterial blood flow and measure arterial flow velocities. An experienced operator may visualize vessels and collateral flows among the cavernous, dorsal, and spongiosal arteries that may be crucial in planning penile vascular and reconstructive surgeries. It may also be used for the diagnosis of high-flow priapism and localization of arterial rupture *(11)*.

ICI of a vasodilator produces arterial and arteriolar dilatation, cavernous smooth muscle relaxation, and a drop of the peripheral vascular resistance within the penis. Together, these changes cause an increase in penile arterial inflow. This increase is then manifested sonographically as detectable increases in cavernous arterial diameter and blood flow velocity. The timing of ultrasonography in relation to the state of erection is important for interpretation of the results. Schwartz and coworkers *(12)* correlated changes in Doppler waveforms with hemodynamic changes in corporeal pressure during progression to full erection**.** After vasoactive injection, the filling phase (5 min) is characterized by low sinusoidal resistance and a waveform that demonstrates high forward flow during diastole. As intrapenile pressure increases, diastolic velocities decrease; with full erection, the systolic waveforms sharply peak and may be slightly less than during full tumescence; in rigid erection, diastolic flow is zero. In rigid erection, cavernous pressure may transiently exceed systemic diastolic blood pressure, and reversal of diastolic flow occurs in the cavernous artery. With color duplex ultrasound, reversal of diastolic flow is associated with a dramatic color shift (from red to blue) in the cavernous artery. The absence of these expected Doppler spectral waveform changes allows the experienced sonographer to document significant penile hemodynamic pathology.

Parameters used to infer the adequacy of penile circulation include PSV, end diastolic flow velocity (EDV), systolic rise time (measured in milliseconds from the start of systolic velocity to the maximum value), and cavernous artery acceleration, which is calculated by dividing PSV by systolic rise time *(13,14)*. Flow velocities should be measured 5 to 10 min after injection; a delay in response is typical in both the hypertensive and the anxious patient.

Total blood flow is a function of both arterial diameter and blood flow velocity. By evaluating a large number of patients with nonarteriogenic causes of impotence (e.g., neurogenic or psychogenic), Lue and associates *(15,16)* established that the PSV within the cavernous arteries should exceed 25 cm/s within 5 min of ICI. Others *(17–21)* have

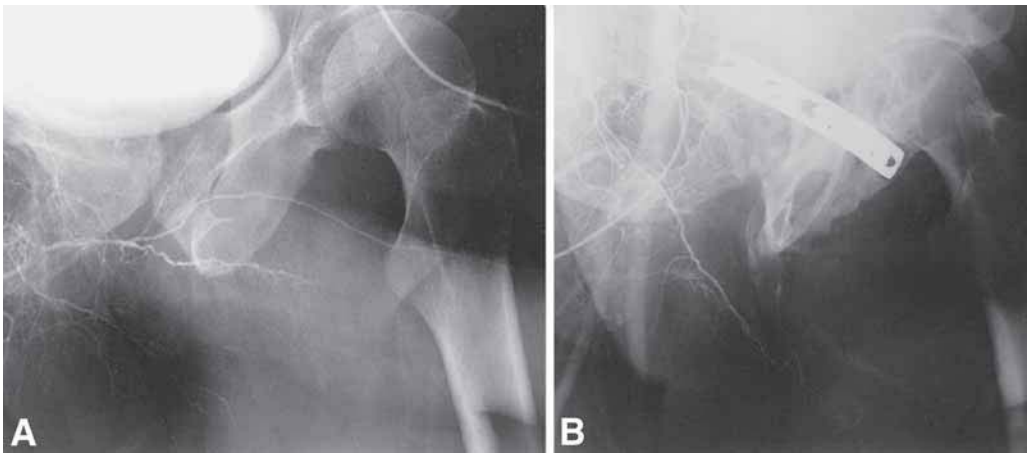

Fig. 2. Arteriograms. **(A)** Normal. **(B)** Absent corporal artery.

confirmed these findings. In the University of California San Francisco series, normal subjects had mean PSVs of 34.8 cm/s *(22)*, whereas studies from Baylor *(23)* and Harvard *(24)* reported normal volunteer mean PSVs of 40 and 47 cm/s, respectively.

When penile angiography is compared to duplex Doppler examinations of the same patients, PSV less than 25 cm/s is consistently associated with severe arterial disease. In the Mayo Clinic series, PSV less than 25 cm/s had a sensitivity of 100% and a specificity of 95% in select patients with abnormal pudendal arteriography *(25)*. The Mayo Clinic suggests that arteriography is not necessary if a patient has a good clinical response to vasodilating injection and bilateral PSVs are more than 30 cm/s. When PSV is compared with cavernous arterial systolic occlusion pressures generated during dynamic infusion cavernosometry and cavernosography, a PSV more than 25 cm/s predicts a normal cavernous arterial systolic occlusion pressure with a sensitivity of 95% and a specificity of 95% *(26)*. Severe unilateral cavernous arterial insufficiency results in asymmetry of PSV more than 10 cm/s.

Abnormalities found on duplex ultrasonographic testing may lead to suspicion of either arteriogenic or venogenic etiologies of ED. A poor PSV despite a typically adequate dose of an intracavernosal vasodilator combined with self-stimulation should lead to further evaluation of an arterial cause. A persistently elevated EDV and/or transient rigidity after self-stimulation, despite appropriate arterial response (>25 cm/s), should lead to further evaluation of a venous problem. Quam and colleagues *(17)* found EDVs ranging between 0 and 24 cm/s after intracavernous administration of papaverine (60 mg). When EDV was more than 5 cm/s among patients with PSVs more than 25 cm/s, venous leakage on cavernosometry was predicted with a sensitivity of 90% and a specificity of 56% *(17,25)*.

Arteriography is the gold standard of anatomic localization of arterial lesions that cause ED (Fig. 2). In addition to localization, arteriography allows for pre-operative planning in anticipation of reconstructive surgery. However, it does not provide any detail regarding functional issues. The test is performed by administration of an intracavernosal vasodilator. At the point of maximal vasodilation, contrast is injected into the cannulated internal pudendal artery, allowing visualization of the iliac, internal pudendal, and penile arteries. The interpretation of arteriography is not straightforward, because anatomic variations are extremely common (up to 50% in one study *[27]*). Because the study is expensive,

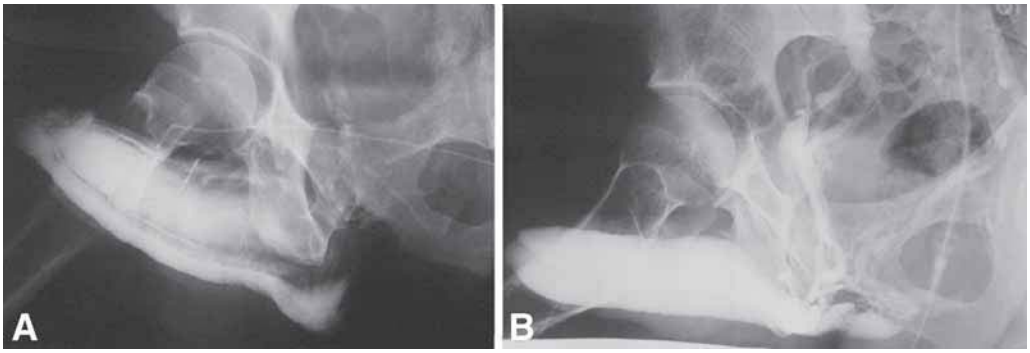

Fig. 3. Venous leakage: leakage into corpus spongiosum **(A)** and crural veins **(B)**.

invasive, and potentially morbid, it should be used only after other studies have demonstrated functional arteriogenic ED. The ideal candidate is a young, otherwise healthy male who has sustained a significant perineal or pelvic trauma for which arteriography is necessary to plan revascularization surgery.

For evaluation of patients in whom a venous etiology is suspected, the most commonly performed test is combination cavernosometry and cavernosography. The principle of cavernosometry is that infusion of saline after dilation of the cavernosal arteries should lead to sustained cavernosal pressure equal to mean systolic blood pressure, and this pressure should remain stable after infusion ceases. A standard definition of normal is that under the conditions of complete smooth muscle relaxation: (a) an infusion of no more than 5 cc/min is necessary to maintain an erection with intracavernous pressure of 100 mmHg, and (b) if infusion is stopped at an intracavernous pressure of 150 mmHg, there should be a drop of less than 45 mmHg over 30 s. A patient should proceed to cavernosography only if cavernosometry reveals abnormalities. This involves infusion of 50% diluted contrast medium into the corpora when the corporal smooth muscles are maximally relaxed. With venous pathology, contrast may be seen leaking to the glans, corpus spongiosum, superficial and deep dorsal veins, cavernous, and crural veins (Fig. 3). In the majority of patients, more than one site is visualized *(28–30)*. Because venous leakage is the consequence of diffuse corporeal smooth muscle pathology rather than discrete diseased areas in the majority of older men with secondary ED *(31)*, cavernosometry/graphy should be reserved for young men with primary ED or a history of trauma, because they may be candidates for venous surgery.

ARTERIAL RECONSTRUCTIVE SURGERY

Generally, arterial reconstructive surgery may be classified as either revascularization or arterialization.

There are numerous revascularization techniques reported in the literature. Our approach is described here. If the angiogram or color duplex ultrasound shows communication between the dorsal and the cavernous arteries, then we prefer epigastric to dorsal artery bypass. Intra-operatively, we routinely measure intraluminal pressure of the epigastric and the dorsal arteries via an arterial line setup. An arterio-arterial bypass is performed only if the pressure in the epigastric artery is 15 mmHg higher than the dorsal artery. If the pressure difference is less than 15 mmHg, than an epigastric artery–dorsal vein anastomosis is performed.

Fig. 4. Completed epigastric-dorsal artery anastamosis.

Dorsal Artery Revascularization: Inferior Epigastric Artery to Dorsal Artery of the Penis

In 1980, Michal reported the results of penile arterial revascularization using the inferior epigastric artery as the donor vessel anastomosed to the dorsal artery of the penis. This technique relies on collateral circulation supplying the corpora cavernosa via perforators in the tunica albuginea from the dorsal artery. Approximately 55 to 80% of patients reported full return of normal erections following this procedure *(32–35)*. We prefer an end-to-side connection from the epigastric to the dorsal artery.

The patient is placed in the supine position. The choice of incision for arterial surgery is the lower abdominal midline, because both inferior epigastric artery vessel bundles can be dissected from the lower surface of the rectus muscle, if necessary. Some surgeons prefer a paramedian incision for dissecting the inferior epigastric artery complex. Recently, we have been able to avoid the relatively large incision required for mobilization of the inferior epigastric artery using a laparoscopic preperitoneal approach, and nine cases using a transperitoneal approach have been reported in the literature *(36–39)*. Arterial branches are clipped or ligated as they are encountered, and the artery is dissected as distally as possible, usually to the level of the umbilicus. Additionally, small branches near its origin are ligated or clipped to maximize arterial length for a tension-free anastomosis. The fundiform and suspensory ligament of the penis may or may not be taken down, depending on the surgeon's preference and the anastomotic site *(40)*, although the penis should be resuspended to the pubic periosteum if the ligament is divided. Adventitia is removed only at the sites of anastomosis of the two vessels. The anastomosis is accomplished microscopically using 8–0 to 10–0 monofilament vascular suture. The vessels are clamped with low-tension vascular bulldog clamps, and the inferior epigastric artery is usually flushed with a dilute heparin and/or papaverine solution just before the anastomosis (Fig. 4).

Dorsal Vein Arterialization: Inferior Epigastric Artery to Dorsal Vein of the Penis

Unlike revascularization of the dorsal artery, penile arterial flow can also be restored by arterialization of the deep dorsal vein of the penis. Virag *(41)* reported on his experience with penile arterial revascularization using the inferior epigastric artery as the donor vessel anastomosed to the deep dorsal vein. The vascular anastomosis is performed at the base of the penis. Subsequently, several modifications have been reported. Virag reported that 60% of his patients experienced improvement in quality of erections. Furlow and Fisher *(42)* reported the results of a modification of the Virag II procedures in which both the proximal and the distal end of the deep dorsal vein and contributing tributaries were ligated. The initial multiple branches of the deep dorsal vein near the glans were ligated with an absorbable suture as were large trunks of the deep dorsal vein that anastomose to the spongiosum laterally along the shaft of the penis. Valves in the deep dorsal vein were removed with a 2-mm LeMaitre valvulotome or a similarly sized Fogarty balloon catheter.

Still others have reported a variation of this technique using antegrade dorsal vein arterialization, which does not require rupture of the venous valves *(43)*. We prefer an end-to-side arterio-venous anastomosis at the base of the penis and ligation of the deep dorsal vein both proximally and distally. Although some expect that retrograde flow into the sinusoids provides additional flow, we believe that an increase in venous resistance is the more likely hemodynamic event following the procedure. Overall, dorsal vein arterialization has been reported to yield a success rate of up to 80% *(41,42,44,45)*, but this depends on patient selection criteria (*see* Table 1).

COMPLICATIONS

Although the incidence of complications associated with penile vascular surgery appears to be rare, there have been occasional reports of glans hyperemia or high-flow priapism *(46–57)*. The glans hyperemia may be associated with glanular ulcers and necrosis as well as urinary retention. Glans hyperemia can be treated by surgical ligation of the distal end of the dorsal artery or vein just proximal to the corona. However, this often results in ED. Other complications include anastomotic thromboses and glans hypoesthesia from injury to the dorsal neurovascular bundle.

VENOUS LIGATION SURGERY

The complexity of the venous drainage of the penis may be a primary problem in explaining the lack of long-term success of venous ligation procedures. Multiple venous leak sites can be visualized in the majority of patients. Common leak sites include the superficial and deep dorsal vein, crural veins, corpus spongiosum, and glans penis. Various surgical procedures have been described to correct the radiographical finding of venous leakage. Although multiple drainage sites and communications may be visualized on cavernosography, the deep dorsal vein and the cavernosal (crural) veins are the main venous drainage of the corpora cavernosa and are the most common sites for ligation procedures.

Various surgical techniques have been developed to treat patients with venogenic ED. We prefer deep dorsal vein resection and crural ligation. The procedure is performed through an inguinoscrotal incision (Fig. 5). After releasing the suspensory ligaments, the penis is detached from the pubic bone. The deep dorsal vein is identified and ligated prox-

Table 1
Arterial Surgery

Reference	*N*	*Success*	*Complications*	*Comments*
Hellstrom *(55)*	13	8 of 13	Glans hyperemia (2)	One patient remained potent after hyperemia repair
Melman *(74)*	18	6 of 18		Most patients had diabetes, hypertension, or an extensive smoking history.
Lizza *(44)*	42	40–56%[a]	Hyperemia (3), penile shortening (1)	Response generally durable up to 5 yr
Manning *(80)*	62	34–69%[a]	Hyperemia (13%), shunt thrombosis (8%), inguinal hernia (6.5%)	One-half of patients with hyperemia required surgical intervention.
Kawanishi *(69)*	51	>80%[a] (3 yr)	Hyperemia (2), anastomotic hemorrhage (1), scar contracture (1)	>60% success at 5 yr
Sarramon *(71)*	114	48%	Hyperemia (15)	Potency preserved in 13 of the hyperemia patients
Vardi *(70)*	52	48–78%[b]		
Wagenknecht *(81)*	15	67%		At 26 mo
McDougal *(35)*	8	75%		67% success at 26 mo
Konnak *(82)*	7	2 of 7		At 31 mos
Janssen *(72)*	21	12 of 21		At 22 mo
Jarow *(83)*	11	64%	Anastomotic breakdown requiring arterial ligation	
Cookson *(73)*	50	48%		At 24 mo
Lobelenz *(75)*	19	11 of 19		At 13 mo

[a]Patients selected with strict criteria: age <60 yr, no diabetes, history of myocardial infarction, history of coronary artery disease, history of atherosclerosis, or use of tobacco.
[b]Highest success if patient is younger than age 28 yr.

imally and distally. Careful microscopic dissection of the cavernous and dorsal arteries and the dorsal and cavernous nerves is then performed at the hilum of the penis (Figs. 6 and 7). Once the entrance of the cavernous arteries is identified and the dorsal neurovascular bundle is lifted from the tunica, a urethral catheter is inserted and a 0.5-cm segment of the crura is isolated. Two umbilical tapes are then looped around each crus and are ligated (Figs. 8 and 9). The penis is then re-attached to the periosteum of the pubis with nonabsorbable sutures, and the tissue is closed in layers to prevent penile shortening.

RESULTS OF PENILE VENOUS SURGERY

Despite the promising early results of penile venous surgery (Table 2), long-term results have been disappointing. Although several authors have reported short-term success rates of up to 70% in select patients, long-term follow-up has shown a significant decline in

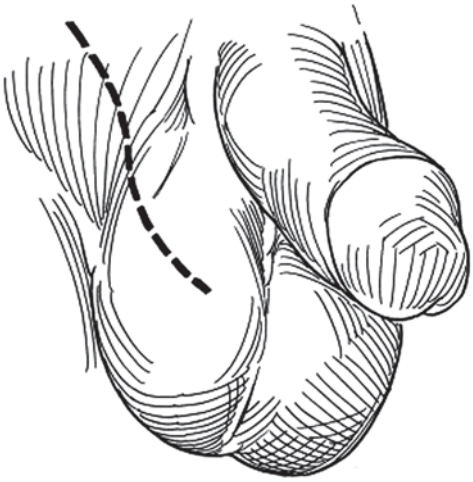

Fig. 5. Inguinoscrotal incision for venous ligation.

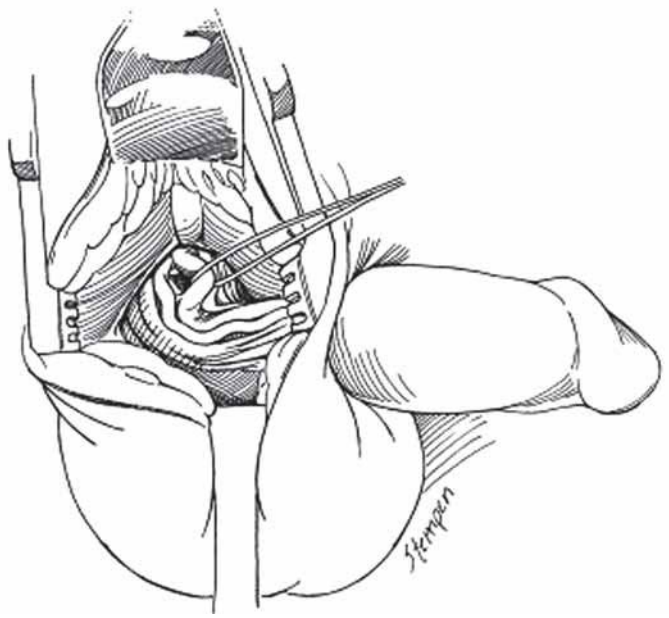

Fig. 6. Identification of deep dorsal vein.

functional improvement *(58–63)*. Similarly, some authors have suggested that results of penile venous surgery should not include patients who have been followed less than 12 mo because of the high late-failure rate of the procedure *(64,65)*.

Development of venous collaterals and persistent venous leakage appear to be contributing factors in many patients who fail to improve following venous surgery. Factors that may predict a poor prognosis include increasing patient age, duration of impotence, the presence of multiple leak sites, a proximal (crural) venous leak site, and concomitant arteriogenic insufficiency *(61,66,67)*. We *(68)* recently reported on 11 cases of crural ligation performed on patients with congenital crural venous leak observed on cavernosography. Of these patients, two reported no change in erection and did not desire further

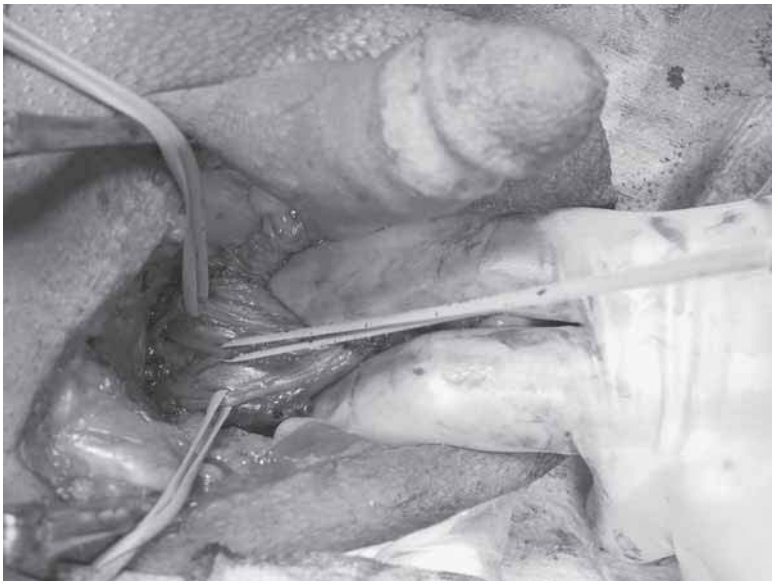

Fig. 7. Intra-operative photograph of dissection of deep dorsal vein.

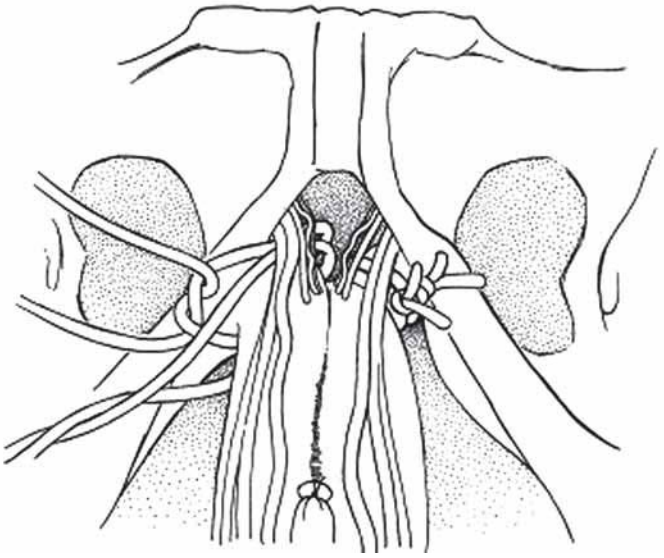

Fig. 8. Crural ligation with umbilical tape.

workup. Four of the remaining nine men required oral intermittent phosphodiesterase-5 inhibitors. Of these four patients, two had progressive decline in erectile function, prompting repeat cavernosograms. They both showed persistent leakage, although not to the degree seen pre-operatively, and both had successful repeat crural ligation surgery. Therefore, 7 of 13 surgeries (including the repeated cases twice) led to a great improvement over the premorbid state, whereas 5 of 13 surgeries resulted in potency without use of pharmacological assistance. In this series, the average age was 28 yr, and all patients had primary ED (i.e., no history of normal erections). Therefore, this represents the most highly selected patient population in whom surgery should yield the best results.

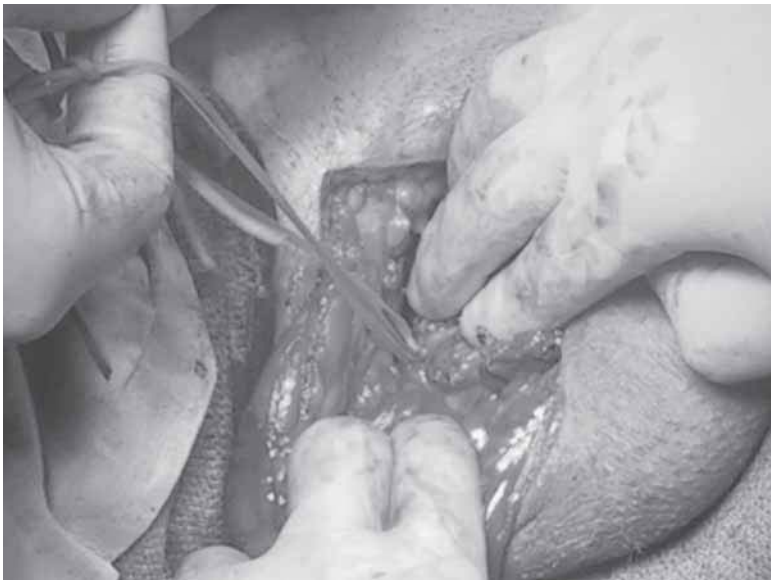

Fig. 9. Intra-operative photograph of crural ligation.

Table 2
Venous Ligation Surgeries

Reference	*N*	*Full success*[a]	*Mean F/U (mo)*	*Short-term success*
Sasso *(76)*	23	12/23	17	17 of 23 at <12 mo
Schultheiss *(77)*	126	14 of 126	33	31 of 126 at <3 mo
Berardinucci *(64)*	94	31%	45	62% at 3 mo
Vale *(59)*	27	10 of 27	12	17 of 27 at 3 mo
Kim *(67)*	15	9 of 15	29	
Montague *(65)*	18	11 of 18	24	17 of 18 at <12 mo (partial success included)
Freedman *(61)*	46	11 of 46	>12	34 of 46 at <6 mo
Knoll *(78)*	41	19 of 46	28	
Schwartz *(79)*	20[b]	5 of 20	Up to 24 mo	
Motiwala *(66)*	24	11 of 20	13 mo	N/A
Rahman *(68)*	11	5 of 11	34 mo	7 of 11

[a]Defined as satisfactory erection without the use of any aids or pharmacological agents.
[b]Patients treated with embolization rather than surgery.

CONCLUSIONS

The vast majority of patients presenting with complaints of ED do not require specialized, and possibly invasive, testing to determine whether there is a vascular etiology of their disease. Few of these patients have a discrete arterial or venous lesion that is amenable to surgical repair. Overall, the results of vascular approaches to erectile disease are disappointing, especially when one examines long-term durability of venous ligation approaches to venogenic causes *(60)*. This results largely from loose surgical selection

criteria. Patients with diffuse involvement of penile vasculature and compromised sinusoidal compliance are poor candidates for vascular penile surgery. However, there is certainly a role for arterial and venous surgery in highly selected patients, such as young men without substantial vascular comorbidities who have sustained trauma or who have congenital anomalies. Even in these patients, outcomes are less than ideal, and there are risks, including need for further procedures that may lead to renewed ED, penile hypoesthesia, penile shortening, and skin breakdown. Patients need to be aware of such risks, as well as alternative therapies, before pursuing these approaches.

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20 Priapism

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Summary

The erection of priapism results from the dysfunction of the mechanisms controlling penile tumescence and flaccidity. Understanding the etiology of the priapism is critical, because urgent therapy aimed at the underlying cause can alleviate the condition and minimize the risk of permanent erectile dysfunction. Priapism may be associated with many physiological and disease states, resulting in ischemic or low-flow priapism, or nonischemic or high-flow priapism. Despite the underlying etiology, most patients with ischemic priapism require immediate active intervention once the appropriate diagnosis has been made, to maximize the chances for resolution and maintenance of good erectile function. For those patients with nonischemic priapism, a high index of suspicion must be maintained. Over the years, many therapeutic alternatives have been proposed for the treatment of priapism and in 2003, the American Urological Association released the Guideline on the Management of Priapism. In this chapter, we explore the current clinical management and therapeutic algorithms of both ischemic and non-ischemic priapism, as well as the medico-legal aspects of priapism and its associated diagnostic and therapeutic interventions.

Key Words: Priapism; ischemic; nonischemic; shunt; expectant management.

INTRODUCTION

The term "priapism" describes a persistent erection arising from malfunction of the mechanisms regulating normal erection, including penile tumescence and flaccidity *(1,2)*. The erection of priapism typically is *not* the result of sexual excitement, and if associated with erotic stimulation, it lasts well beyond the original stimulus and is not relieved by orgasm or ejaculation.

The elucidation of the etiology of the priapism is a matter of some urgency, because correct classification and prompt therapy aimed at the underlying cause may successfully alleviate the condition and minimize potential morbidities. Unfortunately, as a result of embarrassment or "false" expectations of spontaneous resolution based on prior self-limited episodes, patients frequently delay seeking medical assistance, thereby minimizing the chances for successful outcome and increasing the risk of permanent erectile dysfunction (ED; ref. *3*).

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Priapism may be associated with many physiological and disease states (including sickle cell disease), various medications (such as oral trazodone and intracorporal self-injection therapy for ED, resulting in ischemic or low-flow priapism), and penile and perineal injury (culminating in nonischemic or high-flow priapism; refs. *4* and *5*). To initiate appropriate treatment, the clinician must first determine whether the priapism is ischemic or nonischemic. In 2003, the American Urological Association (AUA) released the Guideline on the Management of Priapism *(6)*. This chapter explores the current clinical management and therapeutic algorithms of both ischemic and nonischemic priapism.

ISCHEMIC PRIAPISM

Ischemic priapism is the most common form of this disorder, accounting for more than 95% of all priapism episodes. Ischemic priapism is typically associated with a rigid and painful erection that is not relieved by ejaculation or orgasm. Ischemic priapism is associated with stasis of blood and is a form of "compartment syndrome." Stuttering or intermittent priapism is a recurrent form of ischemic priapism, whereby the painful erections occur repeatedly with periods of intervening detumescence.

Sickle cell disease and other hematological abnormalities and malignancies are most often associated with ischemic priapism. An episode of ischemic priapism may be precipitated by various medications and illicit drugs, such as trazodone, antihypertensive agents, alcohol, marijuana, cocaine, as well as by intracavernous vasoactive agents such as papaverine, prostaglandin E_1, phentolamine, and others. Physical examination typically reveals pain or tenderness and complete rigidity of the corpus cavernosa, sparing the glans and spongiosum. Abdominal and genital examination may reveal evidence of prior trauma or malignancy. Laboratory evaluation, including complete blood count with white blood cell count, reticulocyte count, and hemoglobin electrophoresis when indicated, are useful to rule out infection and hematological abnormalities. Drug screening (e.g., cocaine and its metabolites), corporal blood gas testing, and duplex ultrasound (if available) should be performed. Cavernous blood gas findings in ischemic priapism typically reveal pO_2 less than 30 mmHg, pCO_2 more than 60 mmHg, and pH less than 7.25. Cavernous blood gas findings similar to arterial blood are found in patients with nonischemic priapism *(3)*.

Penile duplex ultrasonography can be performed as an alternative to blood gas measurements. The patient is typically scanned in the lithotomy or frog-leg position along the entire length of the phallus as well as the perineum. Little or absent cavernosal blood flow is typically seen in patients with ischemic priapism. Table 1 shows the key findings seen in ischemic priapism. Once the correct diagnosis of ischemic priapism is made using a combination of a directed history and physical examination, duplex ultrasonography, or corporal blood gas analysis, attention is directed toward swift management and resolution.

Treatment

Historically, several largely unsuccessful therapeutic modalities have been proposed for the treatment of ischemic priapism. These have included placement of hot or cold packs, supplemental or hyperbaric oxygen, ice water enemas, intermittent compression, hypnosis, radiation, and dissociative anesthesia with ketamine to affect the central brain stem function. Unfortunately, these therapies have had poor outcomes and are mentioned only for historical completeness. Generally, immediate surgical intervention should be avoided while less-invasive and often successful alternatives are attempted, especially

Table 1
Key Clinical Findings in Priapism

Findings	*Ischemic priapism*	*Nonischemic Priapism*
Corpora cavernosa fully rigid	Usually	Seldom
Penile pain	Usually	Seldom
Abnormal cavernosal blood gas	Usually	Seldom
Blood abnormalities and malignancy	Sometimes	Seldom
Recent intracorporal injection	Sometimes	Seldom
Chronic, well-tolerated tumescence	Seldom	Usually
Perineal trauma	Seldom	Sometimes

Adapted from ref. *6*.

in cases less than 6 h in duration. It is important to remember that the duration of priapism is defined by the actual time of onset of the episode rather than by the time of presentation for medical care.

Previous recommendations for priapism episodes associated with sickle cell disease included prolonged treatments with oxygen, analgesics, and intravenous hydration before intracorporal therapy or surgical intervention because of the often repetitive and self-limiting nature of their priapism episodes. Unfortunately, this regimen is often unsuccessful, results in an increased rate of corporal fibrosis and ED, and is no longer recommended as primary therapy. In very select cases of priapism associated with sickle cell disease, the use of exchange transfusions to reduce the fraction of abnormal HbS hemoglobin can lead to detumescence. Hypertransfusion with packed red blood cells to double the hematocrit and diminish the fraction of HbS present has been described to achieve detumescence. Early hemoglobin electrophoresis to determine the fractional percentage of HbS that is present serves as a useful guideline for monitoring subsequent transfusion therapy. Similar to any transfusion of blood or blood products, the associated risks (including disease transmission and human immunodeficiency) should be discussed with the patients before transfusion, and the potential benefits should be weighed against the disadvantages *(7)*.

Aspiration of stagnant corporal blood and subsequent saline irrigation is often used a first-line therapy in the treatment of ischemic priapism of any etiology. Adding α-adrenergic agents, including phenylephrine or epinephrine, to the irrigating solution is often efficacious. Direct intracavernous injection of α-adrenergic solution into the corporal bodies following aspiration is frequently successful, especially in cases of relatively short duration. However, as time passes and venous stasis worsens, these agents may exacerbate the ischemic state, increasing the rate of corporal fibrosis and the risk of permanent ED.

The AUA Guidelines Committee recommends the use of phenylephrine, an α-selective adrenergic agonist with no indirect neurotransmitter-releasing action *(6)*. This agent minimizes the risk of cardiovascular side effects that are more commonly observed with other sympathomimetic agents, such as epinephrine. For intracavernosal use in adult patients, phenylephrine is diluted with normal saline to a concentration of 100 to 500 μg/mL.

One-milliliter injections are made every 5 min as needed, up to 1 h. During treatment, patients should be observed for symptoms, such as acute hypertension, headache, reflex bradycardia, tachycardia, palpitations, and cardiac arrhythmia. Lower doses are recommended for children or those with severe cardiovascular disease. In the patients with severe cardiovascular disease, it is prudent to monitor blood pressure and pulse rate in a controlled surveillance setting.

The use of oral terbutaline, a β-agonist, has been suggested both for the preventive and active treatment of ischemic priapism. However, there are no studies demonstrating clear efficacy over placebo, and the use of terbutaline in the management of priapism is not recommended.

For patients with recurrent or "stuttering" priapism, a monthly regimen of gonadotropin-releasing hormone analogs can be effective in decreasing the occurrence of priapism *(8,9)*. Similarly, the use of oral digoxin at therapeutic levels has been shown to be safe and efficacious for decreasing the frequency of recurrent priapism episodes while allowing for normal sexual function and libido. Surgical intervention is advised when initial conservative therapy is deemed ineffective with no improvement on physical examination or in penile blood gases, reduction in intracorporal pressure, or detumescence. In fact, investigators have clearly demonstrated that there is an increased rate of ED in patients whose attacks lasted longer than 24 h. Unfortunately, more than 25% of patients with priapism can develop some degree of ED, despite any conservative management or surgical intervention *(10)*.

Surgical Management

A thorough knowledge of the venous drainage of the penis is important because the mechanism of low-flow priapism partly involves a failure of emptying of the cavernosal bodies through the deep venous system. The basis of the surgical shunting procedures involves rerouting the stagnant blood via the corpus spongiosum and glans into the superficial drainage system, thereby bypassing the deep venous system *(3,6)*.

Several different surgical shunting procedures have been used to treat ischemic priapism *(3,11)*. The underlying principle involves the re-establishment of adequate venous outflow and restoration of circulation within the corporal bodies. One feature of surgical shunts is that they are temporary, with spontaneous closure once normal venous drainage returns.

In 1964, Grayhack described a caverno–saphenous shunt draining the corpora via a saphenous vein bypass. Quackels described a spongiosum–cavernosum shunt in the same year using a side-to-side caverno–spongiosum fistula. In 1975, Ebbehoj described a shunt that was performed by puncturing the cavernous body through the glans penis with a narrow scalpel blade to allow sufficient shunting to the corpus spongiosum. This shunt was modified by Al-Ghorab via the creation of a larger cavernosal–glans shunt using a subcoronal incision under direct vision. The ability to manually drain the corporal bodies after shunting by squeezing the shaft of the penis as needed is an advantage of this surgical technique.

In 1976, Barry described a shunt created by anastamosing the dorsal vein of the penis to a single corporal body. In 1996, Hashmat and Hakim described a successful modification of this technique using a microsurgical anastamosis from the deep dorsal vein of the penis to both corpora cavernosa, leading to complete detumescence and resolution of even long-standing priapism.

In 1978, Winter described a procedure that was similar to the Ebbehoj shunt by creating a fistula between the glans penis and the corpora cavernosa using a biopsy needle under local anesthesia. Because of the numerous intercorporal communications, both corporal bodies need not be penetrated. Elegant in its simplicity, the Winter's shunt is often used as a first-line surgical therapy.

In clinical practice, the simpler corporal-glandular (Winters or Al-Ghorab) shunt procedures are usually attempted first. If they are unsuccessful, then creation of a more formal

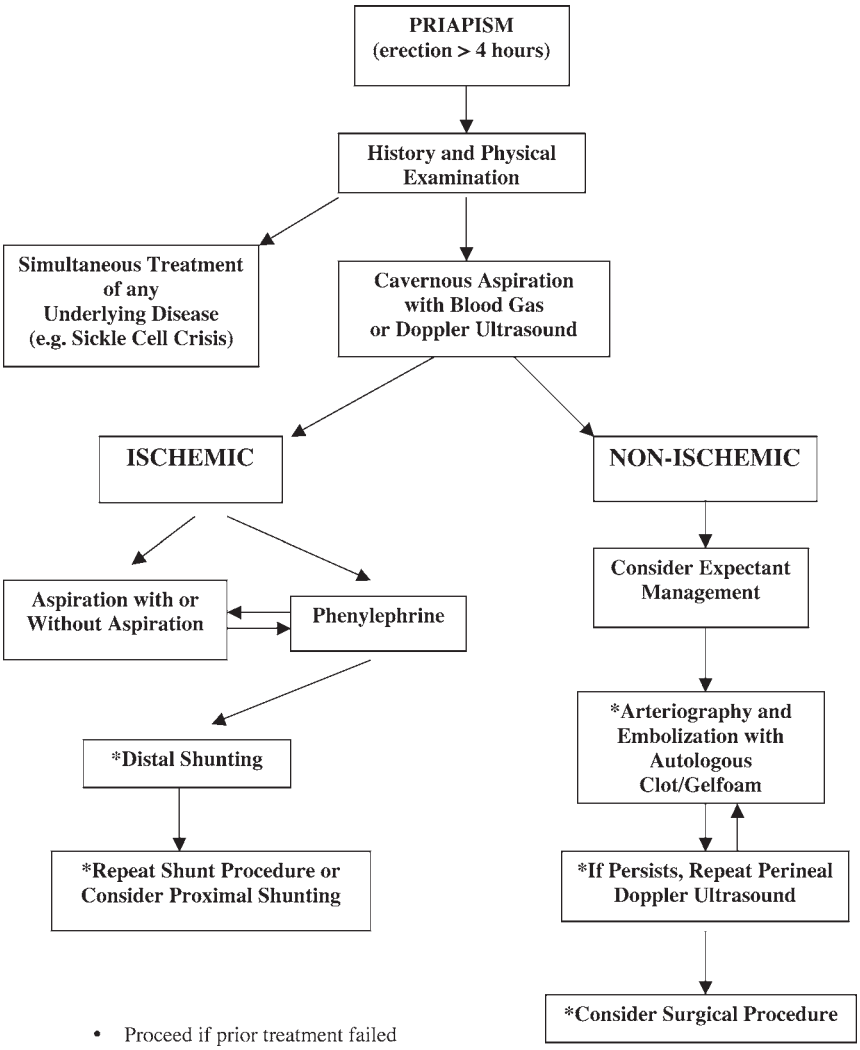

Fig. 1. Management algorithm for priapism.

shunt, such as a cavernosa–spongiosum (Quackels) shunt, saphenous vein bypass (Grayhack shunt), or microsurgical dorsal vein–cavernosal shunt may be attempted.

The current algorithm for the evaluation and management of patients with lowflow (ischemic) priapism is outlined in Fig. 1.

Associated Issues

Some of the more troubling issues associated with ischemic priapism are persistence and recurrence despite active intervention *(10)*. In fact, many patients with low-flow priapism—especially those associated with sickle cell disease—suffer from more than 10 episodes of priapism over a lifetime. Additionally, when the priapism episode is of long duration, it is not uncommon for a partial erection to remain, despite surgical shunting. This can result from corporal fibrosis and scarring or edema of the penile skin and induration

of the corporal bodies. Often, the resultant edema and induration from aspiration and irrigation resolve using only local therapy, such as warm baths or nonsteroidal anti-inflammatory agents, and do not require further surgical intervention.

ED is not uncommon in patients with priapism, despite conservative management or aggressive surgical intervention. It is estimated that more than 25% of patients with priapism have some degree of ED. However, many patients who experience worsening of erectile function immediately following intervention recover most, if not all, of their function over 6 to 12 mo. Therefore, any surgical treatment of ED in these patients (i.e., penile prosthesis) should be delayed until adequate time has elapsed. However, oral ED medications can certainly be used more immediately, when appropriate. Additionally, many patients gradually develop ED later, as corporal fibrosis and scarring occurs that may not respond to simple medical therapy. Although this can be technically challenging to manage surgically, the development of narrow-based inflatable penile prosthetic devices has enabled these patients to benefit from the placement of a three-piece penile implant. Advanced surgical techniques (including sharp corporal incision and excision) and specialized dilating tools often allow the experienced surgeon to successfully place the device without the need for grafting, downsized malleable devices, or abandonment of the procedure.

Notably, care must be taken during sharp dissection of the corporal space to avoid inadvertent perforation of the corporal body or urethra, which would necessitate postponement of the procedure. Additionally, adequate antibiotic prophylaxis and hematological optimization for anesthesia must be assured before surgery. Rare complications of surgical management of these patients can include infection, necrosis, chordee (an abnormal curvature of the phallus resulting from tethering of the distal penile shaft), urethral fistula, or gangrene.

NONISCHEMIC (HIGH-FLOW) PRIAPISM

Nonischemic or high-flow arterial priapism is a form of priapism typically caused by traumatic cavernosal artery laceration or injury that enables unregulated flow of arterial blood directly into the lacunar spaces of the corpora, bypassing the protective, high-resistance helicine arterioles *(12)*. This constant, unregulated flow results in the pathognomonic arterial-lacunar fistula of arterial priapism. The clinical characteristics of nonischemic priapism typically include a premorbid history of trauma; delayed onset of priapism following the trauma; incomplete rigidity of the phallus compared with premorbid sexually stimulated erectile rigidity; and a constant erection that is painless and nontender, with persistent partial rigidity throughout the day and night and the potential to increase to full rigidity with sexual stimulation *(13)*. Although spontaneous resolution may occur, with nonischemic priapism, the painless, partial erection often continues unless "active" intervention is performed.

The goal of clinical intervention is to reverse the priapism state and restore normal physiological function. Unlike ischemic priapism, in which the closed "compartment syndrome" necessitates immediate therapy, the optimal clinical management for patients with nonischemic priapism is somewhat more controversial. This results partly from the rarity of the disorder and the paucity of large clinical trials.

Selective internal pudendal arteriography has been the mainstay of diagnostic and therapeutic maneuvers for nonischemic priapism *(14)*. The pathognomonic arteriographical finding is an arterial-lacunar fistula, a characteristic intracavernosal cone-shaped blush of contrast at the site of the cavernosal artery laceration *(15)*.

Therapeutically, traditional management has consisted of active intervention. Active treatment options have included conservative measures such as mechanical intervention (consisting of prolonged external compression of the perineum for several hours, with or without local application of ice packs) and intracavernosal pharmacological administration of agents that counteract smooth muscle relaxation, such as the nitric oxide antagonist methylene blue or the α-adrenergic agonist phenylephrine or metaraminol bitartrate *(16)*. Surgical resection of the arterial-lacunar fistula and ligation of the internal pudendal or cavernosal arteries have resulted in permanent occlusion of the lacerated cavernosal vessel as well as disruption of the corporal bodies with subsequent corporal fibrosis, veno-occlusive dysfunction, and permanent ED. Unfortunately, these therapies have had little success in reversing the nonischemic priapism state and are currently not recommended by the AUA guidelines for priapism therapy.

The current standard of intervention is selective internal pudendal arteriography with transcatheter autologous clot embolization *(17)*. The goal of this therapy is to induce temporary occlusion of the cavernosal artery to allow the injured site to heal. The temporary nature of this occlusion allows for the subsequent re-establishment of physiologically controlled, normal cavernosal blood flow with preservation of erectile tissue viability and normal long-term erectile function. This form of minimally invasive intervention has a high probability for resolution of the priapism and restoration of erectile potency compared with more invasive techniques, including permanent coil embolization and surgical ligation of the cavernosal artery *(18)*.

The technique of selective internal pudendal arteriography is performed under local anesthesia with intravenous sedation. Retrograde puncture of the left or right femoral artery is performed, and a 5.5-Fr catheter is used to selectively catheterize the internal pudendal arteries under fluoroscopic control. A characteristic unilateral cavernosal artery blush, consistent with extravasation of contrast material from the lacerated cavernosal artery and extending deep into the erectile tissue of the corpus cavernosum, confirms the diagnosis of the arterial-lacunar fistula.

When the therapeutic embolization is performed, a coaxially placed Tracker catheter is then advanced superselectively via the internal pudendal artery through the common penile artery, as close as possible distally to the site of the fistula. Embolizing agents such as autologous blood clot with or without an incorporated Gelfoam are introduced via the catheter to occlude the fistula. Immediately following embolization, a repeat selective internal pudendal arteriogram is performed to confirm the arterial occlusion *(19)*. Long-term follow-up with embolizing agents has shown an excellent rate of priapism resolution (almost 100%) and re-establishment of long-term erectile potency (86%). The use of permanent embolizing agents, including alcohol or coils, should not be considered because of the high potential for irreversible occlusion of the arterial inflow, with resultant ED.

Exclusive reliance on selective internal pudendal arteriography for the diagnosis and treatment of nonischemic priapism has potential disadvantages, such as radiation exposure, invasiveness, cost, restricted availability, and limited expertise. Additionally, there is up to a 50% rate of "recurrent" arterial priapism following initial embolization, most likely as a result of embolus migration that necessitates re-intervention.

Other reported side effects following selective internal pudendal arteriography include bleeding, cavernosal abscess and infection from an infected embolus, persistent cavernosal artery occlusion, site-specific veno-occlusive dysfunction, femoral artery access complications and thrombosis of the femoral artery that requires vascular surgery, cardiac

arrhythmias that require medical intervention, extravasation of contrast at the injection site, and apparent irreversible alteration in erectile function *(20)*.

There are important concepts associated with the management of arterial priapism that differ from ischemic priapism. The historic use of selective internal pudendal arteriography as the basic means of diagnosing arterial priapism has been challenged. The efficacy of perineal duplex Doppler ultrasonography has been demonstrated during the diagnostic and follow-up stages of management of arterial priapism *(21)*. Perineal duplex Doppler ultrasonography (the combination of high-frequency, high-resolution ultrasonography with quantitative pulsed Doppler spectrum analysis) offers numerous advantages over selective internal pudendal arteriography. Perineal duplex is noninvasive and widely available and has yielded an 83% sensitivity of detecting arterial stenoses compared with pelvic arteriography *(22)*. The turbulent flow associated with the arterial-lacunar fistula of nonischemic priapism is readily visualized. In the ultrasound application for arterial priapism, the probe is placed in the region of the perineum rather than overlying the pendulous penis. This placement is important because the cavernosal artery laceration typically occurs in the perineum following a crush-like injury between the object striking the perineum and the bony support of the pelvis, including the inferior pubic ramus and the pubic symphysis. Technically, this is best achieved by placing the patient comfortably on his back in the frog-leg position with the scrotum elevated. On rare occasions, the cavernosal artery may be lacerated during an intracavernosal injection, and the probe may then be best placed over the pendulous portion of the phallus.

Studies comparing perineal duplex ultrasound and concomitantly preformed selective internal pudendal arteriography have revealed excellent sensitivity in detecting the arterial-lacunar fistula on ultrasound that is seen angiographically.

On both the selective internal pudendal arteriography and perineal duplex study, the arterial-lacunar fistula was noted at the same location. In one reported case in which physical examination suggested incomplete return to flaccidity following embolization resulting from recurrent fistula, the negative perineal duplex Doppler ultrasound study correctly predicted the final clinical outcome of complete priapism resolution and full erectile function. Therefore, if the follow-up clinical examination is equivocal for recurrence of the arterial-lacunar fistula, then perineal duplex Doppler ultrasound may better predict the need for repeat arteriography and embolization.

The concept of "expectant management" (or watchful waiting) for patients with nonischemic priapism has become well-established as a therapeutic alternative to embolization *(23)*. Despite the annoyance of the persistent erection, some men with untreated high-flow priapism claimed satisfactory or even improved sexual function. Additionally, there is no established proof that unabated arterial flow into the corporal tissue is harmful. Unlike ischemic priapism, which is associated with complete bilateral cavernosal artery obstruction (thereby requiring immediate intervention), arterial priapism does not propose the same risk to erectile function. The arterial-lacunar fistula results in a state of high oxygen tension, with the production of various endogenous endothelial and smooth muscle substances that are potentially beneficial to trabecular smooth muscle. The longest reported follow-up for a patient with arterial priapism was almost four decades and occurred with a patient who pursued a self-prescribed course of "watchful waiting" for arterial priapism and was able to achieve normal erections with sexual stimulation during the entire 36 yr.

Because there are definite potential risks to active intervention, a trial of expectant management in sexually active men who develop nonischemic priapism may be an acceptable

therapeutic approach. In clinical practice, most of these men have adapted to the nuisance of the chronic partial, painless erection in a form of adaptation not very different from men receiving a nonhydraulic penile prosthesis. Additionally, one must consider that although expectant management precludes pharmacological, angiographical embolization or surgical intervention, patients still must undergo diagnostic and follow-up perineal duplex studies at the time of the initial evaluation as well as subsequent serial duplex follow-up studies. Delaying active intervention allows further detailed objective erectile function testing to be performed to better define the extent of any pretherapeutic damage to the nonlacerated cavernosal artery and corporal or crural tissue resulting from the blunt perineal and corporal trauma. Blunt trauma to the region has been well-documented to cause site-specific cavernosal artery blockages and veno-occlusive dysfunction. Interestingly, these patients may benefit from the unregulated arterial-lacunar fistula, which may allow their ED to be more easily managed by penile constricting bands or pharmacological therapy. Such patients are often identified on clinical history by diminished penile rigidity—even with sexual simulation. These patients should consider formal vascular erectile function testing before any therapeutic intervention for their priapism.

Figure 2 shows the current algorithm for the management of nonischemic priapism. The algorithm emphasizes patient history, physical examination, premorbid and current erectile function status, and the use of perineal duplex Doppler ultrasonography for initial identification of the pathognomonic arterial-lacunar fistula. If an active course of treatment is chosen, selective internal pudendal arteriography and embolization with autologous clot, with or without Gelfoam, should be employed. Although complete detumescence is ideally seen immediately following selective embolization, partial tumescence may be related to long-standing edema, reinforcing the concept that physical examination alone cannot be used to determine the endpoint of treatment or as the sole means of follow-up evaluation. Serial perineal and penile duplex studies over the days and weeks following embolization should be a part of the overall regimen to ensure adequate resolution of the arterial-lacunar fistula. If further intervention is required, then perineal duplex studies can reduce the reliance on multiple subsequent angiographical procedures with their associated risks.

For select patients, expectant management can reasonably be proposed, once active treatment options and their inherent risks, as well as the possible natural course of the priapism, is explained to the patient. Meticulous documentation of the discussion of benefits and risks of active intervention and expectant management is prudent. Regarding long-term follow-up, a reasonable approach would involve continued clinical testing over the first year at intervals up to 3 or 4 mo. Any significant clinical changes in erectile function or rigidity at rest may warrant further diagnostic evaluation and a more aggressive approach. As long as the patient's condition remains unchanged or continues to improve and good sexual function is maintained, a continued course of expectant management may be warranted.

CONCLUSION

Over the years, many therapeutic alternatives have been proposed for the treatment of ischemic or priapism. Unfortunately, their overall success—especially regarding long-term potency—has been disappointing. Traditional therapeutic regimens (especially in the case of sickle cell priapism) tend to be nonaggressive and may have been responsible for poor outcomes and high rates of permanent ED. Despite the underlying etiology, most patients with ischemic priapism require immediate active intervention once the

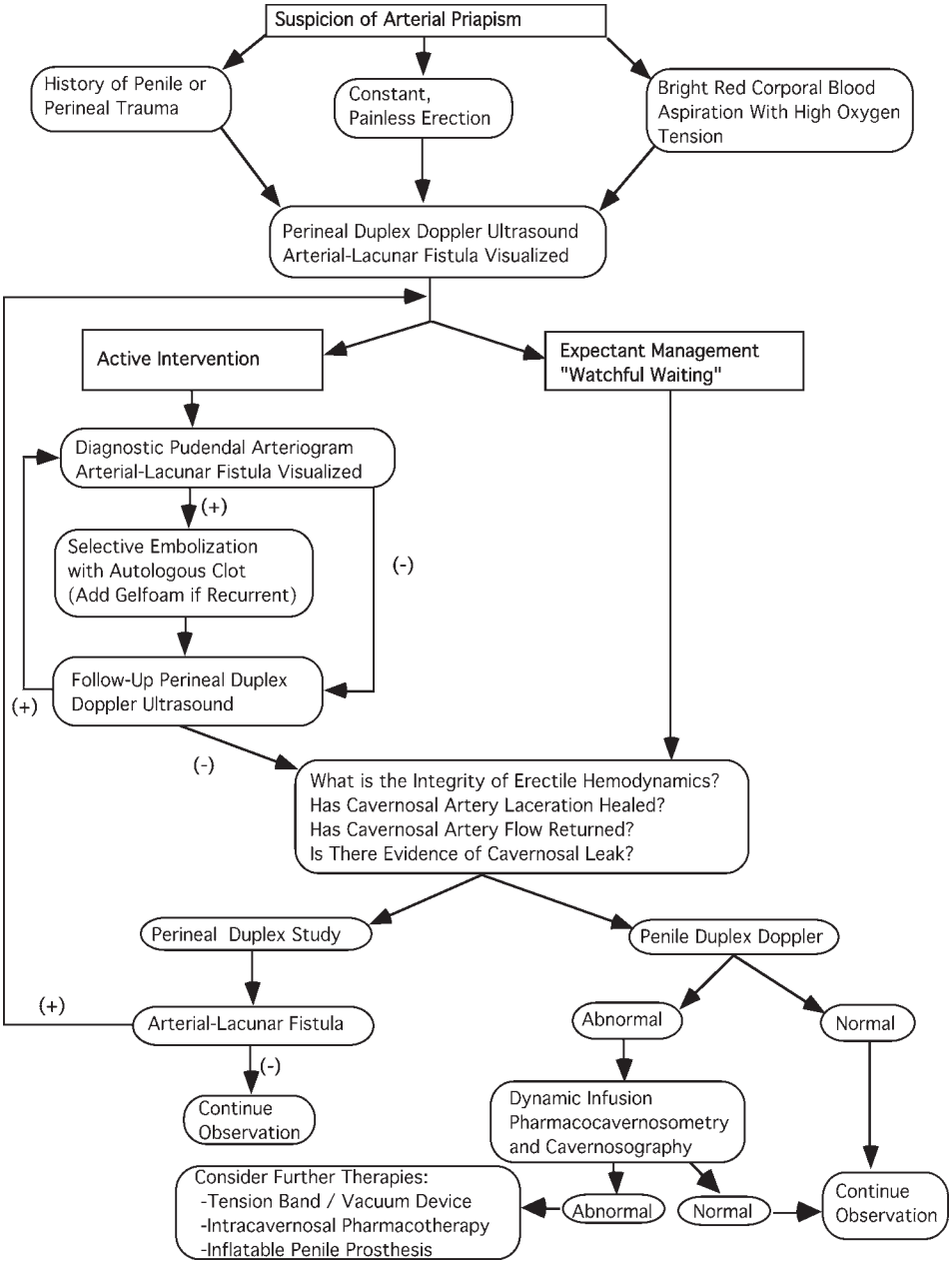

Fig. 2. Expanded algorithm for arterial priapism.

appropriate diagnosis has been made to maximize the chances for resolution and maintenance of good erectile function.

For those patients with nonischemic priapism, a high index of suspicion must be maintained, and ischemic component necessitating immediate intervention must be ruled out. The use of perineal duplex Doppler ultrasonography remains an integral tool in making the correct diagnosis and is extremely useful for subsequent serial evaluation. Once the

correct diagnosis is made and all therapeutic alternatives have been discussed, a course of expectant management may be considered.

The medico-legal aspect of priapism and its associated diagnostic and therapeutic interventions remains important in our litigious society. The physician should explain the natural history of the disease and that he is at extremely high risk of developing ED, early or late, despite active or no intervention. Discussion should include the advantages and potential disadvantages of the various treatment alternatives as well as the risks associated with no treatment at all. Documentation of this as well as any prior ED and all counseling sessions should be meticulous.

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21 Ejaculatory Disorders

Chris G. McMahon, MBBS, FAChSHM

Summary

Ejaculatory dysfunction, especially premature ejaculation (PE), is a common male sexual disorder. Most epidemiological studies on the prevalence of PE are limited by their reliance on diagnosis by patient self-report. Recently reported normative intravaginal ejaculatory latency time data have expanded our understanding of this condition. Although there is insufficient empirical evidence to identify the etiology of PE, there is limited correlational evidence to suggest that men with PE have high levels of sexual anxiety and altered sensitivity of central 5-hydroxytryptamine receptors. Pharmacological modulation of the ejaculatory threshold using daily or on-demand selective serotonin re-uptake inhibitors offers patients a high likelihood of achieving improved ejaculatory control within a few days of initiating treatment as well as consequential improvements in sexual desire and other sexual domains, and it is well-tolerated. It fails to directly address causal psychological or relationship factors, and data are either lacking or scarce on the efficacy of combined psychosexual counseling and pharmacological treatment as well as on the maintenance of improved ejaculatory control after drug withdrawal.

The management of inhibited ejaculation is likely to evolve toward combination treatment using integrated pharmacotherapy and sex therapy approaches. Integration of sexual counseling and pharmacotherapy is likely to assist patients seeking adaptation to and rehabilitation from multiple medical conditions (e.g., retrograde ejaculation secondary to prostatic surgery). However, large controlled prospective studies are needed to define an appropriate treatment algorithm. The development of new pharmaceuticals will only refine such an algorithm and improve our opportunity for enhancing orgasmic function.

Key Words: Premature ejaculation; selective serotonin re-uptake inhibitors (SSRIs); intravaginal ejaculatory latency time (IELT); inhibited ejaculation; delayed ejaculation; retrograde ejaculation; anejaculation; anorgasmia.

Competing interests: Dr McMahon is a paid consultant, investigator, member of an advisory board and speaker's panel for Johnson & Johnson and Pfizer.

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Table 1
The Three Stages of Normal Antegrade Ejaculation

Emission	Sympathetic spinal cord reflex
	Considerable voluntary control
	Genital and/or cerebral erotic stimuli
	Sequential contraction of accessory sexual organs
	Sensation resulting from distension of posterior urethra
Ejection	Sympathetic spinal cord reflex
	Limited voluntary control
	Bladder neck closure
	Rhythmic contractions of bulbocavernous/pelvic floor muscles
	Relaxation of external urinary sphincter
Orgasm	Smooth muscle contraction of accessory sexual organs
	Build-up and release of pressure in posterior urethra
	Contraction of urethral bulb
	Cerebral processing of pudendal nerve sensory stimuli

INTRODUCTION

Ejaculatory dysfunction (EjD) is one of the most common male sexual disorders. The spectrum of EjD extends from premature or rapid ejaculation through delayed ejaculation to a complete inability to ejaculate (anejaculation) and includes retrograde ejaculation. The sexual response cycle comprises four interactive, nonlinear stages: desire, arousal, orgasm, and resolution. In males, the fourth stage of orgasm usually coincides with ejaculation but represents a distinct cognitive and emotional cortical event. EjD is a disruption of the fourth stage of orgasm.

PHYSIOLOGY OF EJACULATION

Ejaculation is a reflex comprising sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centers, spinal motor centers, and efferent pathways. There are three basic mechanisms involved in normal antegrade ejaculation: emission, ejection, and orgasm (Table 1) *(1)*. Emission is the result of a sympathetic spinal cord reflex initiated by genital and/or cerebral erotic stimuli and involves the sequential contraction of accessory sexual organs. Considerable initial voluntary control of emission progressively decreases until the point of ejaculatory inevitability *(2)*. Ejection also involves a sympathetic spinal cord reflex, upon which there is little or no voluntary control. Ejection involves bladder neck closure; rhythmic contractions of bulbocavernous, bulbospongiosus, and other pelvic floor muscles; and relaxation of the external urinary sphincter *(2)*. Orgasm is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from the veramontanum, and contraction of the urethral bulb and accessory sexual organs.

The ejaculatory reflex is predominantly controlled by a complex interplay between central serotonergic and dopaminergic neurons, with secondary involvement of cholinergic, adrenergic, nitrergic, oxytocinergic, and γ-aminobutyric acid (GABA)-ergic neurons. Seminal emission and ejection are integrated into the complex pattern of copulatory behavior by several forebrain structures, including the medial pre-optic area (MPOA) and the nucleus paragigantocellularis (nPGi) (Fig. 1) *(3,4)*. Descending serotonergic pathways

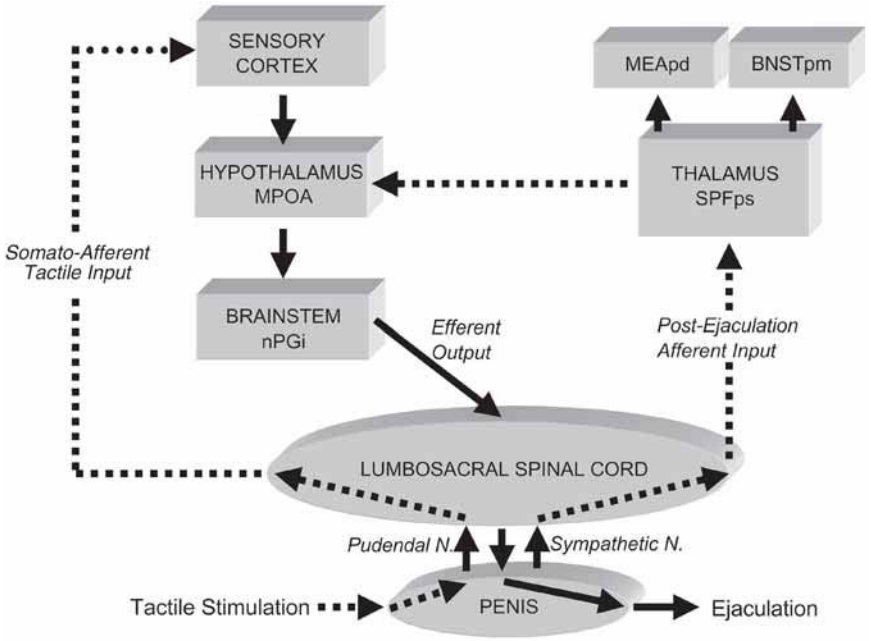

Fig. 1. CNS areas involved before, during, and after ejaculation. Somatosensory tactile input form the penis/genitals ascends to the cerebral cortex. Efferent pathways project from the hypothalamus to the sacral spinal cord and genitals. After ejaculation, information is returned from the genitals to several brain areas. MEApd, posterodorsal medial amygdala; BNSTpm, posteromedial bed nucleus of stria terminalis; SPFps, medial parvicellular subparafasicular nucleus of thalamus *(51)*.

from the nPGi to the lumbosacral motor nuclei tonically inhibit ejaculation *(4)*. Disinhibition of the nPGi by the MPOA facilitates ejaculation. Several brain areas are activated after ejaculation by ascending fibers from the spinal cord and may have a possible role in satiety and the postejaculatory refractory time.

Animal and human sexual psychopharmacological studies have attributed a serotonergic basis and a possible genetic etiology to premature ejaculation (PE) *(5–8)*. Male rat studies have demonstrated that serotonin and 5-hydroxytryptamine (5-HT) receptors are involved in the ejaculatory process. The speed of ejaculation appears to be determined by 5-HT2C and 5-HT1A receptors. Stimulation of 5-HT2C receptors with nonselective 5-HT2C agonists delayed ejaculation in male rats, whereas stimulation of postsynaptic 5-HT1A receptors resulted in shorter ejaculation latency *(9)*. Administration of selective serotonin re-uptake inhibitors (SSRIs) results in active blockade of presynaptic membrane 5-HT transporters, and the resultant higher synaptic cleft levels of 5-HT activate postsynaptic 5-HT2C and 5-HT1A receptors and delay ejaculation *(6,10)*.

PREMATURE EJACULATION

PE is one of the most common male sexual disorders and has been estimated to occur in 4 to 39% of men in the general population *(11–17)*.

The World Health Organization 2nd International Consultation on Sexual Health defined it as "...persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration, and before the person wishes it, over which the sufferer has

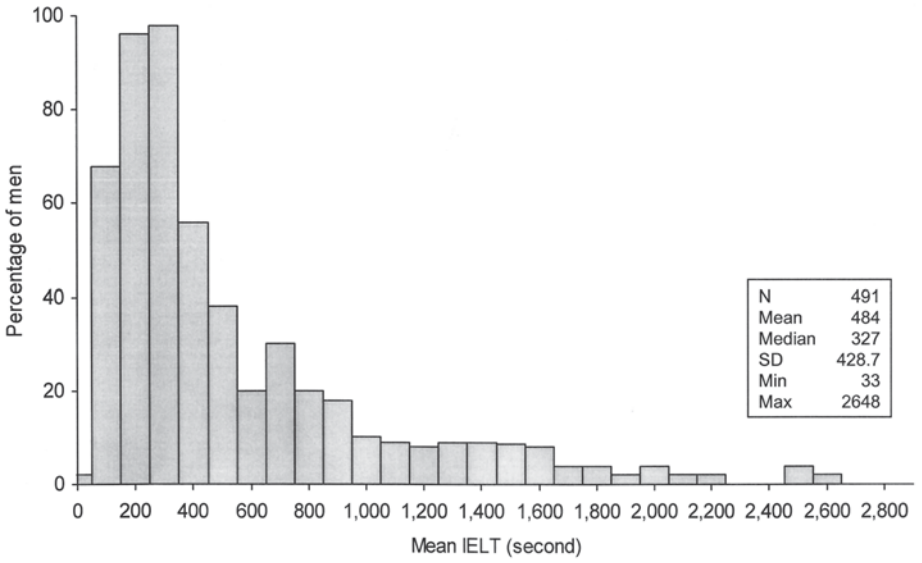

Fig. 2. Distribution of IELT values in a random cohort of 491 men *(24)*.

little or no voluntary control which causes the sufferer and/or his partner bother or distress..." *(18)*. This multivariate definition encompasses the main dimensions of PE: ejaculatory latency, control, and sexual satisfaction.

Over the last 15 yr, an increasing number of publications have reported the pharmacological treatment of PE with various medications that act centrally or locally to retard the psychoneurological control of ejaculation and subsequent orgasm. It is well-established that major tranquilizers and SSRIs significantly retard ejaculation and, in a small percentage of men, will result in anejaculation *(19–21)*. The efficacy of SSRIs in delaying ejaculation together with the low profile of side effects make them first-line agents for PE that can be administered on either a daily or an on-demand basis *(22,23)*.

Epidemiology of PE

Most community-based epidemiological studies are limited by their reliance on either patient self-report of PE or inconsistent, poorly validated definitions of PE and true normative data are lacking. A recent multinational community-based, age-ranging study of an unselected "normal" population of 500 heterosexual couples involving stopwatch timing of the intravaginal ejaculatory latency time (IELT) during sexual intercourse provided previously lacking normative data *(24)*. This study demonstrated that the distribution of the IELT was positively skewed, with a median IELT of 5.4 min (range: 0.55–44.1 min; Fig. 2). The median IELT decreased with age and varied between countries. The authors regarded the 0.5 and 2.5 percentiles as acceptable standards of disease definition in this type of skewed distribution and proposed that men with an IELT of less than 1 min (i.e., belonging to the 0.5 percentile) have "definite" PE, whereas men with IELTs between 1 and 1.5 min (i.e., between the 0.5 and 2.5 percentile) have "probable" PE *(25)*.

Little published data exists regarding the impact of birth country, religion, or culture on the prevalence of PE. An increased susceptibility to PE in men from the Indian subcontinent has been reported *(26,27)*. Kinsey's observation that Asian men have shorter times

to ejaculation than Caucasians, who in turn have shorter times to ejaculation than Afro-Caribbeans, has been interpreted to suggest that some races are more "sexually restrained" than others *(28,29)*. A recent study reported a higher incidence of PE in men of Middle Eastern and Asian backgrounds than the general population *(30)*.

Classification of PE

In 1943, Schapiro *(31)* first suggested the premise that PE is a psychosomatic disturbance and results from a psychologically overanxious personality. He classified PE as either primary (lifelong) or secondary (acquired) *(31)*. Masters and Johnson *(32)* first proposed the behavioristic view that chronic PE results from performance anxiety related to a disturbing initial episode of PE. Most of the behavioral treatments currently used are based on this premise.

In 1326 consecutive men with PE, lifelong PE was present in 736 (74.4%) and acquired PE was present in 253 (25.6%) *(33)*. Men with self-reported PE have a lower frequency of sexual intercourse, report higher levels of intercourse-related anxiety, and note greater impairment in intercourse satisfaction and sexual relationship satisfaction compared with men without PE *(34)*. However, they do not report a reduced quality of life, reduced sexual desire, or a reduced ability to become sexually aroused *(18,34)*.

Defining PE

Medical literature contains several uni- and multivariate operational definitions of PE. The lack of agreement regarding what constitutes PE has hampered basic and clinical research into the etiology and management of this condition. Quantitative measures of intercourse, such as the IELT, the patient's assessment of his voluntary control over ejaculation or self-efficacy, the extent of patient sexual satisfaction, and the level of bother or distress have been described and employed as patient-related outcomes in PE clinical trials. Each of the three criteria has been operationalized, although not always with consistency *(35)*.

Intravaginal Ejaculatory Latency Time

Operationalization of PE using the length of time between penetration and ejaculation (i.e., IELT) forms the basis of most current clinical studies on PE. There is considerable variance of the latencies used to identify men with PE who demonstrate IELTs ranging from 1 to 7 min, and none of the definitions is based on normative data or offer any supportive rationale for the proposed cut-off time *(36–39)*. Gebhard *(40)* reported an average duration of intercourse of 4 to 7 min, suggesting that ejaculation before 4 min after intromission should be considered premature.

Waldinger et al. *(41)* reported IELTs of less than 30 and 60 s in 77 and 90% of 110 men with PE, respectively. McMahon et al. *(33)* reported similar results in 1346 consecutive men with PE, with a mean IELT of 43.4 s. Predominant ante portal ejaculation (during foreplay) occurred in 5.6% of men. Although normative data are lacking, it is reasonable for clinicians to regard men who ejaculate within 2 min of penetration as suffering from PE. Ante portal ejaculation or ejaculation within 1 min should be regarded as severe PE.

Sexual Satisfaction

Men with PE report lower levels of sexual satisfaction compared with men with normal ejaculatory latency. Patrick et al. *(42)* reported ratings of very poor or poor for sexual

satisfaction in 31% of men with PE compared with 1% in a group of controls. Masters and Johnson proposed *(43)* the inability to control and defer ejaculation until the female partner was sexually satisfied on at least 50% of intercourse attempts as a definition of PE.

An inherent problem exists in defining a man as dysfunctional based on the sexual responsiveness of his partner. This definition implies that any male whose female partner has difficulty in reaching orgasm should be labeled as a premature ejaculator. This definition clashes with the report that only 30% of women achieve orgasm during sexual intercourse, regardless of the extent of their partner's ejaculatory control and latency. Rowland *(44)* reported that more than 89.4% of men with self-reported PE regarded fulfilling their partner's sexual needs as very or extremely important.

Voluntary Control

Kaplan and other authors *(45–48)* have suggested that an inability to voluntarily defer ejaculation defines PE. This definition has yet to be adequately operationalized to allow comparison across subjects or studies. Grenier and Byers *(15)* failed to demonstrate a strong correlation between ejaculatory latency and subjective ejaculatory control. They reported that some men with a brief ejaculatory latency time reported adequate ejaculatory control and vice versa and concluded that the dimensions of ejaculatory control and latency are distinct concepts. Conversely, Waldinger et al. *(41)* reported a moderate correlation between the IELT and the feeling of ejaculatory control.

Distress

Existing definitions of PE include distress as an important dimension of PE *(18,49,50)*. However, the word "distress" has negative social implications, and its existence is denied by most men with PE. This dimension of PE is better captured by the term "bother." The extent of bother defines the severity of PE. One study reported that 64% of men with PE rated their extent of personal distress as "quite a bit" or "extremely," compared with 4% in a group of control subjects *(42)*.

Although partner distress is perhaps the most common reason for men with PE to seek treatment, there is limited information regarding the effect of PE on the partner. Patrick et al. *(42)* reported that 44% of partners of men with PE rated their extent of personal distress as "quite a bit" or "extremely," compared with 3% in a group of partners of control subjects.

The design of all future studies regarding any aspect of PE should include a uniform, operationalized, multivariate definition of PE in which the dimensions of latency, control, and satisfaction are defined, measured, and analyzed as continuous variables without arbitrary cut-off values.

Etiology of PE

Historically, attempts to explain the etiology of PE have included a diverse range of biological and psychological theories (Table 2). Most of these proposed etiologies are not evidence-based and are at best speculative.

Little empirical evidence exists to suggest a causal link between PE and any of the factors believed to cause PE. However, there is limited correlational evidence to suggest that lifelong PE results from altered sensitivity of central 5-HT receptors and that acquired PE results from high levels of sexual anxiety, erectile dysfunction, or lower urinary tract infection.

Table 2
Proposed Etiologies of Premature Ejaculation

Psychogenic	Anxiety
	Early sexual experience
	Frequency of sexual intercourse
	Ejaculatory control techniques
	Psychodynamic theories
Biological	Penile hypersensitivity
	Hyperexcitable ejaculatory reflex
	Arousability
	Endocrinopathy
	Genetic predisposition
	Evolutionary
	5-HT receptor dysfunction

Ejaculatory latency time is probably a biological variable that is genetically determined and may differ between populations and cultures, ranging from extremely rapid through average to slow ejaculation. Hyposensitivity of the 5-HT2C, hypersensitivity of the 5-HT1A receptors, or both has been suggested as a possible explanation of lifelong PE *(10,51)*. Men with low 5-HT neurotransmission and probable 5-HT2C receptor hyposensitivity may have their ejaculatory threshold genetically "set" at a lower point and may ejaculate quickly and with minimal stimulation, whereas men with a higher set-point can sustain more prolonged and higher levels of sexual stimulation and can exert more control over ejaculation. Men with a very high set-point may experience delayed or absent ejaculation despite achieving a full erection and prolonged sexual stimulation. Treatment with an SSRI class drug activates the 5-HT2C receptor, lowers the ejaculatory threshold set-point, and delays ejaculation. The extent of ejaculatory delay may vary widely in different men according to the dosage and frequency of administration of SSRI and the genetically determined ejaculatory threshold set-point. Cessation of treatment results in re-establishment of the previous set-point within 5 to 7 d in men with lifelong PE.

Anxiety has been reported as a cause of PE by multiple authors and is entrenched in the folklore of sexual medicine as the most likely cause of PE, despite scant empirical research evidence to support any causal role *(31,45,52)*. Several authors have suggested that anxiety activates the sympathetic nervous system and reduces the ejaculatory threshold as a result of an earlier emission phase of ejaculation *(45,52)*. Additionally, several authors have suggested that high levels of anxiety and excessive and controlling concerns about sexual performance and potential sexual failure might distract a man from monitoring his level of arousal and recognizing the prodromal sensations preceding ejaculatory inevitability *(47,48,53–55)*. The causal link between anxiety and PE is speculative, is not supported by any empirical evidence, and is contrary to empirical evidence from some researchers *(56)*.

Recent data demonstrate that almost half of men with ED also experience PE. *(57)* Men with early ED may intentionally "rush" sexual intercourse to prevent premature loss of their erection and may ejaculate with a brief latency. This may be compounded by the presence of high levels of performance anxiety related to their ED, which serves only to worsen prematurity. In the absence of a thorough sexual history, these men may be incorrectly diagnosed as suffering from PE rather than the underlying ED.

PE Drug Trial Design

The results of PE drug clinical trials are only reliable, interpretable, and capable of being generalized to patients with the disorder when conducted in well-defined and consistent populations using a double-blind, placebo-controlled study design with consistent objective physiological measures or sensitive, validated outcome assessment instruments as study end points *(18)*.

In PE studies, the study population should be well-characterized, representative of the overall patient population, and defined using a multivariate definition of PE. Because the population of men with PE is not homogenous, lifelong and acquired PE should be treated as demographically and etiologically distinct disorders and should be analyzed as separate PE subgroups *(33)*.

Subjects should be involved in a stable, monogamous heterosexual relationship, should be prepared to attempt intercourse on a regular basis, and should provide written informed consent. The presence of comorbid ED should be evaluated using a validated instrument such as the International Index of Erectile Function, and patients with any degree of ED should either be excluded from the study or treated as a separate subgroup. Patients with hypoactive sexual desire or other sexual disorders, urogenital infection, major psychiatric disorders, a history of drug and alcohol abuse, or contraindications to the study drug should be excluded from the study.

Measurement of the IELT by stopwatch is the best method to categorize the severity of PE, and the response to treatment and should be used as a primary efficacy endpoint. IELTs lasting less than 1 or 2 min have been suggested as cut-points for inclusion in a clinical trial *(22,35)*. Subjective patient-reported outcomes of ejaculatory control, sexual satisfaction, and bother/distress are important additional efficacy endpoints and can be evaluated using validated patient-reported outcome instruments *(58–60)*. Research into the development of validated, reliable, and consistent patient-reported outcome measures is ongoing.

Treatment

Psychosexual Counseling

In many relationships, PE causes few, if any, problems. In others, the couple may reach an accommodation of the problem through various strategies—young men with a short refractory period may often experience a second and more controlled ejaculation during a subsequent episode of lovemaking. Frequently, however, PE eventually leads to significant relationship problems, with partners regarding the man as selfish and developing a pattern of sexual avoidance. This only worsens the severity of the prematurity on occasions when intercourse does occur.

The cornerstones of behavioral treatment are the Seman's "stop–start" maneuver and its modification, the squeeze technique (proposed by Masters and Johnson). Both are based on the theory that PE occurs because the man fails to pay sufficient attention to pre-orgasmic levels of sexual tension *(43,61)*. Because most men with PE are aware of their anxiety and the sources of that anxiety tend to be relatively superficial, treatment success with these behavioral approaches is relatively good in the short term; however, convincing long-term treatment outcome data are lacking *(46,62,63)*.

Pharmacological Treatment

Pharmacological modulation of ejaculatory threshold represents a novel and refreshing approach to the treatment of PE and a radical departure from the psychosexual model

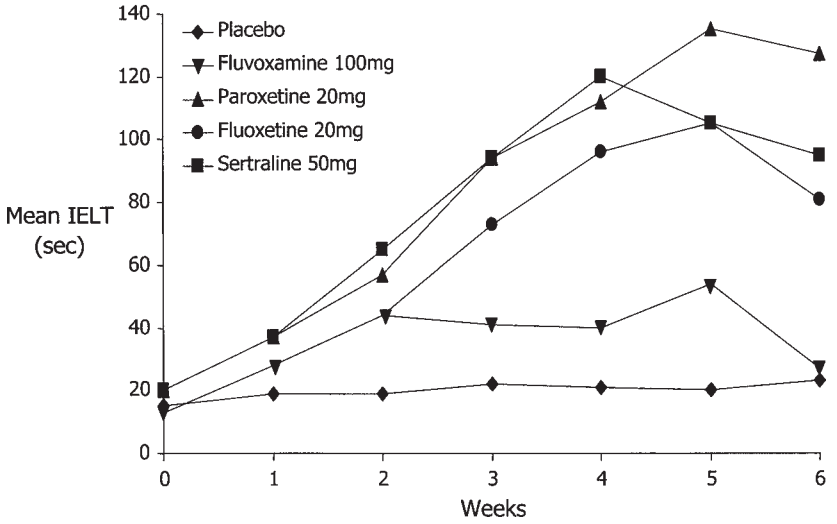

Fig. 3. Selective serotonin re-uptake inhibitors produce ejaculatory delay within 5 to 10 d *(22)*.

of treatment, previously regarded as the cornerstone of treatment. The introduction of the SSRIs has revolutionized the approach to, and treatment of, PE. SSRIs encompass five compounds (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) with a similar pharmacological mechanism of action. Although the methodology of the initial drug treatment studies was poor, later double-blind and placebo-controlled studies replicated the genuine effect of clomipramine and SSRIs to delay ejaculation. Despite a development toward more evidence-based drug treatment research, the majority of studies still lack adequate design and methodology *(64)*. A recent meta-analysis of all drug treatment studies demonstrated that only 14.4% had been performed according to the established criteria of evidence-based medicine and that open design studies and studies using subjective reporting or questionnaires showed a higher variability in ejaculation delay than double-blind studies in which the ejaculation delay was prospectively assessed with a stopwatch *(64)*.

Daily Treatment With SSRIs. Daily treatment can be performed with 20 to 40 mg of paroxetine, 10 to 50 mg of clomipramine, 50 to 100 mg of sertraline, and 20 to 40 mg of fluoxetine (Fig. 3). Paroxetine appears to exert the strongest ejaculation delay, increasing IELT approx 8.8-fold over baseline *(64)*. Ejaculation delay usually occurs within 5 to 10 d, but it may occur earlier. Adverse effects are usually minor; they usually start in the first week of treatment, gradually disappear within 2 to 3 wk, and include fatigue, yawning, mild nausea, loose stools, or perspiration. Diminished libido or mild erectile dysfunction is infrequently reported. Significant agitation has been reported by a small number of patients, and treatment with SSRIs should be avoided in men with a history of bipolar depression.

On-Demand Treatment With SSRIs. Administration of clomipramine, paroxetine, sertraline, and fluoxetine 4to 6 h before intercourse is efficacious and well-tolerated but is associated with less ejaculatory delay than daily treatment. Daily administration of an SSRI is associated with superior increases in IELT compared with on-demand administration because of greatly enhanced 5-HT neurotransmission resulting from several adaptive processes that may include presynaptic 5-HT1A and 5-HT1B/1D receptor desensitisation

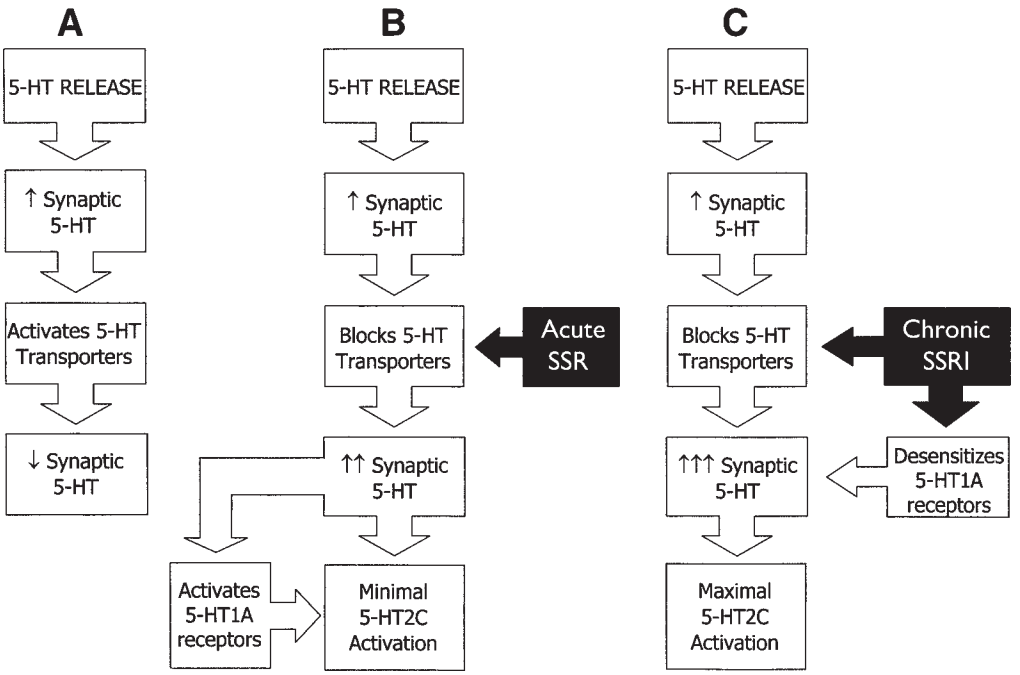

Fig. 4. **(A)** Synaptic cleft 5-HT and 5-HT neurotransmission are regulated by somatodendritic 5-HT1A autoreceptors, presynaptic 5-HT1B/1D autoreceptors, and a 5-HT transporters re-uptake system. As 5-HT is released into the synaptic cleft from presynaptic axonal vesicles, 5-HT transporters re-uptake and remove 5-HT from the synaptic cleft, preventing overstimulation of the postsynaptic receptors. **(B)** After blockage of 5-HT transporters by acute administration of SSRIs, synaptic cleft 5-HT increases but is counteracted by activation of 5-HT1A autoreceptors, which further inhibit 5-HT release. **(C)** Chronic administration of SSRIs results in greatly enhanced 5-HT neurotransmission caused by several adaptive processes that may include presynaptic 5-HT1A and 5-HT1B/1D receptor desensitization *(6)*.

(Fig. 4; ref. *10*). On-demand treatment may be combined with either an initial trial of daily treatment or concomitant low-dose daily treatment *(23,65,66)*.

Several rapid-acting, short half-life SSRIs (dapoxetine, Johnson & Johnson, UK-369,003-Pfizer) are under investigation as on-demand treatments for PE. Preliminary data suggest that dapoxetine (Johnson & Johnson) administered 1 to 2 h before planned intercourse is effective and well-tolerated, is superior to placebo, and increases IELT two- to threefold over baseline in a dose-dependent fashion *(67)*. In randomized, double-blind, placebo-controlled, multicenter, phase III 12-wk clinical trials involving 2614 men with a mean baseline IELT of 2 min or less, 30 or 60 mg of dapoxetine was more effective than placebo for all study endpoints *(68)*. IELT increased from 0.91 min at baseline to 2.78 and 3.32 min at study end with 30 and 60 mg of dapoxetine, respectively. Mean patient rating of Control Over Ejaculation as fair, good, or very good increased from 2.8% at baseline to 51.8 and 58.4% at study end with 30 and 60 mg of dapoxetine, respectively. Treatment-related side effects were uncommon and dose-dependent and included nausea, diarrhea, headache, and dizziness; they were responsible for study discontinuation in 4 (30 mg) and 10% (60 mg) of subjects.

Anesthetic Topical Ointments. The use of topical local anesthetics, such as lignocaine and/or prilocaine, as creams, gels, or sprays is well-established and moderately effective in retarding ejaculation. Their use may be associated with significant penile hypoanesthesia and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia, unless a condom is used *(69–71)*.

Phosphodiesterase Inhibitors. Nitric oxide (NO) is becoming recognized as one of the important intracellular messengers in the brain *(72)*. Several studies have suggested that elevation of extracellular NO in the MPOA accelerates dopamine release and facilitates male copulatory behavior of rats, whereas a decrease of NO reduces copulatory behavior *(73–75)*.

Several authors have reported their experiences with phosphodiesterase (PDE)-5 inhibitors alone or in combination with SSRIs as a treatment for PE *(76–80)*. The proposed mechanisms for the effect of sildenafil on ejaculatory latencies include a central effect involving increased NO and reduced sympathetic tone, smooth muscle dilatation of the vas deferens and seminal vesicles (which may oppose sympathetic vasoconstriction and delay ejaculation), reduced performance anxiety caused by better erections, and downregulation of the erectile threshold to a lower level of arousal so that increased levels of arousal are required to achieve the ejaculation threshold. Most of these studies are uncontrolled, and the results are confusing and difficult to interpret. The only double-blind, placebo-controlled, multicenter study showed no significant difference in the IELT of subjects treated with sildenafil compared with those treated with placebo but did demonstrate significant improvements in the ejaculatory control domain and the ejaculatory function global efficacy question. The latter is possibly consistent with the erectile response of sildenafil *(81)*. It is unlikely that PDE inhibitors have a significant role in the treatment of PE, with the exception of men with acquired PE secondary to comorbid ED. However, the growing number of publications claiming a role for use of PDE-5 inhibitors in combination with SSRIs or topical local anesthetics for the treatment of PE suggests a need for larger placebo-controlled studies.

Surgery

Several authors have reported the use of surgically induced penile hypo-anesthesia via selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation in the treatment of lifelong PE refractory to behavioral and/or pharmacological treatment *(82)*. The role of surgery in the management of PE remains unclear; the results of further studies are currently under investigation.

Office Management of PE

Men with PE should be evaluated with a detailed medical and sexual history, a physical examination, and appropriate investigations to establish the true presenting complaint and any identifiable obvious biological causes such as genital or lower urinary tract infection (Fig. 5).

Men with PE secondary to erectile dysfunction, other sexual dysfunction, or genitourinary infection should receive appropriate etiology-specific treatment. Men with lifelong PE should be initially managed with pharmacotherapy. Men with significant contributing psychogenic or relationship factors may benefit from concomitant behavioral therapy. Men with PE secondary to ED can be treated with either ED-specific pharmacotherapy (e.g., PDE-5 inhibitors) as monotherapy or in combination with PE specific pharmacotherapy (e.g., daily or on-demand SSRIs). Recurrence of PE is highly likely to occur following

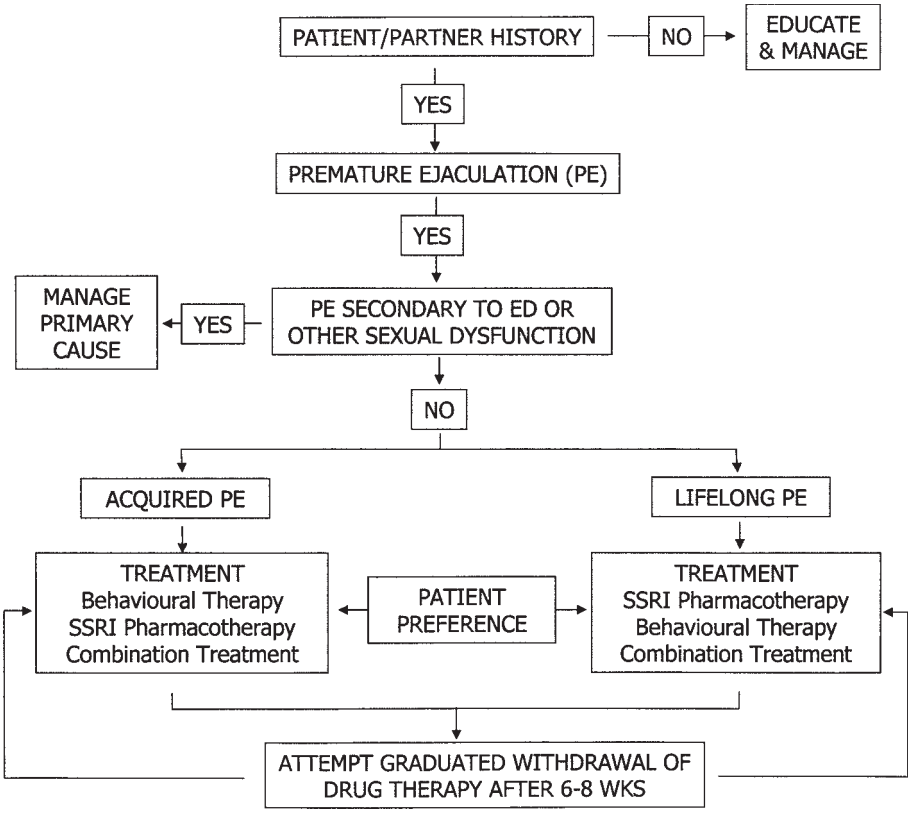

Fig. 5. Algorithm for the office management of premature ejaculation *(18)*.

withdrawal of treatment. Men with acquired PE can be treated with pharmacotherapy, behavioral therapy, or both according to patient/partner preference. Restoration of ejaculatory control in men with acquired PE is likely to occur following completion of. Behavioral therapy may augment pharmacotherapy to enhance relapse prevention.

INHIBITED EJACULATION, ANEJACULATION, AND ANORGASMIA

The Diagnostic and Statistical Manual of Mental Disorders defines inhibited ejaculation as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation, which causes personal distress *(50)*. Inhibited ejaculation or anejaculation can be classified as either lifelong or acquired or as global or situational. Any single or combination of psychological or medical diseases, surgical procedure, or drug that interferes with either central control of ejaculation or the afferent or efferent nerve supply to the vas, bladder neck, pelvic floor, or penis can result in inhibited ejaculation, anejaculation, and anorgasmia (Table 3).

Like other sexual dysfunctions, inhibited ejaculation is more prevalent as men age *(50)*. The progressive loss of the fast-conducting peripheral sensory axons that begins to be apparent in the third decade of life as well as the dermal atrophy, myelin collagen infiltration, and pacinian corpuscle degeneration observed in older men may result in a degree of age-related degenerative penile hypo-anesthesia and difficulty in achieving the ejaculatory threshold.

Table 3
Causes of Inhibited Ejaculation, Anejaculation, and Anorgasmia

Psychogenic	Inhibited ejaculation
Congenital	Mullerian duct cyst
	Wolfian duct abnormaility
	Prune belly syndrome
Anatomic causes	Transurethral resection of prostate
	Bladder neck incision
Neurogenic causes	Diabetic autonomic neuropathy
	SCI
	Radical cystectomy or prostatectomy
	Proctocolectomy
	Bilateral sympathectomy
	Abdominal aortic aneurysmectomy
	Para-aortic lympthadenectomy
Infective	Urethritis
	Genitourinary tuberculosis
	Schistosomiasis
Endocrine	Hypogonadism
	Hypothyroidism
Medication	α-methyl Dopa
	Thiazide diuretics
	Tricyclic and SSRI antidepressants
	Phenothiazine
	Alcohol abuse

SCI, spinal cord injury; SSRI, selective serotonin re-uptake inhibitors.

Inhibited ejaculation may be associated with cultural and religious beliefs, concurrent psychopathology (such as unconscious aggression and unexpressed anger), insufficient sexual arousal, preconditioning for inhibited ejaculation resulting from a preference for masturbation over partnered sex, or fear of pregnancy or sexually transmissible disease *(43,83–87)*. Apfelbaum *(84)* observed that some males achieve erections sufficient for intercourse despite a relative absence of subjective arousal and incorrectly regard themselves as ready for sex and capable of achieving orgasm. This process likely causes increased anecdotal clinical reports of inhibited ejaculation in patients using pharmacological treatments for ED *(88)*.

The ability to ejaculate is severely impaired by spinal cord injury (SCI) and depends on the level and completeness of SCI *(89)*. Unlike erectile capacity, the ability to ejaculate increases with descending levels of spinal injury (ref. *90*; Table 4). Less than 5% of patients with complete upper motor neuron lesions retain the ability to ejaculate. Semen for use with artificial reproductive techniques may be obtained from men with SCI by vibratory stimulation, electro-ejaculation, or percutaneous aspiration of semen from the vas deferens *(91–93)*. Testicular biopsies in men with SCI demonstrate a wide range of testicular dysfunction, and sperm density and motility are higher in men with incomplete lesions *(94)*.

Treatment of Inhibited Ejaculation, Anejaculation, and Anorgasmia

Treatment should be etiology-specific and should address the issue of infertility in men of a reproductive age.

Table 4
Correlation of Erection, Ejaculation, and Intercourse With Level and Severity of Spinal Cord Injury

Cord lesion	*Reflexogenic erections (%)*		*Psychogenic erections (%)*	*Successful coitus (%)*	*Ejaculation (%)*
Upper Motor Neuron	Complete	92	9	66	1
	Incomplete	93	48	86	22
Lower Motor Neuron	Complete	0	24	33	15
	Incomplete	0	1	100	100

From ref. *91*.

Psychological Treatment

Although multiple psychodynamic and behavioral treatments for IE have been suggested, empirical evidence to support treatment efficacy is lacking *(43,95–99)*. Most reports are uncontrolled case reports, with treatment ranging from a few brief sessions of sex education to the nearly 2 yr of multiple-modality treatment in more complex, multiple etiological cases.

Drug Treatment

There are multiple reports in the literature of the use of various drugs in the treatment of inhibited ejaculation *(100–109)*. The drugs facilitate ejaculation by either a central dopaminergic or antiserotoninergic mechanism of action. There are no published placebo-controlled studies, and most reports are anecdotal case reports/series dealing with the treatment of SSRI-induced ejaculatory dysfunction (Table 3). Although medical treatment may not always produce normal ejaculation, it may convert a patient with lack of emission into one with retrograde ejaculation and may result in small amounts of viable sperm sufficient for use in standard artificial insemination techniques to produce a pregnancy.

RETROGRADE EJACULATION

Antegrade ejaculation requires a closed bladder neck and proximal urethra. Surgical procedures that compromise the bladder neck closure mechanism may result in retrograde ejaculation. Transurethral incision of the prostate results in retrograde ejaculation in 5 to 45% of patients and is probably related to the decision of whether to make one or two incisions and whether or not the incision includes primarily the bladder neck or extends to the level of the verumontanum *(110,111)*. The importance of contraction of the urethral smooth muscle at the level of the verumontanum has been hypothesized to be important in preventing retrograde ejaculation *(112)*. Transurethral resection of the prostate carries a higher incidence of retrograde ejaculation than transurethral incision of the prostate. The reported incidence of retrograde ejaculation following transurethral resection of the prostate ranges from 42 to 100% *(113,114)*. Although these men may have some antegrade ejaculation and usually experience orgasmic sensation, both may decrease in frequency as part of the changes that occur in the male sexual response as a man ages. Retrograde ejaculation and failure of emission can be distinguished by examination of a postmasturbatory specimen of urine for the presence of spermatozoa and fructose.

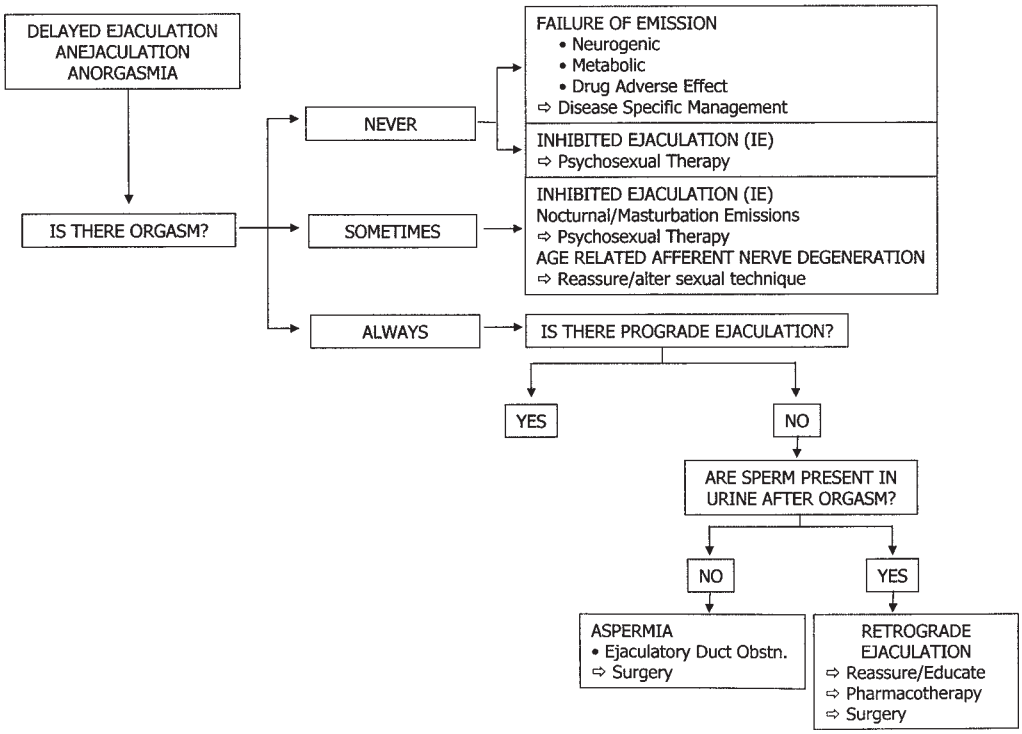

Fig. 6. Algorithm for the office management of inhibited ejaculation and anejaculation *(18)*.

Treatment

Retrograde ejaculation can be surgically treated with bladder neck reconstruction, but results remain consistently poor *(115)*. Drug treatment is the most promising approach. α-adrenergic sympathetic nerves mediate both bladder neck closure and emission. Several sympathomimetic agents have been described as useful, with mixed results *(116)*. These drugs include pseudo-ephedrine and ephedrine as well as phenylpropanolamine. These agents work by stimulating the release of noradrenaline from the nerve axon terminals but may also directly stimulate both α- and β-adrenergic receptors. The most useful is pseudo-ephedrine, which is administered at a dose of 120 mg precoitally for 2 to 2.5 h. The tricyclic antidepressant imipramine, which blocks the re-uptake of noradrenaline by the axon from the synaptic cleft, is also occasionally useful *(117)*. The usual dose is 25 mg twice daily. The current belief is that long-term treatment with imipramine is likely to be more effective.

Although medical treatment may not always produce normal ejaculation it may result in some prograde ejaculation. In patients who do not achieve prograde ejaculation with either surgery or medication, sperm retrieval and artificial insemination is an alternative approach. The basic method of sperm retrieval involves recovery of urine by either catheter or voiding after masturbation followed by centrifugation and isolation of the sperm.

OFFICE MANAGEMENT OF INHIBITED EJACULATION, ANEJACULATION, AND ANORGASMIA

Men with inhibited ejaculation, anejaculation, and/or anorgasmia should be evaluated with a detailed medical and sexual history, a physical examination, and appropriate

imaging and/or electrophysiological investigations to establish the true presenting complaint, identify obvious biological causes (such as medication, diabetes mellitus, or recent pelvic surgery), and uncover sufficient detail to establish the optimal treatment plan (Fig. 6). The exact site of ejaculatory duct obstruction may be identified by transrectal ultrasonography, vasography, or percutaneous puncture of the seminal vesicles. Four neurophysiological tests are routinely used: pudendal somatosensory-evoked potentials, pudendal motor-evoked potentials, sacral reflex arc testing, and sympathetic skin responses.

Men who never achieve orgasm and ejaculation are suffering from a biogenic failure of emission, psychogenic-inhibited ejaculation, or both. Management involves identification of the etiology and disease-specific treatment. Men who occasionally achieve orgasm and ejaculation are usually suffering from psychogenic-inhibited ejaculation or penile hypnoanesthesia secondary to age-related degeneration of the afferent penile nerves. The former is managed with behavioral therapy, psychotherapy, or both. Men with age-related penile hypnoanesthesia should be educated, reassured, and instructed in revised sexual techniques that maximize arousal.

The majority of men who always achieve orgasm but never experience prograde ejaculation or who experience a greatly reduced prograde ejaculatory volume have retrograde ejaculation. The presence of spermatozoa and fructose in centrifuged postejaculatory-voided urine confirms the diagnosis. Management involves education and reassurance of the patient, pharmacotherapy, or, in rare cases, bladder neck reconstruction. The absence of spermatozoa suggests congenital absence or agenesis of the testis or vas/vasa or acquired ejaculatory duct obstruction. Management involves investigation by ultrasonic or radiological imaging to identify the site of obstruction and disease-specific treatment.

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22 Gene Therapy for Erectile Dysfunction

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Summary

Our current understanding of the underlying mechanisms of erectile dysfunction suggests that gene therapy will become a therapeutic treatment in the near future. Over the past decade, erectile dysfunction has been ameliorated in animal models using viral- and plasmid-based vectors. Genes that stimulate smooth muscle cell relaxation, such as neuronal, inducible, and endothelial nitric oxide synthase, or that inhibit smooth muscle cell constriction can restore erectile function in aging, diabetic, and other model systems. The future of erectile dysfunction gene therapy may lie in the use of tissue-specific and regulated gene expression, advanced viral vectors, or the combination of multiple genes to fine tune smooth muscle relaxation.

Key Words: Erectile dysfunction; gene therapy; nitric oxide synthase; nitric oxide; cGMP; phosphodiesterase.

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. The remarkable scientific achievement of decoding the human genome *(2)* combined with the impact of the rapidly evolving micro-array and proteomic technologies is allowing researchers to reveal the "epigenome," the sum total of how the genome executes all information *(3–6)*. Understanding the epigenome allows precise identification of key targets for gene therapy. 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 *(7,8)*. Cystic fibrosis *(9)*, adenosine deaminase deficiency *(10)*, and Canavan disease *(11)* are some diseases in which 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.

Comparatively, 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 underway, including suicide genes,

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immunomodulatory genes, autologous vaccines, tumor suppressor genes, antisense strategies, and anti-oncogenes *(12,13)*. The same strategies are being tested with bladder cancer *(14)*; 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 *(15)*. Similar approaches are being applied to renal transplantation, certain kidney diseases, and renal hypertension *(16,17)*.

Within this background of considerable clinical and scientific interest for the treatment of life-threatening diseases, male erectile dysfunction (ED) initially appears to be an unlikely candidate for gene therapy. The main reason is that although impotence is a serious condition that hampers the quality of life, it does not involve physical pain or endanger life, and, therefore, the perceived risks of gene therapy may not yet justify this approach. This article provides evidence showing that gene therapy for the treatment of ED is a logical and well-established 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 complementary DNA (cDNA) delivery. Additionally, stem cell therapies can be combined with gene therapy for possible tailoring of treatment to each patient.

GENERAL STRATEGIES OF GENE THERAPY

Most gene therapy trials focus on the treatment of inborn errors of metabolism and cancer *(7–11,18)*, with several hundred ongoing clinical studies and a larger number of preclinical trials in animal models. The main objective is to restore or modulate a biochemical pathway that is crucial for the desired physiological or pharmacological response by adding a recombinant cDNA to the affected tissue. The recombinant cDNA must be transfected with a DNA complex or infected with a viral DNA vector into the selected tissue, organ, or the body in general. The goal is to express the recombinant messenger RNA (mRNA) and, in turn, the enzymatic protein preferentially in the target tissue or organ at a therapeutic intracellular concentration for as long as necessary.

In some cases, the desired effect is to correct an inactivating mutation, in which case the cDNA must replace the silent gene by homologous recombination. In other cases, the protein is active but is expressed at low levels or its biological activity is downregulated so that the recombinant cDNA aims to hyperexpress the normal protein. Finally, in some conditions, it is fundamental to block the expression of a noxious protein. This can be done using an antisense cDNA that blocks its mRNA translation or a ribozyme (a small catalytic RNA) that cleaves specifically the target mRNA. Alternatively, antisense oligonucleotides representing a fraction of the coding sequence, rather than whole cDNAs, can be used to block mRNA transcription, or a small interfering RNA (siRNA) that activates a degradation pathway specific to the target mRNA may be used to achieve the same inhibition.

The success of gene therapy essentially depends on six main factors: (a) efficient delivery of the cDNA construct or siRNA; (b) preferential tissue or organ targeting; (c) selective tissue or organ expression; (d) persistent hyperexpression or inhibition of the desired active protein; (e) absence of immune responses against the proteins encoded by the recombinant vector or cDNA; (f) if possible, conditional activation of protein expression to permit selective time frames for biological effects. The overall objective is to satisfy as many of these requirements as possible so that an efficient, sustained expression of the desired gene product eventually 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 express the most advantageous protein—preferably, an autologous protein. Expression of an autologous protein provides the best chance of proper interaction with cellular receptors or other specific biochemical targets and also reduces possible antigenic rejection. This is a caveat of many animal preclinical trials in which 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 delivery vector for expression in the target tissue.

There are two main types of delivery vectors: plasmid and viral. The plasmid vector is a circular episomal DNA in which cDNA can be cloned and the vector propagated in large quantities in bacteria. The purified plasmid can then be introduced into mammalian tissues. Expression of cDNA in the tissue can be driven by either a nonregulable strong eukaryotic promoter, such as cytomegalovirus (CMV) or herpes simplex virus (virus-derived promoters), 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; in the body, this can occur by systemic or local injection of either an aqueous suspension ("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. Additionally, application of short pulses of electric current through the tissue, referred to as *electroporation*, can facilitate uptake of DNA by opening of transient pores in membranes.

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 of the same plasmid vector that contain a cDNA that expresses a reporter protein such as green fluorescent protein, β-galactosidase, or luciferase. Each can be detected 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 paired to span the vector and cDNA sequences, and the cDNA expression is demonstrated at the mRNA level (real-time PCR, Northern blot, etc.) or protein level (Western blot, immunocytochemistry, enzyme-linked immunosorbent assay, enzyme reactions, etc.). The desired functional effects in terms of modifying a biochemical pathway or getting a physiological response are then assessed, but this may not be possible in cell cultures that may not resemble the situation in the tissue or whole body. Finally, the plasmid construct must be tested in animals; this usually occurs by injection but can also be given by continuous infusion, transdermally, orally, and other routes. The determination of efficiency of delivery, expression, and physiological effects is performed as in the in vitro testing. Additionally, both tissue distribution and safety can be evaluated using routine tests.

Although plasmid constructs were the first to be used both in vitro or in vivo *(19)*, they suffer from several disadvantages—namely, poor efficiency of cell uptake, nonintegration of the recombinant DNA into the host genome, and a relatively short period of expression at pharmacological levels (usually days or a few weeks). The usefulness of plasmids in gene therapy may depend on the development of more efficient liposomal preparations or the use of electroporation or slow-release methodologies. Advances in this area have recently been reviewed *(20)*. As described in detail later, a plasmid-based gene therapy protocol is currently being evaluated in a phase I safety clinical trial for the treatment

of ED *(21,22)*. If the efficiency of plasmid transfection and the stability of its episomal expression succeed, plasmid DNA may offer safety advantages over viral constructs.

Viral constructs have the advantage of increased efficiency of transfection because the recombinant virus will, in theory, infect 100% of the cells it hits, based on binding to cell receptors specific for each type of virus. The packaged viruses used for gene therapy are replication-defective, which means that they can only replicate in the presence of a helper virus or in cells engineered to express a missing crucial protein. Therefore, no new viral production is possible following injection. To deal with various concerns, more advanced viral vectors have been developed to express a minimum of viral proteins to reduce antigenicity (e.g., the "gutted" class of vectors seen with adenovirus and lentiviruses) or to include "self-destruct" sequences to prevent replication or recombination with viruses resident in the target tissue *(23)*.

The more widely employed viral vectors belong to either adenovirus (AdV) or adeno-associated viruses (AAVs) for nondividing cells in vivo or to retrovirus (RV) for ex vivo modification of tissues or cells to be re-injected into the patient. In the case of AdV, the recombinant cDNA is not integrated into the genome. The development of helper-dependent AdV (HD-AdV, "gutted"), in which all sequences coding for viral proteins have been removed except for the packaging signals, reduces immunogenicity and increases the duration and intensity of the recombinant protein expression *(24,25)*. The removal of virally expressed proteins is a critical safety factor. In 1999, an 18-year-old teenager died after being injected with a first-generation adenoviral vector for the treatment of ornithine transcarbamylase deficiency in a phase I clinical trial *(26)*. The adenoviral vector induced a massive immune reaction, leading to systemic organ failure. Addressing this type of safety issue, the modified HD-AdV should remove objections raised against the use of first-generation AdV *(24)*. The third-generation AdV may completely eliminate the risk of unforeseen immunoreactions. New purification procedures also will avoid any contamination with helper virus or factors that may allow replication of a recombinant virus *(27)*.

AAV is a novel vehicle for delivery of cDNA because if has a series of potential advantages *(28,29)*, including: (a) no immunogenicity; (b) nonpathogenicity; (c) long-term expression of the recombinant gene resulting from integration into the host genome; and (d) infectivity of both replicating and nonreplicating cells. However, its cloning capacity is smaller than AdV, and it is difficult to produce in the large amounts needed for clinical trials.

A series of vectors have been developed that include co-expression of green fluorescent protein for tracking expression and various cell-type-specific promoters *(30,31)*. Their ability to sustain long-term expression in skeletal and cardiac muscle and neural tissue was observed in mouse animal models for 1 to 2 yr *(29,32)*. The same result occurred with an AAV construct of insulin-like growth factor-1 administered directly to the skeletal muscle of adult mouse muscle, which was effective in preventing aging-associated sarcopenia over 6 mo *(33)*. Clinical trials with AAV have been progressing in the last few years with trials targeting Parkinson's disease, Canavan's disease (a pediatric leukodystrophy), Alzheimer's disease, and Batten's disease (a lysosomal storage disorder; ref. *34*).

Conversely to AdV and AAV, retroviral vectors (RV and lentivirus) are mainly restricted to anticancer approaches because they require actively dividing cells or to ex vivo therapies, in which cells or tissues are transfected efficiently in culture and then implanted into the live animal or patient *(35)*. Modification of cells ex vivo is a promising approach, because a patient's autologous cells can be harvested, genetically modified, cryo-stored, and

implanted when needed for gene therapy. These vectors have the advantage of long-term expression because of integration into the host genome, but the integration site is random, which has led to the activation of oncogenes in some patients *(36)*. Because of the safety concerns of these viruses, clinical trials have slowed, but several studies for treatment of diseases are being pursued, including human immunodeficiency virus, adenosine deaminase deficiency, familial cholesterolemia, and various antitumor therapies *(7,8,18,19)*.

The Journal of Gene Medicine Clinical Trial website (http://www.wiley.co.uk/genmed/clinical/) provides a comprehensive resource on clinical gene therapy trials and allows a search of the database by vector, gene, disease, investigator, country, and other features. According to a recent search, more than 900 trials are listed, of which 669 occurred in the United States *(37)*. The vast majority involves cancer, followed by monogenic diseases, infectious diseases, and gene marking. Vascular disease is represented by 85 trials using vascular endothelial growth factor (VEGF), fibroblast growth factor, inducible nitric oxide synthase (NOS), and others.

GENE THERAPY WITH NOS cDNA CONSTRUCTS FOR CONDITIONS OTHER THAN ED

NO is the main mediator of penile erection. One of the obvious targets for gene therapy of ED is to increase NO production in the penile corpora cavernosa by gene transfer of NOS cDNA constructs *(38–40)*. This enzyme is responsible for NO synthesis in a 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 concentration of cyclic guanosine monophosphate (cGMP). This causes a reduction of cytosolic Ca^{2+} and subsequent smooth muscle relaxation. Three NOS isoforms have been identified *(41–43)*: (a) the neuronal NOS (nNOS, or NOS I) found in the brain, nerves, and epithelial cells; (b) the endothelial NOS (eNOS, or NOS III) present in the endothelium and certain neurons; and (c) the macrophage or inducible NOS (iNOS, or NOS II) found in a wide variety of cells—mainly macrophages, smooth muscle cells, chondrocytes, and hepatocytes.

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 believed to be controlled exclusively at the level of enzyme activity. Conversely, 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 was named as such. Additionally, iNOS was assumed to be refractory to enzyme activity modulation. Most—if not all—of these concepts have now been revised because of current findings. All three NOS genes have alternative splicing, both nNOS and eNOS are also subject to transcriptional regulation under physiological and developmental conditions, and iNOS has increased expression during aging in the absence of exogenous inducers *(44–48)*. eNOS enzymatic activity has also recently been shown to be regulated by the Akt phosphorylation pathway *(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 *(40)*. 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. Therefore, the manipulation of NOS expression has been an objective of early and current gene therapy approaches aimed at correcting vascular conditions, transplant rejection, cancer, and wound healing in animal models. Clinical trials with NOS constructs have focused on the use of iNOS constructs to treat coronary artery stenosis *(37)*. These experimental studies are promising and very relevant to the approaches intended to overexpress NOS within the penis for the treatment of ED. Additionally, these studies are important to explain 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 for conditions other than ED is presented here.

Historically, the first successful attempt to employ NOS gene therapy was based on a construct of a bovine eNOS cDNA applied in a liposome/Sendai virus vehicle into the rat carotid artery. The artery was pretreated by balloon injury of the endothelium, and the neo-intimal vascular lesion was inhibited *(49)*. The general purpose of this and subsequent studies was to devise an antiproliferative strategy to avoid smooth muscle proliferation and intimal hyperplasia in restenosis after angioplasty *(50,51)*.

Because of the need to efficiently transfect cells regardless of their rate of proliferation, adenoviral vectors are the preferred delivery vehicles. Using this approach, researchers showed that human saphenous veins could be transduced in vitro, resulting in functional transgene expression with increased NO release and relaxation of the tissue rings *(52)*. Additionally, the usefulness of eNOS gene therapy of cerebral vasospasm following subarachnoid hemorrhage was shown to improve the impaired NO-mediated relaxation of rings of basilar arteries from dogs exposed to this condition *(53)*. A related possible therapeutic application was also evident from the efficacy of eNOS in vitro transfer to inhibit the contractions of radial artery conduits, suggesting that this strategy could prevent vasospasms in the implantation of arterial grafts *(54)*. Similarly, in vitro transduction of rat hearts with AdVeNOS has attenuated the complications of heart ischemia and neo-intimal formation *(55,56)*. Finally, eNOS has recently been transduced into endothelial progenitor cells and then seeded into carotid arteries subjected to balloon angioplasty *(57)*. Neo-intimal thickening was significantly reduced and thrombosis was eliminated, suggesting that a combination stem cell and gene therapy approach may perform well in future studies.

The protection exerted by eNOS in avoiding the development of allograft arteriosclerosis was also demonstrated with iNOS gene therapy when performed in eNOS knockout mice. This confirmed the role of iNOS in both suppressing neo-intimal smooth muscle cell accumulation and inhibiting adhesion of platelets and leukocytes to the endothelium *(56)*. iNOS gene transfer has been intensively studied for gene therapy for almost a decade. Billiar et al. showed that because tetrahydro-biopterin (BH4) is an essential factor for iNOS that is not synthesized in unstimulated vascular smooth muscle cells, there may be an obstacle to successful vascular iNOS gene therapy. They showed *(58)* that cotransfection with a construct of guanosine triphosphate 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 administered to rats receiving aortic allografts with strong genetic disparity completely suppressed the development of allograft atherosclerosis in both untreated recipients and recipients treated with cyclosporin *(59)*. The same group showed that the AdV iNOS completely reversed 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 *(60)*. RV constructs of iNOS have also been used to infect in vitro highly metastatic human renal carcinoma cells and to induce autotoxicity, suppression of tumorigenicity, and abrogation of the metastasic lesions *(61)*. Additionally, plasmid iNOS in sponges placed subcutaneously in male rats with cutaneous incisions succeeded in enhancing collagen synthesis during normal wound healing *(62)*. AdViNOS achieved 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 *(63)*. These and other uses of iNOS for vascular disease have recently been reviewed *(64)*.

Besides direct transfer of iNOS to target tissue in vivo, the ex vivo transfer of AdViNOS to organ isografts has been tested in the case of the liver *(65)* and vein grafts *(66)*. 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. AdViNOS was demonstrated to efficiently transduce vein segments ex vivo; when this is performed via cotransfection with GTPCH, the iNOS enzymatic activity is optimized, suggesting that this cotransfer technique may be used to engineer vein grafts before coronary artery bypass *(67,68)*. The nonviral delivery of iNOS cDNA in cationic liposomes for cardiovascular disease also has therapeutic relevance, as demonstrated by experiments in which rabbit smooth muscle cells were successfully transfected with high efficiency both in vitro and in vivo without inducing necrosis or apoptosis *(69)*. Several preclinical and clinical studies with iNOS cDNA constructs for the therapeutic prevention and treatment of restenosis have been initiated in recent years *(37,70)*.

In contrast to the other two NOS isoforms, nNOS gene therapy has not received as much attention, except for one study demonstrating that an AdV-nNOS vector inhibited smooth muscle cell hyperplasia resulting from pathological vascular remodeling in venous bypass grafts *(71)*. The lack of nNOS gene therapy is probably caused by the fact that nNOS is located predominantly in neuronal and epithelial cells; 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 *(72)*. These problems are addressed in the following section.

GENE THERAPY OF ED WITH NOS cDNA CONSTRUCTS

Within this context, the goal for gene therapy of organic impotence is to induce the ability to sustain physiologically elicited erections without resorting to pharmacological treatment immediately before the sexual act. This implies a stable biological correction of some facet of the impaired erectile mechanism; this could be defined as a medium- or long-term cure rather than a palliative intervention to ameliorate the underlying symptoms. Therefore, although the cDNA construct needs to be injected into the penis, the treatment is expected to last for weeks, months, or even years, depending on the vector, promoter, or 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 *(72–74)*, possibly combined with a putative increase in the response to, or the levels of, contractile factors. Therefore, the modulation of endogenous penile NO synthesis by gene therapy with NOS cDNA may achieve a more physiologically relevant effect with fewer side

effects than that caused by vaso-active drugs taken orally or injected into the corpora cavernosa. Based on what is known regarding the neural control of penile erection and the mechanism of NOS activation, NOS constructs would potentiate the neural dependence for eliciting an erectile response and would resemble the effects of oral phosphodiesterase inhibitors such as sildenafil (Viagra®; refs. *75* and *76*), with the exception that the correction would be long-term or even permanent.

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 *(77,78)* and even in the hypothalamic regions involved in the central control of penile erection *(79)*, PnNOS is a reasonable candidate for gene therapy of ED. Additionally, although the penile-specific activation occurs via 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, therefore, NO synthesis. This results from the assumption that the catalytic activity of this nNOS splice variant is regulated by factors acting on the 34-amino acid sequence absent in the brain type counterpart. Our laboratory utilized a third-generation HD-AdV, which is essentially nonimmunogenic because of the "gutting" of virtually all viral genes. Aged rats were injected with the HD-AdV–PnNOS construct into the corpora cavernosa and were then evaluated for erectile function based on the amount of intracavernosal pressure produced following electrical field stimulation of the cavernosal nerve *(80)*. This viral system showed expression of nNOS up to nearly 2 mo, especially when combined with electroporation (electrical pulses to the tissue that facilitates molecular uptake). The improvement essentially restored erectile function to levels observed in young animals. We are currently attempting to improve the system by increasing viral titers and optimizing electroporation parameters.

The role of eNOS in cavernosal relaxation is not entirely clear, but several lines of data support the role of eNOS in maintaining erections. eNOS is phosphorylated by the Akt signaling pathway, which can be activated by sheer stress. Therefore, once the penis is filled with blood, sheer stress on endothelial cells within the sinusoids activates continuous release of NO in addition to NO released from cavernosal neurons *(81)*. Additionally, it has recently been suggested that eNOS may play a role in cGMP homeostasis. eNOS knockout mice have low basal levels of cGMP but show overexpressed cGMP following prolonged sexual stimulation *(82)*. Additionally, the mice show signs of sporadic priapism. The theory is that under certain abnormal conditions, eNOS activity is low and phosphodiesterase-5A expression is compensatorily downregulated in response to understimulation of NO *(83)*. Therefore, prolonged neurostimulation would produce a localized cGMP "spike" that would lead to priapism. These results suggest that gene therapy vectors may require regulated control to prevent priapism. Several studies have shown that expression of eNOS from viral vectors can ameliorate ED in aging, diabetes, and other conditions (summarized in Table 1). All of these gene therapies involve expressing eNOS from a strong unregulated promoter for relatively short periods of time.

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 *(101)*. Paradoxically, it was not the cDNA for eNOS or nNOS that was selected but, rather, the cDNA for iNOS, which is not normally expressed in the body unless induced during inflammation or an immune response (however, *see* refs. *46–48*). The rationale was based on the availability of the recombinant variant cloned from rat penile smooth muscle cells induced with cytokines and the fact that the iNOS enzyme catalytic activity would be independent from factors

Table 1
Preclinical Gene Therapy Studies in Rat Animal Models

Gene	*Vector*	*Rat model system*	*Reference*
iNOS	Plasmid	Aging	*101*
iNOS	AAV	Normal	*84*
iNOS	Myoblasts	Normal	*84*
iNOS	Plasmid	Peyronie's disease plaque	*85*
nNOS	HD-AdV	Aging	*80*
eNOS	AdV	Aging	*86*
eNOS	AdV	Aging	*87*
eNOS	AdV	Diabetes	*88*
eNOS	AdV + sildenafil	Diabetes	*89*
eNOS	Adult stromal stem cells transduced with AdV	Aging	*90*
CGRP	AdV	Aging	*91*
Dominant-negative RhoA	AAV	Normal	*92*
SOD	AdV	Aging	*93*
BDNF	AAV	Neurogenic "nerve crush"	*94*
BDNF	AAV + VEGF	Neurogenic "nerve crush"	*95*
Maxi-K	Plasmid	Normal	*96*
Maxi-K	Plasmid	Aging	*97*
Maxi-K	Plasmid	Diabetes	*98*
Neurotrophin-3	Herpes simplex virus	Diabetes	*99*
VIP	Plasmid	Diabetes	*100*

iNOS, inducible nitric oxide synthase; eNOS, endothelial NOS; nNOS, neuronal NOS; AAV, adeno-associated virus; AdV, adenovirus; HD-AdV, helper-dependent AdV; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor; VIP, vaso-activity interstitial peptide.

controlling PnNOS and eNOS enzymes, such as Ca^{2+} or phosphorylation. The expression of recombinant iNOS then would allow for a potentiation of the nitrergic 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.

This study reported that treatment of rats with 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 cavernosa) improved aging-related ED. At 10 d after injection, the 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 who did not receive iNOS injection. The maximal intracavernosal pressure in the "old" rats even surpassed the 5-mo-old controls. No significant changes in mean arterial pressure occurred. The plasmid iNOS cDNA was detected in the penile DNA preparation by PCR, and iNOS overexpression was shown by real-time PCR and Western blot analysis. 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.

Interestingly, 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 *(102)*.

eNOS has also been shown to improve ED in the aged rat via administration into the corpora cavernosa of an AdVeNOS construct where the expression of the recombinant protein was driven by the CMV promoter *(86)*. As expected, eNOS gene transfer increased the expression of eNOS and the Ca^{2+}-dependent NOS activity in penile tissue as well as 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 observed in the earlier study with iNOS, but measurements were restricted to 1 d following 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 (*87*), the same group changed the adenoviral vector to prolong the time of expression. By using a β-galactosidase construct with the same vector, they demonstrated 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 again limited to a short period (5 d) after transfection.

As for iNOS, two studies using a plasmid and viral vector have succeeded in restoring erectile function *(84,101)*. An interesting use of AdV–iNOS involved the reported in vitro transduction of skeletal muscle myoblasts with the constructs and their subsequent implant into the corpora cavernosa of adult rats *(84)*. The authors claimed that their procedure was more efficient than direct plasmid or AdV injection into the penis in inducing a transient increase (1 wk) in the erectile response to EFS. It was later reported that myoblasts are lost rapidly, limiting the applicability of this approach. A similar approach applied to penile smooth muscle cells in vitro may be more successful in this respect, and it may actually be a logical paradigm because of the current interest in tissue and organ reconstruction *(103)*.

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 *(78,79)*. The recent cloning of PnNOS *(101)* has allowed 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 an auto-inhibitory element *(104)*, and speculatively, the auto-inhibitory sequence may provide better specificity to NOS activation during the erectile response compared with the brain type nNOS. PnNOSβ, a truncated spliced form of PnNOS, is also synthesized in the penis *(78)*. PnNOSβ lacks the ability to bind physiological modulators of nNOS catalytic activity (protein inhibitor of NOS [PIN], (carboxy-terminal PDZ ligand of nNOS [CAPON], and, possibly, the *N*-methyl-D-aspartate receptor *(105,106)*; 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 (*see* Table 1). One example is

the hSlo cDNA, which encodes for the α-subunit of the human smooth muscle maxi-K^+ channel *(107)*. The study first demonstrated that expression of reporter β-galactosidase triggered by a plasmid driven by the CMV promoter persisted for up to 75 d in the corpora cavernosa when transfected into the rat penis as naked DNA *(96)*. Intracorporeal injection of a similar vector encoding the hSlo cDNA (100 μg) increased intracavernosal pressure response to EFS in aged rats over their respective controls for at least 2 mo. This study shows that an overexpression of the maxi-K^+ channel in the cavernosal smooth muscle is an effective way to modulate intracellular Ca^{2+} levels and transmembrane Ca^{2+} flux in this tissue and, therefore, is an effective method for improving ED. This group has also demonstrated amelioration of ED in both aged *(97)* and diabetic rats *(98)*.

Expanding on the use of maxi-K^+ gene therapy, Melman et al. *(21,22)* has begun the first gene therapy trial for the treatment of ED. Following Food and Drug Administration approval, a phase I clinical trial was started in the spring of 2004 to evaluate the safety of a hSlo plasmid vector based on the same protocol shown to be efficacious in aging and diabetic ED-related animal studies. To date, the researchers have injected hSlo plasmid DNA into the corpora of three men at a single injection dosage of 500 μg and three additional men at a single injection dose of 1000 μg. A 5000-μg injection is also planned. Results have shown no detrimental side effects at either of the doses tested *(21,22)*. All the patients enrolled have moderate-to-severe ED. The purpose of the trial is to evaluate the safety profile of hSlo plasmid injection. If successful, a phase II trial will be initiated to establish the efficacy of the treatment using up to 400 patients. To date, none of the six men has shown an improvement in erectile function. Notably, the doses used in the phase I trial are the same range as in the rat studies, although the rat penis is considerably smaller than the average human penis. Based on a rough estimate that the erect human penis has a total volume at least 500 times that of the erect rat penis, it is likely that much higher doses, or perhaps repeated injections of the plasmid, may be needed for efficacious therapy.

Various other genes have been used to increase smooth muscle relaxation in the penis (*see* Table 1). Besides the NOS and maxi-K^+ applications, prepro-calcitonin gene-related peptide *(91)* and vaso-activity interstitial peptide *(100)* (both of which are vaso-active peptides) have been able to increase smooth muscle cell relaxation, facilitating erectile function in aging and diabetic animal models. Alternatively, attenuating contractile forces with the dominant-negative RhoA factor expressed from AAV have also shown promise *(92)*. Free radicals are known to oppose the action of NO and to stimulate fibrosis of the cavernosal tissue *(108)*. Hellstrom et al. *(93)* found that superoxide dismutase, a superoxide free-radical quencher, could improve erectile function.

Another approach *(109)* has been based on the possibility of using gene transfer to increase the expression of growth factors in the penis 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 be superior to at least the early generation AdV vectors because it reduces immunogenicity and prolongs expression. Additionally, AAV are neurotrophic, and this may be particularly useful for nerve regeneration interventions. In one study *(94)*, researchers showed histochemically that intracavernosous injection of the construct for brain-derived neurotrophic factor (AAV-BDNF) can prevent the degeneration of nNOS-containing neurons in the pelvic ganglia and stimulation of nerve regeneration in rats after bilateral cavernous nerve freezing or crushing. Consequently, the erectile response to EFS in the animals with neurogenic impotence, which were treated with AAV-BDNF, was notably increased after 4 wk and was particularly increased at 8 wk.

A recent report combined both AAV-BDNF vector with VEGF administration *(95)* to determine an improvement over each alone. Finally, the neutrophin-3 growth factor expressed from a herpes simplex virus vector was able to improve erectile function in a diabetic rat model *(99)*.

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 others extrapolatable from the advancement of gene therapy in general.

In the first category, in the case of NOS gene therapy, the selection of the NOS isoform cDNA initially may be based on studies in the rat similar to the ones presented earlier, 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 (i.e., electroporation, slow-release polymer matrixes, etc.). Different dosages and possible re-inoculations or methods of continuous infusion into the corpora cavernosa should be tested.

The isoform selected will 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 *(110)* should restrict expression to nerves and ganglia. 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 that determines the increase in NO synthesis, and this should occur only in the penis after 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 *(111)* may provide the necessary tissue specificity. Additionally, 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 siRNA, ribozyme, or antisense approaches *(112,113)* or on competing with their binding to PnNOS. The same considerations can be applied to the other genes discussed earlier, regarding selection of promoters, vectors, or cofactors. Any delivery procedure that can enhance the efficacy of plasmid vectors or decrease the required viral load will simplify the regulatory procedures. Therefore, the possibility of turning the expression of the transfected gene on and off at will may facilitate approval of protocols, because the treatment can be interrupted at the desired stage to avoid reaching a potentially excessive level of the recombinant protein. Novel vectors and transgenic mice are available in which the recombinant cDNA is placed under a promoter that is both active only in a given tissue and regulable by very low nonhazardous doses of a drug, such as doxycycline, ecdysone**,** or RU486 *(38)*.

If a regulable 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 may be activated only in a specific tissue when the drug is administered *(114)*. Suspension of the drug halts 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, then it would be possible to activate their expression separately or together, according to the drug used. It is hypothetically possible to combine temporal expression of oral treatments with cofactors or regulators of the respective enzyme activity so that the basal frame of the gene product is enhanced at will; then the

protein is activated in a more conventional way via direct modulation of a temporarily hyperexpressed product.

The advances in recombinant DNA technology and delivery procedures in the recent years have drastically changed the timing of gene therapy for ED. The first clinical trial is underway. More should follow once safety issues involving viral vectors are resolved. Therapies may one day target not only modulation of smooth muscle cell relaxation but may also impact the underlying pathophysiology of the cavernosal tissue. Repair or remodeling of tissue using a molecular approach should be possible in the foreseeable future.

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