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ORAL PHARMACOTHERAPY
FOR MALE SEXUAL DYSFUNCTION

A GUIDE TO CLINICAL MANAGEMENT

Edited by
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For the generation that reached sexual maturity in the 1960s, the “pill” became synonymous with sexual freedom and started a sexual revolution. For women it meant freedom from the fear of pregnancy, and for men enhanced sexual opportunity. The new era of the pill has nothing to do with fertility, but everything to do with sex. The first orally effective prescription drug for treating erectile dysfunction (ED) was marketed in 1998. Sildenafil (Viagra®) has rejuvenated the aging male veterans of the sexual revolution, forever changed the science of sexual medicine, and transformed society’s perspective on aging and sex. This class of drugs, known as oral phosphodiesterase inhibitors (PDE-type 5), is highly effective in the treatment of ED. Since its introduction there has been a much greater awareness of ED, its comorbidities, and its effects on the quality of life. In 1997, while preparing to address the Endocrine Society on the occasion of the 92nd American Urological Association meeting, I first looked at the preclinical studies of sildenafil. I thought “this will change everything” and it clearly has—changing practice patterns in sexual medicine, and the attitudes of patients, potential patients, and their partners. Two new PDE-type 5 inhibitors, tadalafil (Cialis®) and vardenafil (Levitra®), were first approved by the European Committee for Proprietary Medicinal Products and subsequently by the Food and Drug Administration in 2003 and 2004.

The new PDE-5 inhibitors have given health care providers a choice in prescribing therapy for ED, but it remains to be seen whether these or subsequent agents will provide the opportunity to treat more patients or, for that matter, to treat the same patients more effectively and safely. Pharmacological management of ED can now be given as a tablet, as a sublingual preparation, as an intraurethral pellet, as a topical gel, and as an injection. Current lines of study are looking at inhalation as a faster route of treatment delivery. These various drugs work through differing physiological mechanisms: amplifying penile blood flow elicited by sexual stimulation, enhancing neural signaling, and in some instances can even induce erection without sexual stimulation.

The 1970s saw the development of safe and effective surgery; the penile implant was a specific surgical solution addressing only one aspect of male sexual dysfunction. This compendium addresses each aspect of male sexual dysfunction: interest, performance, and orgasm. With the advent of oral
medications, the burden of first evaluation has fallen on the primary care provider. *Oral Pharmacotherapy for Male Sexual Dysfunction* is written for the urologists, family physicians, internists, and residents-in-training who need to be familiar with the diagnostic approaches to male sexual dysfunction and pharmacological strategies for its safe and effective management.

*Oral Pharmacotherapy for Male Sexual Dysfunction* begins with a review of penile anatomy, physiology, and pharmacology written by Dr. Tom Lue, who first described the hemodynamics of erection, and inspired me some 20 years ago to take up this subspecialty. Dr. John Mulhall of Cornell University addresses common medical risk factors for ED, and the controversial issue of whether lower urinary tract symptoms independent of aging are causally linked to ED? Dr. Irwin Bischoff has devoted a lifetime of effort to pharmaceutical research, and I am grateful that prior to his retirement he accepted this task of summarizing the pharmacology and development of PDE-type 5 inhibitors. Dr. Harin Padma-Nathan has a unique practice devoted to clinical trials, and shares his insights on the preclinical data and five years postmarketing data on sildenafil. Dr. Culley Carson of the Department of Urology at the University of North Carolina has been extensively involved with the design and conduct of US clinical trials of tadalafil. Dr. Ajay Nehra, a consultant for Mayo Clinic, independently reviews the preclinical data on vardenafil. Dr. Louis Kuritzky from the Department of Family Medicine University of Florida, is a lecturer, teacher, and advocate of sexual health in the primary care setting. Dr. Ira Sharlip is a practicing urologist in San Francisco and past president of the Sexual Medicine Society of North America; he addresses who should be referred to a urologist and shares his strategy on how to evaluate and manage men who have atypical presentations that require focused testing. Dr. Robert Kloner of the Keck School of Medicine at the University of Southern California describes how to assess the risk of sexual function in the cardiac patient and just how safe PDE inhibitors are for these men. Dr. Vivian Fonseca of Tulane University tackles the complex pathophysiology of diabetic ED and reviews treatment outcomes in this difficult patient group. Dr. Raymond Rosen, author of a widely used research instrument, the International Index of Erectile Function, specifically looks at the epidemiology of depression and ED, and reviews the mechanisms of antidepressant-associated ED. Dr. Wayne Hellstrom of Tulane University reviews the literature on intracavernous, transurethral therapies, and on topical therapies. Dr. Hellstrom further provides a strategy for using combinations of drugs in refractory patients. Drs. Alvaro Morales, Jeremy Heaton, and Michael Adams of Queens University, Ontario, Canada
together review the impact of androgen deficiencies, the neural regulation of erection, and neuropharmacological therapies for ED. I have asked Dr. Ronald Lewis, of the Division of Urology at the Medical College of Georgia to write the only chapter on vacuum erection devices and surgical implants; despite the abundance of drugs for ED, every clinician should be familiar with these options and outcomes. Every day in my practice I am confronted by patients who self-medicate with dietary supplements; every clinician will appreciate Dr. Mark Moyad’s review of this topic and for addressing lifestyle changes in the management of male sexual health. No one in the United States can match the clinical experience of my Australian colleague Dr. Chris McMahon; he reviews the topic of rapid ejaculation and the emerging pharmaceutical therapies for its management. Dr. Andrew McCullough of New York University reviews the literature on prostatectomy; he shares his prospective series on these patients giving us an idea of the pathophysiology, natural rates of recovery, and medical management of post-prostatectomy ED. The last chapter is written by Dr. Ridwan Shabsigh of Columbia University. Female sexual dysfunction (FSD) is emerging as a new subspecialty. I have challenged Dr. Shabsigh to share what is currently known about the types of FSD and its epidemiology, pathophysiology, and current treatments.

I am indebted to all the authors for the year they have spent compiling these reviews and I know the readers will learn much from their various treatment strategies for male sexual dysfunction.

Gregory A. Broderick, MD
# Contents

Preface ........................................................................................................ v
Contributors ................................................................................................ xi

1 Physiology and Pharmacology of Erectile Dysfunction ...................... 1
   Rafael Carrion, Derek Bochinski, Nadeem Rahman, and Tom F. Lue

2 Epidemiology of Erectile Dysfunction ................................................. 25
   Jonathan D. Schiff and John P. Mulhall

3 Pharmacology of Phosphodiesterase Inhibitors .................................... 43
   Erwin Bischoff

4 Sildenafil Citrate, the Classical PDE5 Inhibitor: A Five-Year Review of its Efficacy and Safety in the Arena of Erectile Dysfunction .......... 65
   Harin Padma-Nathan

5 Tadalafil: Clinical Trials Experience .................................................... 85
   Culley C. Carson, III

6 Vardenafil: Clinical Trials Experience ............................................... 109
   Ajay Nehra

7 Erectile Dysfunction Assessment and Management in Primary Care Practice .............................................................................. 149
   Louis Kuritzky and Martin Miner

8 When to Refer the Patient With Erectile Dysfunction to a Specialist ....................................................................................... 185
   Ira D. Sharlip

9 Erectile Dysfunction: Assessing Risk and Managing the Cardiac Patient ............................................................................................. 199
   Thorsten Reffelmann and Robert A. Kloner

10 Is Diabetic Erectile Dysfunction More Difficult to Treat? ................. 221
    Pierre Theuma and Vivian A. Fonseca

11 Depression and Antidepressant-Associated Erectile Dysfunction ....... 237
    Raymond C. Rosen

    Hans-Martin A. Fritsche, Mustafa F. Usta, and Wayne J. G. Hellstrom
13 Androgen Deficiency of the Aging Male: *Enhancing Erectile Response to Oral Pharmacotherapy* ................................................... 279
   *Alvaro Morales and Jeremy P. W. Heaton*

14 Central Activation of Erection and Clinical Experience ................. 301
   *Jeremy P. W. Heaton, Alvaro Morales, and Michael A. Adams*

15 Sustaining the Cure: *Oral Pharmacotherapy Failures Salvage With Vacuum Devices and Penile Implants* ........................................ 323
   *Ronald W. Lewis*

16 Prevention and Treatment of Erectile Dysfunction Utilizing Lifestyle Changes and Dietary Supplements: *What Works and What is Worthless?* .................................................. 339
   *Mark A. Moyad*

17 Pharmacological Strategies in the Management of Rapid Ejaculation ... 379
   *Chris G. McMahon*

18 Sexual Dysfunction After Radical Prostatectomy and the Use of PDE-5 Inhibitors ................................................................. 409
   *Andrew McCullough*

19 Female Sexual Dysfunction: *Is There a Magic Pill?* ......................... 423
   *Ridwan Shabsigh, Anne R. Davis, Aristotelis G. Anastasiadis, Nawras Makhsida, and Grace Yan*

Index ....................................................................................................... 445
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INTRODUCTION

Erectile dysfunction affects a significant proportion of the male population, making it a common urological disorder. It is defined as the inability to obtain or maintain an erection that is sufficient for satisfactory sexual intercourse. Many factors contribute to erectile physiology and pathophysiology. Much of the current understanding of erectile physiology was acquired in the 1980s and 1990s. In addition to the role of smooth muscle in regulating arterial and venous flow, the three-dimensional structure of the tunica albuginea and its role in venous occlusion have been elucidated. Pivotal research identified the importance of nitric oxide (NO), which is the major neurotransmitter for penile tumescence, and its counterpart, the phosphodiesterases (PDEs), which return the penis to a flaccid state. Subsequent studies have shown an important distinction between neurogenic- and endothelial-generated NO, in that the latter essentially helps in maintaining penile erection. Moreover, the role of endothelium in regulating smooth muscle tone and the intercellular link by means of gap junctions have also been uncovered. More recently, research has shown that changes to the
downstream signaling pathways (RhoA/Rho-kinase pathway) may be of physiological importance in regulating cavernosal smooth muscle tone. In the pathophysiology of erectile dysfunction, the changes in the smooth muscle, endothelium, and fibroelastic framework with hypertension, diabetes, atherosclerosis, and aging have also been identified. The anatomy and physiology of erectile function are discussed in detail in this chapter (1).

ANATOMY OF THE PENIS

The penis is composed of three cylindrical structures: the paired corpora cavernosa and the corpus spongiosum. The urethra traverses the corpus spongiosum. A cross-section of the midpenis depicts the relationship between the various anatomical elements (Fig. 1) (2).

The flaccid length of the penis is controlled by the contractile state of the erectile smooth muscle and varies considerably. Studies have shown that neither age nor the size of the flaccid penis accurately predicts erectile length and that 15% of men have a downward curve during erection (3,4). Regarding penile morphology and erection, a study shows that during erection, the penile buckling forces are dependent not only on intracavernosal pressures but also on penile geometry and erectile tissue properties. Therefore, patients can have inadequate penile rigidity despite having normal penile hemodynamics (5–7).

Tunica Albuginea

The tunica affords great flexibility, rigidity, and tissue strength to the penis (8). The tunical covering of the corpora cavernosa is a bilayered structure with multiple sublayers and is predominantly collagenous. The inner circular layer contains the corpora cavernosa. Radiating from this inner layer are intracavernosal pillars acting as struts, providing essential support to the erectile tissue. Outer-layer bundles are oriented longitudinally, extending from the glans penis to the proximal crura. The corpus spongiosum lacks an outer layer or intracorporeal struts, ensuring a low-pressure structure during erection (Fig. 2) (1,2,9).

The tunica is composed of elastic fibers that form an irregular, latticed network on which the collagen fibers rest. The detailed histological composition of the tunica is dynamic, changing with specific anatomical locations. Emissary veins run between the inner and the outer layers for a short distance, often piercing the outer bundles in an oblique manner. The cavernous artery and the communicating arteries between the cavernous and the dorsal artery (both from the common penile artery) take a more direct route and are surrounded by a periarterial soft tissue sheath. The latter structure helps protect the arteries from occlusion by the tunica albuginea during penile tumescence (10).
Fig. 1. Cross-section of the penis demonstrating relationships between penile layers and various components.
The outer tunical layer appears to play an additional role in compression of the emissary veins during erection. This important layer essentially determines tunical thickness and strength (8). Studies have shown that the tunica is thickest at the 11- and 1-o’clock positions and thinnest at the 5- and 7-o’clock positions. This results in different corresponding measured stresses on the tunica.

The strength and thickness of the tunica correlate in a statistically significant fashion with location. Predictably, the most vulnerable area is
located on the ventral groove (between the 5- and the 7-o’clock positions), which lacks the longitudinally directed outer-layer bundles discussed earlier. This fact is important because most of the prosthetic extrusions occur here \((8,10)\).

**Corpora Cavernosa, Corpus Spongiosum, and Glans Penis**

As stated earlier, the corpora cavernosa comprise two spongy, paired cylinders contained in the thick envelope of the tunica albuginea. Their proximal ends—the crura—originate at the undersurface of the puboischiyal rami as two separate structures but merge under the pubic arch and remain attached up to the glans. The septum between the two corpora cavernosa are typically incomplete but may be functionally complete in some congenital anomalies, such as in epispadias.

The corpora cavernosa are supported by a fibrous skeleton that includes the tunica albuginea, the septum, the intracavernous pillars, the intracavernous fibrous framework, and the periarterial and perineural fibrous sheath \((8,11)\). Some studies have hypothesized that the intracavernous framework adds significant strength to the tunica albuginea \((12)\). Within the tunica are the interconnected sinusoids, which are separated by smooth muscle trabeculae surrounded by elastic fibers, collagen, and loose areolar tissue. The terminal cavernous nerves and helicine arteries are intimately associated with the smooth muscle. Each corpus cavernosum is a conglomeration of sinusoids, larger in the center and smaller in the periphery. In the flaccid state, the blood slowly diffuses from the central to the peripheral sinusoids, and the blood gas levels are similar to those of venous blood. During erection, the rapid entry of arterial blood to both the central and the peripheral sinusoids changes the intracavernous blood gas levels to those of arterial blood. The structure of the corpus spongiosum and the glans is similar to that of the corpora cavernosa, except that the sinusoids are larger. Moreover, as previously discussed, the tunica is thinner in the corporus spongiosum and absent in the glans.

**Arterial Supply**

The main source of blood supply to the penis typically arises from the internal pudendal artery, which travels through Alcock canal, becomes the common penile artery, and then gives its branches to supply the penis (Fig. 3).

In addition to this rich vascular supply, accessory arteries can exist. These can arise from the external iliac, obturator, vesical, or femoral arteries. Clinically, this becomes important because the accessory blood supply may become the dominant or only arterial supply to the corpus cavernosum \((13)\). Damage to these accessory arteries during radical prostatectomy or
cystectomy may result in vasculogenic erectile dysfunction (ED) after surgery (14,15). The three terminal branches of the penile artery are the dorsal, the bulbourethral, and the cavernous arteries. The bulbourethral artery enters proximally to supply the urethra, corpus spongiosum, and glans. The cavernosal artery pierces the corporal body in the penile hilum and subsequently gives off straight and helicine arteries that supply the cavernous sinuses. These helicine arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection (16). The dorsal artery courses the dorsal surface of the corpora cavernosa in between the dorsal nerve and vein, and as it travels to the glans it branches to the cavernosum, spongiosum, and urethra. Distally, these three arterial branches join to form a vascular ring near the glans.

**Venous Drainage**

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. Once outside the tunica albuginea, the venous drainage follows one of three patterns:

1. The skin and subcutaneous tissue: Multiple superficial veins 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.

2. The pendulous penis: The emissary veins from the corpus cavernosum and spongiosum drain dorsally to the deep dorsal vein, laterally to the circumflex vein, and ventrally to the periurethral vein. 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. This venous pathway runs upward behind the symphysis pubis to join the periprostatic venous plexus.

3. The infrapubic penis: Emissary veins draining the proximal corpora cavernosa join to form cavernous and crural veins. These veins join the periurethral veins from the urethral bulb to form the internal pudendal veins.

**Fig. 3.** (opposite page) (A) Schematic showing the longitudinal view of the penile arterial supply. (B) Transverse section of the penis from a human male specimen at 36 wk of gestation, stained with hematoxylin and eosin. (Courtesy of Dr. Antonio E. P. de Souza, Jr., and Laurence S. Baskin, University of California at San Francisco, Children’s Medical Center.) (C) Magnification of the penile dorsal area showing the various neurovascular structures. DA, dorsal artery; DV, dorsal vein, NB, nerve bundle.
The veins of the three systems communicate variably with each other. Variations in the number, distribution, and termination of the venous systems are common (1,17).

**Nerve Supply of the Penis**

The penis is innervated by both the autonomic and somatic nervous systems. Somatic innervation is derived from the S2 to S4 sacral nerve roots and travels via the pudendal nerve. These paired nerves supply the pelvis, perineum, and penis. They terminate as the dorsal nerve of the penis.

The somatosensory pathway originates at the sensory receptors in the penile skin, glans, and urethra and within the corpus cavernosum. The nerve fibers from the receptors converge to form bundles of the dorsal nerve of the penis, which joins other nerves to become the pudendal nerve. The latter enters the spinal cord via the S2 to S4 roots to terminate on spinal neurons and interneurons in the central gray region of the lumbosacral segment (18). Activation of these sensory neurons sends messages of pain, temperature, and touch by means of spinothalamic and spinoreticular pathways to the thalamus and sensory cortex for sensory perception. The dorsal nerve of the penis was previously regarded as a purely somatic nerve; however, nerve bundles testing positive for nitric oxide synthase (NOS), which is autonomic in origin, have been demonstrated (19,20). Thus, the dorsal nerve is a mixed nerve with both somatic and autonomic components, which enable it to regulate both erectile and ejaculatory function.

Onuf’s nucleus in the S2 to S4 spinal segments is the center of somatomotor penile innervation. These nerves travel in the sacral nerves to the pudendal nerve to innervate the ischiocavernosus and bulbocavernosus muscles. Contraction of the ischiocavernosus muscles produces the rigid-erection phase. Rhythmic contraction of the bulbocavernosus muscle is necessary for ejaculation.

Studies in animals have identified the medial preoptic area (MPOA) and the paraventricular nucleus of the hypothalamus and hippocampus as important integration centers for sexual function and penile erection (21). Electrostimulation of this area induces erection, and lesions at this site limit copulation. Efferent pathways from the MPOA enter the medial forebrain bundle and the midbrain tegmental region (near the substantia nigra). Pathological processes in these regions, such as Parkinson’s disease or cerebrovascular accidents, are often associated with ED.

In the autonomic nervous system, the preganglionic parasympathetic fibers also arise from S2 to S4, then travel to the pelvic plexis (joined with the hypogastric nerves), where they become pelvic nerves and subsequently form three to six trunks that lie deep to the parietal pelvic fascia and cover the piriformis muscle. The sympathetic nerves arise from the
segments T10–L2. They synapse at the sympathetic chain ganglia and then pass along the lumbar splanchnic nerves, superior hypogastric plexus, and finally caudally to the pelvic plexus. Here they intermingle with the parasympathetic fibers. The pelvic plexus innervates the prostate, seminal vesicles, bladder, and rectum. Caudally, fibers from the plexus give rise to the cavernous nerves, which traverse the posterolateral aspect of the prostate to finally supply the corpora cavernosa, corpus spongiosum, and penile urethra (2,17,22,23). Finally, the interactions of the autonomic nervous system, coupled with the mediating transmitters, play an integral role in the contraction and relaxation physiology of the cavernous smooth muscle cell (Fig. 4).
Stimulation of the parasympathetic nerves induces penile tumescence, and stimulation of the sympathetic fibers results in detumescence. Moreover, studies have shown that even with pathological processes that knock off the reflex erectile response (sacral parasympathetic centers), erection can be obtained with stimulation of the MPOA or thoracolumbar sympathetic pathways (24,25). Because the number of synapses between the thoracolumbar outflow and the postganglionic parasympathetic and somatic neurons is less than the sacral outflow, the resulting erection will not be as strong. Hence, many patients with sacral spinal cord injury retain psychogenic erectile ability even though reflexogenic erection is abolished. These cerebrally elicited erections are found more frequently in patients with lower motor neuron lesions below T12 (26). No psychogenic erection occurs in patients with lesions above T9 (27).

In general, there are three types of erections: psychogenic, reflexogenic, and nocturnal. *Psychogenic erection* is a result of audiovisual stimuli or fantasy. Impulses from the brain modulate the spinal erection centers (T11–L2 and S2–S4) to activate the erectile process. *Reflexogenic erection* is produced by tactile stimulation of the genital organs. The impulses reach the spinal erection centers; some then follow the ascending tract, resulting in sensory perception, whereas others activate the autonomic nuclei to send messages through the cavernous nerves to the penis to induce erection. This type of erection is preserved in patients with upper spinal cord injury. *Nocturnal erection* occurs mostly during rapid-eye-movement (REM) sleep. Positron emission tomographic scanning of humans in REM sleep shows increased activity in the pontine area, the amygdalae, and the anterior cingulate gyrus, but decreased activity in the prefrontal and parietal cortices. The mechanism that triggers REM sleep is located in the pontine reticular formation. During REM sleep, the cholinergic neurons in the lateral pontine tegmentum are activated, whereas the adrenergic neurons in the locus caeruleus and the serotonergic neurons in the midbrain raphe are silent. This differential activation may be responsible for the nocturnal erections during REM sleep.

**PHYSIOLOGY OF NORMAL ERECTION AND DETUMESCENCE**

Penile tumescence results from an interplay of neurogenic, vascular, psychogenic, and hormonal factors (16,28–31). The penile erectile tissue, specifically the cavernous smooth musculature and the smooth muscles of the arteriolar and arterial walls, plays a key role in the erectile process. The phases of penile erection are as follows:

1. Flaccid phase—minimal arterial inflow and venous outflow.
2. Latent phase—stimulation causes initial increase in arterial flow secondary to increased parasympathetic tone.
3. Tumescence phase—penile elongation and expansion. Incoming blood is trapped in the expanding sinusoids because of the compression of the subtunical venular plexus (between the tunica albuginea and peripheral sinusoids).
4. Full erection phase—complete penile expansion, arterial inflow decreasing, venous outflow minimal.
5. Rigid erection phase—ischiocavernosus muscle contraction with further increase in intracavernosal pressure.
6. Detumescence phase—increased venous outflow and decreased arterial inflow (32,33).

Without any stimulation, the penis remains in a flaccid state, where the cavernosal smooth muscles are tonically contracted, allowing only a small amount of arterial inflow for nutritional purposes.

During an erection, the smooth muscle cells of the corpora cavernosa relax and the arterial flow increases; however, the pressure in the corpus spongiosum and glans is only one-third to one-half that in the corpora cavernosa because the tunical covering (thin over the corpus spongiosum and virtually absent over the glans) ensures minimal venous occlusion. During the full-erection phase, partial compression of the deep dorsal and circumflex veins between Buck’s fascia and the engorged corpora cavernosa contribute to glanular tumescence, although the spongiosum and glans essentially function as a large arteriovenous shunt during this phase. In the rigid-erection phase, the ischiocavernosus and bulbocavernosus muscles forcefully compress the spongiosum and penile veins, which results in further engorgement and increased pressure in the glans and spongiosum. Ejaculation is facilitated by rhythmic contractions of the bulbocavernosus muscles. Finally, withdrawal of the sexual stimulation results in return of baseline tone and degradation of cyclic guanosine monophosphate (GMP) by PDEs within the trabecular smooth muscle.

**NEUROTRANSMITTERS**

The sympathetic nervous system with its adrenergic impulses plays an active role during the state of penile detumescence. \( \alpha \)-adrenergic nerve fibers and receptors have been demonstrated in the cavernous trabeculae and surrounding the cavernous arteries, and norepinephrine has generally been accepted as the principal neurotransmitter in the control of penile flaccidity and detumescence (34,35). \( \alpha \)-Adrenoceptors outnumber \( \beta \)-adrenoceptors 10 to 1 (36); it is suggested that sympathetic contraction is mediated by activation of postsynaptic \( \alpha_{1a}^- \), \( \alpha_{1b}^- \), and \( \alpha_{1c}^- \)-adrenergic receptors (37,38) and modulated by presynaptic \( \alpha_2^- \)-adrenergic receptors (39).
Endothelin, a potent vasoconstrictor produced by the endothelial cells, has also been suggested to be a neurotransmitter for detumescence (40,41). In addition, other vasoconstrictors, such as thromboxane A<sub>2</sub>, prostaglandin F<sub>2α</sub>, leukotrienes, and angiotensin II, have been proposed (42–44).

In summary, the maintenance of the intracorporeal smooth muscle in a semicontracted (flaccid) state probably results from three factors: intrinsic myogenic activity, adrenergic neurotransmission, and endothelium-derived contracting factors, such as prostaglandin F<sub>2α</sub> and endothelins (45).

On the other hand, detumescence after erection may be a result of cessation of NO release, the breakdown of second messengers by PDEs, or sympathetic discharge during ejaculation. Acetylcholine has been shown to be released with electrical field stimulation of human erectile tissue (46). Although acetylcholine is not the predominant neurotransmitter, it does contribute indirectly to penile erection by the presynaptic inhibition of adrenergic neurons and stimulation of the release of NO from endothelial cells (47).

Most researchers still agree that NO released from nonadrenergic/noncholinergic (NANC) neurotransmission and from the endothelium is the principal neurotransmitter mediating penile erection. NO increases the production of cGMP, which in turn relaxes the cavernous smooth muscle (48–57).

NO was first described in 1979 as a potent relaxant of peripheral vascular smooth muscle, with an action mediated by cGMP (58). Subsequently, endothelium-derived relaxing factor was identified as NO or a chemically unstable nitroso precursor (59,60). NO is synthesized from endogenous L-arginine by NOS, which can be inhibited by N-substituted analogues of L-arginine. NO is inactivated by hemoglobin.

In the penis, the NO that is released from nerve endings or endothelial cells diffuses into smooth muscle cells, where it activates soluble guanylyl cyclase, producing cGMP. The exact mechanism by which intracellular cGMP promotes smooth muscle relaxation has not been defined. The most likely mechanism is the activation of cGMP-specific protein kinase, resulting in the phosphorylation and inactivation of myosin light-chain kinase, thereby causing dissociation of myosin and actin and smooth muscle relaxation (61). Both cGMP and cGMP-specific protein kinase may also activate potassium channels, causing hyperpolarization and closure of voltage-dependent calcium channels and a decrease in the level of intracellular calcium. Independent of cGMP, a study also demonstrated that NO may stimulate the opening of Na-K-ATPase and thus cause hyper-polarization (62). A considerable number of studies suggest that cGMP is a more potent relaxant of smooth muscle than cyclic adenosine monophosphate (cAMP). The increased levels of cGMP in response to neurotransmitters
are caused by activation of soluble or particulate forms of guanylyl cyclase in the cell. A study of cGMP-dependent protein kinase I-deficient mice clearly shows that cGMP/cGMP–protein kinase I is the main physiological signaling pathway for penile erection and cannot be substituted by the cAMP-signaling pathway (63).

Other investigators believe that vasoactive intestinal polypeptide (VIP) may be one of the neurotransmitters responsible for erection. VIP-induced relaxation is reportedly inhibited by the NO synthesis blocker N-α-nitro-L-arginine, which has led some researchers to suggest that NO generation is involved in VIP-stimulated smooth muscle relaxation (64).

In a colocalization study, acetylcholine, VIP, and neuronal NOS appear to be colocalized in parasympathetic neurons (65). Thus, they may act synergistically to induce erection through inhibition of α₁ activity by acetylcholine and release of NO by VIP (66).

Acetylcholine, by acting on the presynaptic receptors on adrenergic neurons, has been shown to modulate the release of norepinephrine (39). The release of norepinephrine can also be inhibited by prostaglandin E₁ (67). Conversely, adrenergic neurons, through prejunctional α₂ receptors, can also regulate the release of NO.

A number of factors have been reported to increase both NOS activity and NO release. These include molecular oxygen, androgen, chronic administration of L-arginine, and repeated intracavernous injection of prostaglandin E₁ (68–70). Conversely, decreased NOS activity has been associated with castration, denervation, hypercholesterolemia, and diabetes mellitus.

For adequate penile tumescence, sinusoidal relaxation, arterial dilatation, and venous compression are required (1,16). The importance of smooth muscle relaxation has been demonstrated in animal and human studies (47,51,54,71). There are a variety of relaxant factors, some of which were already discussed, involved in smooth muscle relaxation, and the balance between these and the contractant factors is what predicts the functional state of the penis (Table 1).

As stated earlier, the relaxation of the corpora cavernosa is mediated by increasing levels of either cGMP or cAMP. These important second messengers activate corresponding protein kinases and result in the phosphorylation of certain proteins and ion channels. This event then leads to the opening of the potassium channels (hyperpolarization), sequestration of intracellular calcium by the endoplasmic reticulum, and inhibition of voltage-dependant calcium channels (which block calcium influx). Myosin is subsequently dephosphorylated and detaches from the actin filament, and the muscle relaxes. In smooth muscle contraction, the flux in free Ca²⁺ increases in the cytosole. This calcium will bind to calmodulin and activate
it. The latter catalyzes the phosphorylation of myosin light chains and subsequently triggers the development of force. The intricate molecular mechanisms involved in penile smooth muscle contraction and relaxation are summarized in detail in Figs. 4 and 5\(^\text{(1,16,45,51,54,72–77)}\).

Recently, attention has been brought to studying the effects of the RhoA/Rho-kinase signaling pathway and its role in penile smooth muscle physiology. This is a calcium-sensitizing pathway that is activated through agonist activation of heterotrimeric G protein-coupled receptors, activation of RhoA through the exchange of guanosine triphosphate for guanosine diphosphate, and dissociation from a guanine nucleotide dissociation inhibitor. This activated RhoA then activates Rho-kinase, which inhibits myosin light-chain phosphatase. This results in a net increase in myosin phosphorylation and the promotion of cellular contraction (Fig. 6)\(^\text{(74,78,79)}\).

Studies are now showing that antagonism of Rho-kinase may stimulate penile tumescence and hence provide an alternative approach to the management of erectile dysfunction\(^\text{(80,81)}\).

PDE

During the return to the flaccid state, cGMP is hydrolyzed to GMP by the highly specific cGMP-binding PDE type 5 (PDE5). The PDE super-

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**Table 1**

Factors Involved in Mediating Relaxation and Contraction of Penile Smooth Muscle

<table>
<thead>
<tr>
<th>Contraction</th>
<th>Noradrenaline(^b)</th>
<th>Endothelin-1(^b)</th>
<th>Neuropeptide Y</th>
<th>Prostanoids</th>
<th>Angiotensin II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relaxation</td>
<td>Acetylcholine(^b)</td>
<td>Nitric oxide(^b)</td>
<td>Vasoactive intestinal polypeptide</td>
<td>Pituitary adenyl cyclase-activation peptide</td>
<td>Calcitonin gene-related peptide</td>
</tr>
</tbody>
</table>

\(^a\)This list shows the various factors involved in mediating the degree of relaxation and contraction of the smooth muscle in the penis.

\(^b\)These factors have major implications in modulating penile erectile tissues.
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**Fig. 5.** The molecular mechanism of penile smooth muscle relaxation. The intracellular second messengers mediating smooth muscle relaxation, cyclic adenosine monophosphate and cyclic guanine monophosphate (cGMP), activate their specific kinases, which phosphorylate certain proteins to cause opening of potassium channels, closing of calcium channels, and sequestration of intracellular calcium by the endoplasmic reticulum. The resultant fall in intracellular calcium level leads to smooth muscle relaxation. Sildenafil inhibits the action of phosphodiesterase (PDE) type 5 and thus increases the intracellular concentration of cGMP. Papaverine is a nonspecific PDE inhibitor. ATP, adenosine triphosphate; eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate. (From ref. 72. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)
family comprises 11 families of proteins that are encoded by at least 17 genes \((82–84)\). The N-terminal portion contains regulatory domains that 2-, 3, and 4 are also found in the corpus cavernosum, they do not appear to play a significant role in physiological erections when compared with PDE5 \((85)\). The significance and the possible interactions of the PDEs in the penis have yet to be determined, however.

In addition to corpus cavernosum, where three isoforms of PDE5 have been cloned, many other tissues have been reported to express PDE5, including platelet, lungs, cerebellum, spinal cord, skeletal muscle, heart, placenta, pancreas, intestine, aorta, and adrenal gland \((73,86)\). Although one might expect the PDE5 inhibitor sildenafil to have wide-ranging side effects, in clinical trials these have appeared to be limited to the retina (from inhibition of PDE6) and the cardiovascular and gastrointestinal systems (e.g., blurred vision, headache, facial flushing, and indigestion) \((87)\).

**Central Neurotransmitters and Neural Hormones**

A variety of central neurotransmitters (dopamine, norepinephrine, 5-hydroxytryptamine [5-HT], and oxytocin) and neural hormones (oxytocin,
prolactin) have been implicated in the regulation of sexual function. It is suggested that dopaminergic and adrenergic receptors may promote sexual function and that 5-HT receptors inhibit it (88). Moreover, other substances and hormones, such as endorphins, oxytocin, vasopressin, adrenocorticotropic hormone, and prolactin, also likely participate in the coordinated process of penile tumescence.

**Dopamine**

There are many dopaminergic systems in the brain with ultrashort, intermediate, and long axons. The cell bodies are located in the ventral tegmentum, substantia nigra, and hypothalamus, one of which—the tuberoinfundibular system—secretes the dopamine into the portal hypophysial vessels to inhibit prolactin secretion. The autonomic and somatic nuclei of the lumbosacral spinal cord are innervated by dopaminergic neurons traveling from the caudal hypothalamus; thus, they potentially participate in the regulation of spinal penile reflexes. There are two main types of receptors associated with erectile function: D1 and D2. D1 receptors predominate in the MPOA (erectile responses), and D2 receptors predominate in the paraventricular nucleus (erections). In men, apomorphine, which stimulates both D1 and D2 receptors, induces penile erection that is unaccompanied by sexual arousal (89). The erectile response induced by injection of apomorphine into the paraventricular area can be blocked by both dopamine receptor blockers and blockers of oxytocin receptors (90). Moreover, NO might be involved as well, because apomorphine given subcutaneously can increase the levels of NOS and NO production in the paraventricular nucleus. Injection of oxytocin into the paraventricular area also induces erection, but this cannot be blocked by dopamine receptor blockers. These findings suggest that dopaminergic neurons activate oxytocinergic neurons in the paraventricular area and that the release of oxytocin produces erection (91). Expectantly, dopamine agonists (apomorphine and pergolide) and dopamine uptake inhibitors (nomifensine and buproprion) have been reported to enhance sexual drive in patients (92).

**Serotonin**

5-HT-containing neurons have their cell bodies in the midline raphe nuclei of the brainstem and project to a portion of the hypothalamus, the limbic system, the neocortex, and the spinal cord (93). Currently, 5-HT receptors 1–7 have been cloned and characterized. General pharmacological data indicate that 5-HT pathways inhibit copulation but may be facilitatory depending on the action of the amine at different 5-HT receptors in the central nervous system. Studies have summarized the results of the administration of selective agonists and antagonists as follows: 5-HT-1A receptor agonists inhibit erectile activity but facilitate ejaculation; stimu-
lation of 5-HT-2C and 5-HT-1C receptors causes erection; 5-HT-2 agonists inhibit erection but facilitate seminal emission and ejaculation (45). 5-HT is believed to be an inhibitory transmitter in the control of sexual drive (94). Suppressed libido in patients taking fenfluramine, a 5-HT-releasing agent, and elevated libido in patients taking buspirone, a 5-HT neuron suppressor, have been reported (95). Clinically, trazodone (which selectively inhibits central 5-HT uptake) has been reported to enhance nocturnal penile erection and cause priapism in men (96). Its strong sedative effect limits its clinical usefulness, however.

**Norepinephrine**

Central norepinephrine transmission seems to have a positive effect on sexual function. Animal studies have shown that activation of $\alpha_1$-adrenoceptors facilitates copulation whereas activation of $\alpha_2$-adrenoceptors inhibits copulation. Clinically in humans, inhibition of norepinephrine release by clonidine ($\alpha_2$-adrenergic agonist) is associated with a decrease in sexual behavior, and yohimbine ($\alpha_2$-receptor antagonist) has been shown to increase sexual activity (97).

**Opioid**

Endogenous opioids are known to affect sexual function, but the mechanism of action is far from clear. Injection of small amounts of morphine into the MPOA facilitates sexual behavior in rats. Larger doses, however, inhibit both penile erection and yawning induced by oxytocin or apomorphine. It is suggested that endogenous opioids may exert inhibitory control over central oxytocinergic transmission (98).

**Oxytocin**

Oxytocin is a hormone secreted by the neurons directly into the circulation in the posterior pituitary. Besides the posterior pituitary gland, oxytocin-secreting neurons are also found in the neurons projecting from the paraventricular nuclei to the brainstem and spinal cord; thus, oxytocin can also function as a neurotransmitter. The blood level of oxytocin is increased during sexual activity in humans and animals. It is a potent inducer of penile tumescence when injected into the lateral cerebral ventricle, the paraventricular nucleus, or the hippocampus in laboratory animals. Because neurons in the paraventricular area have been shown to contain NOS, and NOS inhibitors prevent apomorphine- and oxytocin-induced erection, it is suggested that oxytocin acts on neurons whose activity is dependent on certain levels of NO (99,100).

**Prolactin**

Increased levels of prolactin suppress sexual function in men and experimental animals. In rats, high levels of prolactin decrease the genital reflex