

# Male Sexual Function and Its Disorders: Physiology, Pathophysiology, Clinical Investigation, and Treatment

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## ABSTRACT

This review is designed to help the reproductive endocrinologist integrate his or her professional activity with those of other disciplines including urology, radiology, neurology, and psychology in order to successfully manage all of the inseparable aspects of male sexual and reproductive functioning. Significant advances in the field of male sexual physiology and pathophysiology and new methods of investigation and treatment of male sexual disorders are outlined. The review synthesizes available data on the following: norms of sexual organs, aging and sexuality, role of central and peripheral neurochemicals in each stage of the sexual cycle, role of corporeal smooth muscles in the hemodynamic control of erection and detu-

mescence, influence of psychological factors, drugs, and disease on all aspects of sexual functioning, and use of nocturnal penile tumescence monitoring, imaging investigations, and neurophysiologic studies in the diagnostic workup of males with sexual dysfunction. Clinical algorithms are presented where appropriate. Extensive discussions on newly developed strategies in psychological and behavioral counseling, drug therapy, tissue engineering, nonsurgical devices, and surgical treatments for all forms of sexual disorders are also provided. Lastly, the effect of sexual dysfunction and its treatment on quality of life in affected men is addressed, along with recommendations for future research endeavors. (*Endocrine Reviews* 22: 342–388, 2001)

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## I. Introduction

DISORDERS of sexual function are common among men of all ages, ethnicities, and cultural backgrounds. It has been recently estimated that more than 152 million men worldwide experienced erectile dysfunction in 1995, and that this number will rise by 170 million, to approximately 322 million by the year 2025 (1).

Significant advances in the understanding of the physiology and pathophysiology of male sexual function, and in methods of its investigation and treatment, have been attained during the past three decades. In the field of physiology, the nature and elements of the normal sexual response have been delineated, and functional activities of all penile structures have been clarified and integrated. The exact role of the various components of the neural system has also become more fully understood. In the field of pathophysiology, estimations of the relative contribution of psychogenic and organic factors to genesis of the various forms of male sexual dysfunction have approached the reality; and many risk factors for development of organic dysfunction have been identified. In the field of physical and laboratory evaluation, many new psychometric, hormonal, vascular, and neurological investigative procedures have been attempted. As a result, sound techniques for accurate prediction of functional and structural changes are now emerging.

This review describes many of these recent advances in the understanding of male sexual function and its disorders. Currently available methods of investigation are outlined and clinical algorithms for their use are presented. Recently developed strategies in psychological, medical, and surgical treatments are also summarized and related to the relevant pathophysiology. It is hoped that information provided in this review will help scientists and healthcare policy makers

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to develop appropriate and timely strategies to meet current and future demands to prevent and/or alleviate male sexual dysfunction. It is also hoped that material provided in this review will help the reproductive endocrinologist to widen the scope of his or her professional activity from the limited focus on gonadal function to the wider consideration of all inseparable and integrated aspects of human sexual and reproductive capacities.

## II. Physiology of Male Sexual Function

### A. Penile structure, vasculature, and innervation

The penis is composed of two functional compartments: the paired corpora cavernosa and the corpus spongiosum (Fig. 1) (2). Histologically, the tissue of the corpora cavernosa consists of bundles of smooth muscle fibers intertwined in a collagenous extracellular matrix. Interspersed within this parenchyma is a complex network of endothelial cell-lined sinuses, or lacunae, helicine arteries, and nerve terminals.

The penis is innervated by somatic and autonomic nerve fibers. The somatic innervation supplies the penis with sensory fibers and supplies the perineal skeletal muscles with motor fibers. Contraction of the perineal skeletal muscles during erection leads to a temporary increase in corporeal body pressure to a level above the mean systolic pressure, and thus helps to increase penile firmness.

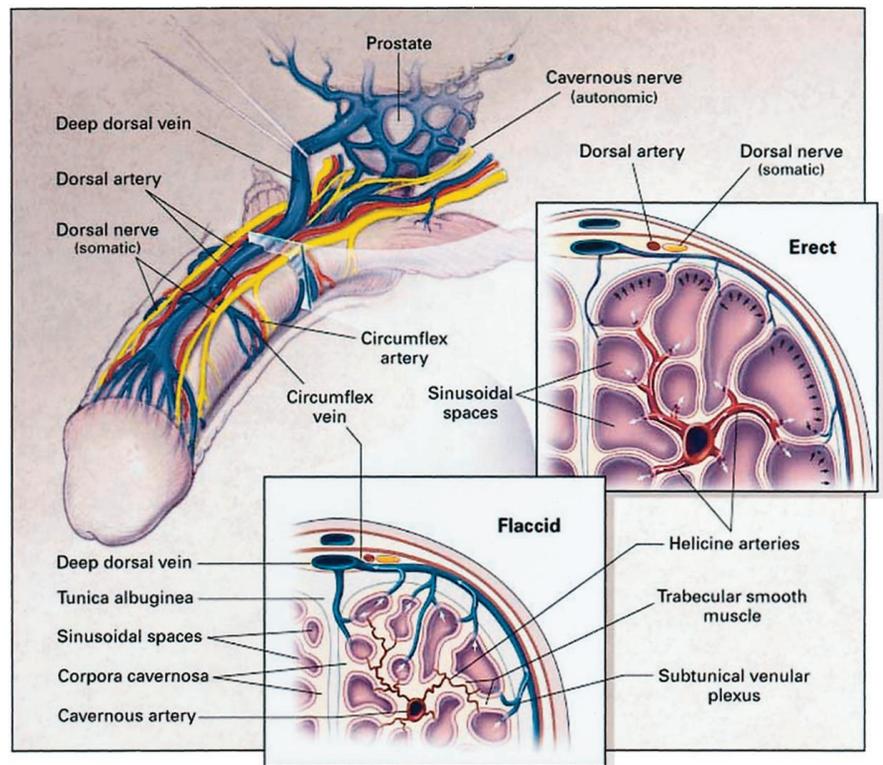
The autonomic innervation of the penis is both parasympathetic and sympathetic (Fig. 2). The major efferent parasympathetic pathway originates in the intermediolateral aspect of the sacral cord ( $S_2$ – $S_4$ ) traveling in the pelvic nerve (Nervi Erigentes) to supply a vasodilating innervation to the corporeal bodies. After the parasympathetic nerve fibers exit

the spinal cord, they run through the retroperitoneal space in the lateral aspect of the rectum and bladder, and then pass inferiorly and laterally toward the prostate and urogenital diaphragm. The cavernous nerve enters the corporeal body alongside the cavernous artery at the crura of the corpora as preganglionic nerve fibers. The most likely neurotransmitter at the synaptic end of these fibers is acetylcholine. The post-ganglionic nerve fiber segments terminate either on the vascular smooth muscle of the corporeal arterioles or the non-vascular smooth muscle of trabecular tissue surrounding the corporeal lacunae (see Ref. 3 for review). The sacral parasympathetic neurons are chiefly responsible for the erectile function and are influenced by a cortical-sacral efferent pathway. The penile erection can be initiated with a single episode of pelvic nerve electrical stimulation. Maintenance of erection for an extended period of time without significant changes in corporeal body blood gases can be achieved with repetitive stimulation for 40–50 sec, with a minimum latency period of 50 sec between each stimulus (3). The sympathetic innervation of the penis mediates the detumescence after the orgasmic relief, and in the absence of sexual arousal it maintains the penis in the flaccid state.

### B. Normal penile and testicular size in adult males

Wessells and colleagues (4) have recently reviewed the normative data on penile size of the adult human male. In these studies sample size ranged from 50 to 2,770 subjects with an age range between 17 and 91 yr. The average unstretched flaccid length ranges from 8.85 cm to 10.7 cm, stretched flaccid length ranges from 12.45 cm to 16.74 cm, and erection length ranges from 12.89 cm to 15.5 cm.

FIG. 1. Anatomy and mechanism of penile erection. The cavernous nerves (autonomic), which travel postarterolaterally to the prostate, enter the corpora cavernosa and corpus spongiosum to regulate penile blood flow during erection and detumescence. The dorsal nerves (somatic), which are branches of the pudendal nerves, are primarily responsible for penile sensation. The mechanisms of erection and flaccidity are shown in the *upper* and *lower insets*, respectively. During erection, relaxation of the trabecular smooth muscle and vasodilatation of the arterioles results in a severalfold increase in blood flow, which expands the sinusoidal spaces to lengthen and enlarge the penis. The expansion of the sinusoids compresses the subtunical venular plexus against the tunica albuginea. In addition, stretching of the tunica compresses the emissary veins, thus reducing the outflow of blood to a minimum. In the flaccid state, inflow through the constricted and tortuous helicine arteries is minimal, and there is free outflow via the subtunical venular plexus. [Reproduced with permission from T. F. Lue: *N Engl J Med* 342:1802–1813, 2000 (2). © Massachusetts Medical Society. All rights reserved.]



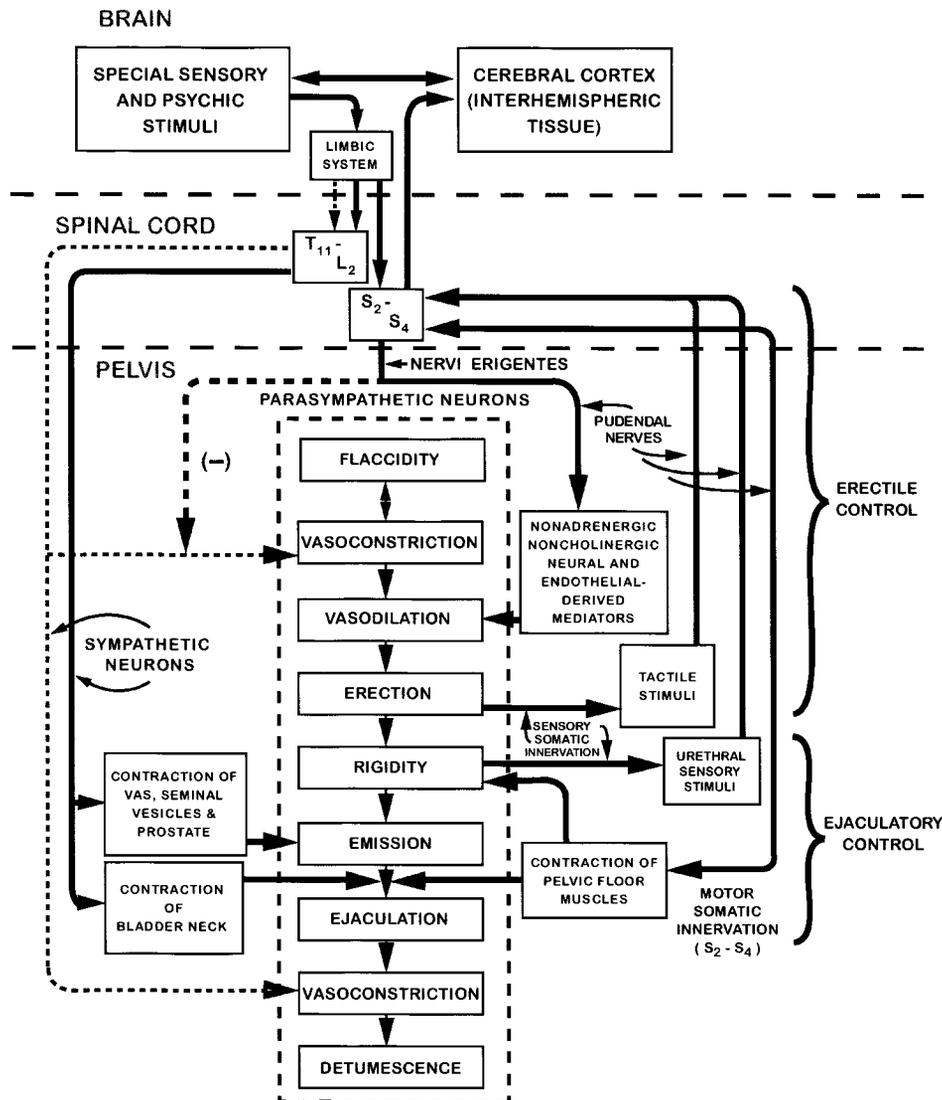


FIG. 2. The interactions between autonomic and somatic innervations in the control of male sexual cycle. The sensory input from the genital tract is carried by the pudendal nerve to the S2–S4 segment of the spinal cord. Ascending sensory fibers synapse in the corticomedullary junction and the thalamus, and then terminate in the contralateral primary sensory area deep in the interhemispheric tissue. The somatic motor fibers originate from the sacral segments S2–S4 and supply the pelvic floor muscles and the external anal sphincter. The higher centers for the erectile function are located in the cortex, interhemispheric area, and limbic system. The descending parasympathetic innervation exits the spinal cord at the S2–S4 level and reaches the penis via Nervi Erigentes. It is responsible for the corporeal vasodilatation and corporeal smooth muscle relaxation, and hence the penile transformation from the flaccid to the erect state. Penile tactile stimuli reaching the spinal cord via the pudendal nerve generates additional reflex arcs to help initiate and/or maintain the erection. The sympathetic innervation exits the spinal cord at T11–L2 level and reaches the penis via the inferior mesenteric, hypogastric, and pelvic plexuses. It is responsible for the emission and ejaculation through coordinated contractions of the vas deferens, ampulla, seminal vesicles, prostate, and the bladder neck. Somatic innervation-mediated contraction of the pelvic floor muscles aids in achieving the maximum penile rigidity and in discharging the ejaculatory fluid. Sympathetic innervation mediates corporeal vasoconstriction and corporeal smooth muscle contraction, and hence it causes penile detumescence after the orgasmic relief. It also maintains the flaccid state in the absence of sexual arousal. Activation of each division of the autonomic nervous system appears to occur in a reciprocal manner (*i.e.*, activation of one division is associated with inhibition of the other). [Derived from (465).]

Reports on penile volume are limited and have relied either upon the measurement of penile circumference manually (5) or penile cross-section by ultrasound techniques (4, 6, 7). The increase in central obesity may contribute to occasionally reported decrease in penile length with age. There is a loss of tensile strength of the tunica as men grow older, but no loss of the tunica albuginea itself.

Normally, the testis increases in size from 1–3 cm<sup>3</sup> during the neonatal period of life to 15–30 cm<sup>3</sup> in adulthood. The

germ cells and seminiferous tubules represent 90% of the testicular volume while Leydig cells contribute to less than 1%. A normal size adult testis has dimensions of 4.1–5.2 cm in length and 2.5–3.3 cm in width (8). Based on the available data, Wessells and colleagues (4) considered adult men with penile length of greater than 4 cm in the unstretched flaccid state or greater than 7.5 cm in the stretched flaccid state or the erect state to have a normal penile length. No parallel suggestions were made for penile girth or volume.

### C. Local control of penile erection

Acetylcholine appears to be the neurotransmitter of the preganglionic parasympathetic neurons. The neurotransmitters for the short postganglionic neurons have not been fully defined. Acetylcholine does not appear to influence the contractility of the corporeal smooth muscle fibers directly, but does so through activation of cholinergic receptors on the endothelial cells (Fig. 3). Nitric oxide (NO) has been identified in the corporeal tissue (9) and is believed to be the endothelial-derived relaxation factor(s). NO is synthesized from its precursor, L-arginine, by the enzyme nitric oxide synthase (NOS). Both constitutive and inducible NOS isoforms are produced in the cavernosal tissues (10, 11). Constitutive NOS is produced by the endothelial cells and the nerve terminals, whereas the inducible NOS appears to be produced by the corporeal smooth muscle cells only.

NO produced by the sinusoidal endothelial cells and by the noncholinergic parasympathetic neurons diffuses into the adjacent smooth muscle cells and activates soluble guanylate cyclase to increase the intracellular cGMP concentration. The cGMP appears to be the major intracellular effector of the smooth muscle cell relaxation (12) via a biochemical

cascade of protein kinases. A putative mechanism for cGMP-induced corporeal smooth muscle relaxation involves protein kinase phosphorylation of myosin light chains directly or as a consequence of lowering intracellular calcium stores (10). Although several types of phosphodiesterase (PDE) isoenzymes have been identified in the human corpora cavernosa, type 5 was found to be the predominant isoenzyme responsible for the inactivation of cGMP (13). Sildenafil (Viagra, Pfizer Inc., New York, NY) inhibits this PDE, which is also found in vascular smooth muscles and platelets (14). Sildenafil, to a lesser extent, also inhibits PDE type 6 in the retinal rod photoreceptors (responsible for metabolism of the light-stimulated cGMP) and has little or no effect on the calcium/calmodulin-dependent PDE-1 and the calcium/calmodulin-independent PDE-3 isoenzymes in the cardiac muscles (responsible for metabolism of cGMP that is involved in regulation of cardiac contractility) (14). Phosphodiesterase inhibitors are emerging as an attractive physiological means for induction and/or prolongation of erection in man (15). In addition to stimulation of cGMP production, NO itself could directly influence the contractility of the corporeal smooth muscle fibers by altering the transcellular ion

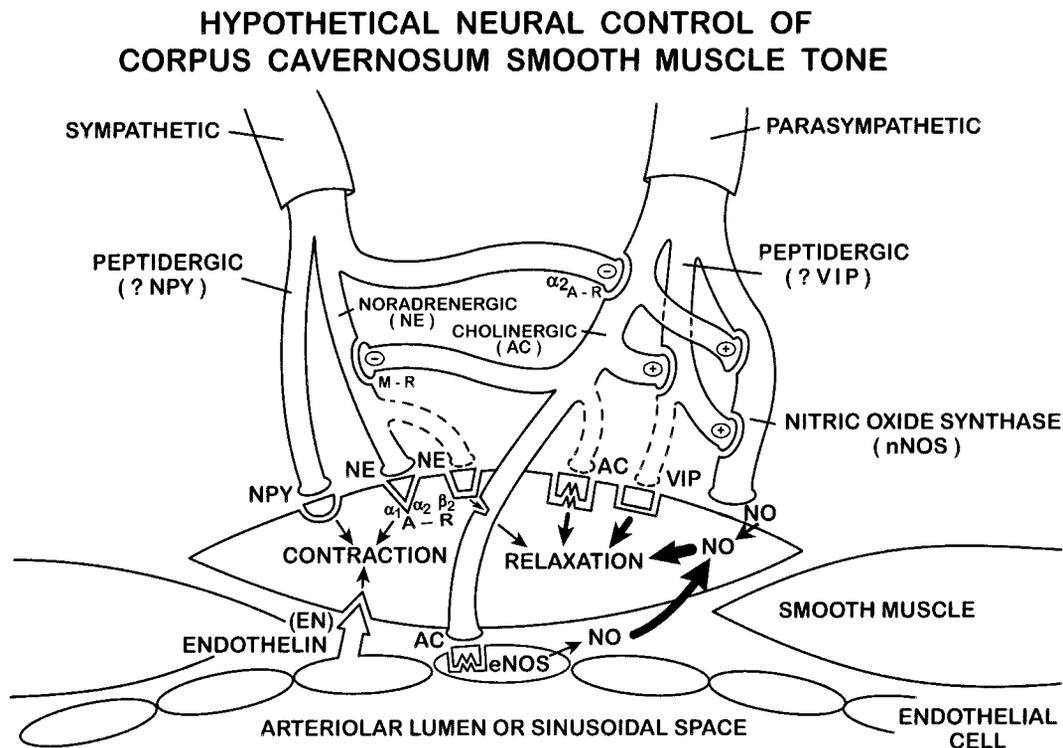


FIG. 3. Proposed neural control of the corporeal smooth muscle function. Parasympathetic fibers directly innervate the corporeal smooth muscle and sinusoidal endothelial cells. Acetylcholine (AC) is the parasympathetic neuromediator at the endothelial cells and it activates the production of constitutive endothelial nitric oxide synthase (NOS) and consequently stimulates nitric oxide (NO) production. Parasympathetic innervation of the smooth muscle cells, on the other hand, is mediated largely by NOS-containing, and to a lesser extent by vasoactive intestinal polypeptide (VIP) containing fibers. NO, produced locally in the smooth muscle cell or reaching it by diffusion from the adjacent endothelial cell(s), is the major mediator of smooth muscle relaxation via stimulation of cGMP production (see the text and Fig. 4 for details). VIP plays a lesser role in direct stimulation of corporeal smooth muscle relaxation. The sympathetic innervation of smooth muscle cells includes norepinephrine (NE) and nonadrenergic (most likely neuropeptide Y fibers).  $\alpha$ -1 and  $\alpha$ -2 adrenoceptor ( $\alpha_1$  &  $\alpha_2$  A-R) activation, together with neuroreceptor Y (NPY) and endothelin-1 (EN) actions, are responsible for smooth muscle cell contraction. Cross-talk between the two divisions of the autonomic innervation appears to exist, via an  $\alpha$ -2 adrenoceptor ( $\alpha_2$  A-R) and a muscarinic receptor (M-R) on the parasympathetic and the sympathetic divisions, respectively. This aids in the inhibition of each division when the other is activated. Arrow size reflects the relative importance of innervation or neurotransmission; +, stimulatory or positive effect; -, inhibitory or negative effect. [Derived from (26).]

flux through activation of the sodium/potassium-adenosinetriphosphatase (16) and the potassium-conductive membrane hyperpolarization pathway (17).

Other noncholinergic parasympathetic neurotransmitters capable of promoting smooth muscle relaxation, and hence the erectile response, include vasoactive intestinal polypeptide (VIP), bradykinin, peptide histidine methionine, pituitary adenylate cyclase-activating polypeptide, helospectin, galanin, calcitonin gene-related peptide (CGRP), and prostaglandin E-1 (18–21). Before the identification of NO in the penile tissue, VIP was thought to be the chief neuromediator of the erectile function; however, VIP was found to colocalize with NOS in penile neurons of rats and humans (22). Its relaxation effect on the corporeal smooth muscle fibers appears to be mediated by the NO-cGMP pathway (23) similar to bradykinin's ability to stimulate the endothelial NOS pathway to generate NO (24). However, the exact mechanisms by which other neuropeptides participate in regulation of the erectile function remain to be determined.

Norepinephrine is responsible for regulation of corpus cavernosum smooth muscle tone via the interaction with  $\alpha$ -1 and  $\alpha$ -2 adrenergic receptors (25). Other neurotransmitters capable of promoting smooth muscle contraction, and hence detumescence, include endothelin-1, substance-P, PGF-2 $\alpha$ , thromboxane A-2, angiotensin II, and calcium (18, 20, 26–30). Some of these agents exert their effect through modulation of the presynaptic  $\alpha$ -2 adrenergic receptors. A role for sympathetic innervation of the penis in mediation of psychologically provoked erection has been suggested, but the validity of such a belief was disputed based upon the observation of a full retainment of erectile capacity in men who undergo bilateral complete sympathectomy (31, 32). However, the recent *in vitro* studies demonstrating the relaxation effect of the  $\beta$ -2 adrenergic receptor agonist isoproterenol on noradrenaline-precontracted human penile smooth muscle cells (33) suggest that, at least in some situations,  $\beta$ -adrenergic innervation could participate in the mediation of human erection.

$\alpha$ -1 Adrenergic receptors are the preponderant subtype in corporeal smooth muscles (34) and the deep dorsal penile vein (35), whereas  $\alpha$ -2 receptors dominate in the cavernosal arteries (34). However, no quantitative differences in the prevalence of the two subtypes have been found in the circumflex veins of either potent or impotent men. Crowe and colleagues (36) found the greatest density of nerves supplying the deep dorsal vein and the vasa vasorum to be (in decreasing order) neuropeptide-Y (NPY), VIP, and dopamine- $\beta$ -hydroxylase-containing nerves. These investigators proposed that NPY, by its prolonged vasoconstricting effect, may aid in penile erection, and the vasodilating effect of VIP may be involved in facilitating the drainage of penile blood during detumescence. A recent series of *in vitro* experiments by Segarra and colleagues (37) using ring segments of human penile dorsal vein has provided additional evidence for an active role of the deep dorsal vein in the total penile vascular resistance through the release of NO from both neural and endothelial elements.

The presence of a critical balance of smooth muscle to connective tissue has been suggested for the successful veno-occlusion and the manifestation of erectile response to occur.

A potential role for transforming growth factor  $\beta$ -1 (TGF- $\beta$ 1) and PGE-1 in maintaining this critical balance of smooth muscle/connective tissue and a role for intracorporeal oxygen tension in regulation of synthesis of these regulatory factors have also been suggested (38). Thus, neuronal dysregulation or poor intrinsic compliance of the corporeal smooth muscle cells could be a significant factor in the pathogenesis of erectile dysfunction (Fig. 4) (39).

Another aspect of the control of corporeal smooth muscle cell function that has recently been described is the role played by the gap junction (18, 38, 39). Gap junction channels interconnect the corpus cavernosum smooth muscle cells and allow them to function as a coordinated network with synchronous myographic activity. Second messengers, such as calcium ion and inositol triphosphate (IP3), are transported between corporeal smooth muscle cells through these junctions. Therefore, cell-to-cell communication is a likely means for synchronization and integration of the corporeal smooth muscle activity that occurs despite the paucity of nerve supply to individual smooth muscle cells.

#### D. Normal control of male sexual response

Sexual stimulation of the human male results in a series of psychological, neuronal, vascular, and local genital changes. At least three different classifications for these changes have been described. Kolodny *et al.* (40) described a psychosexual response cycle that consists of four phases: excitement, plateau, orgasm, and resolution. Table 1 describes neural pathways, end-organ changes, penile hemodynamic changes, and genital responses that occur during each phase of this cycle.

Another classification has characterized the penodynamic changes during the sexual cycle (41, 42). In this classification, each of the psychosexual phases is divided into two interrelated events as follows: excitement into latency and tumescence; plateau into erection and rigidity; orgasm into emission and ejaculation; and resolution into detumescence and refractoriness.

A third classification focuses on the functional activities during the sexual cycle (43). It adds an initial phase of desire or libido to encompass the sex-seeking behavior, pools together excitement and plateau into a single phase of erection, and splits the orgasmic phase into the physical function of ejaculation and the psychological sensation of orgasmic pleasure. Thus, the normal male sexual response cycle can be functionally divided into five interrelated events that occur in a defined sequence: libido, erection, ejaculation, orgasm, and detumescence. Since the functional classification of the male sexual cycle is the most physically quantifiable one, it will constitute the basis for the following discussion.

*1. Libido or sexual desire.* Libido is defined as the biological need for sexual activity (the sex drive) and frequently is expressed as sex-seeking behavior. Its intensity is variable between individuals as well as within an individual over a given time. Little is known about the physiological basis of libido. However, previous and recent sexual activity, psychosocial background, brain and spinal cord dopaminergic receptor activation, and gonadal hormones are among the

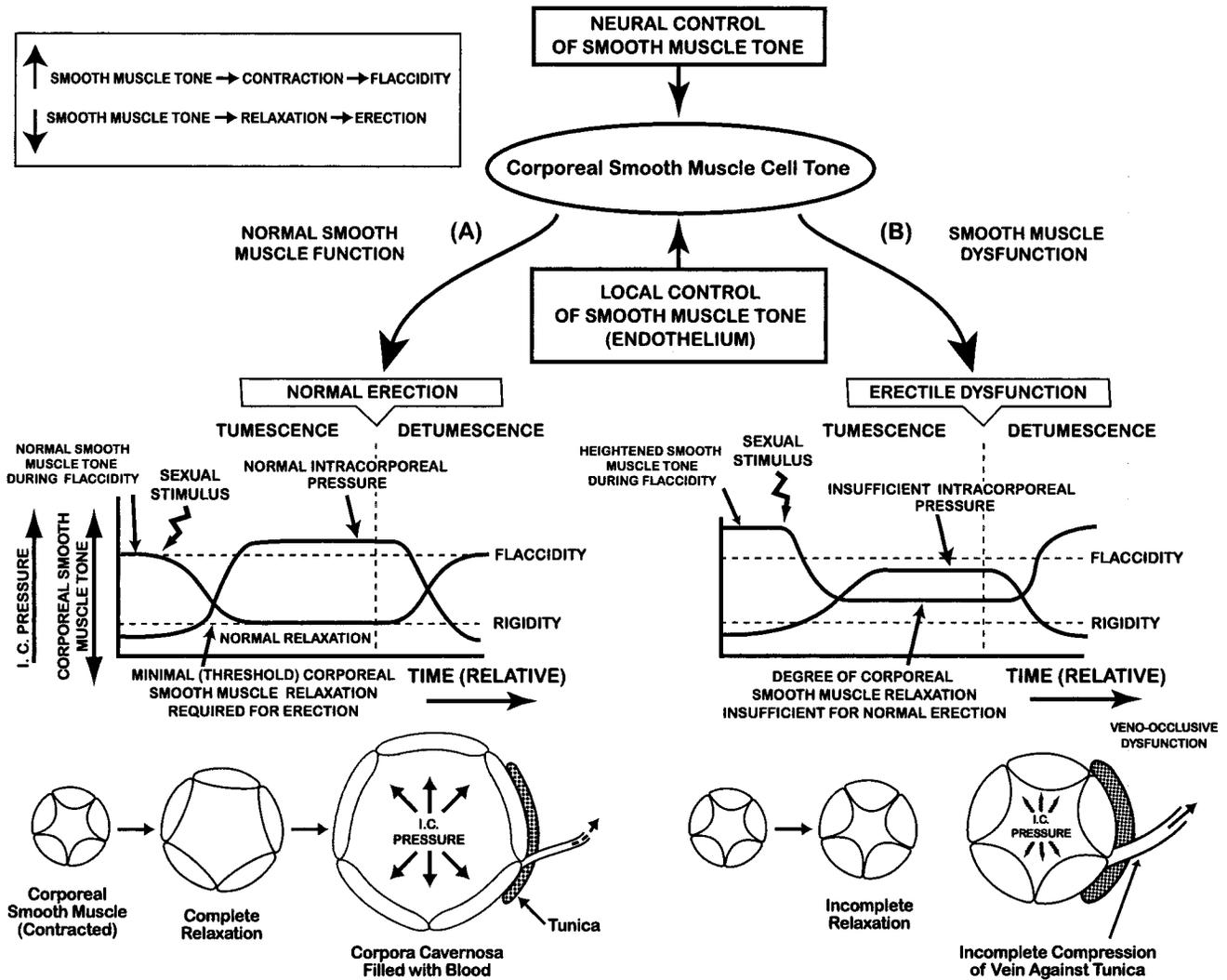


FIG. 4. The illustration depicts the effects of normal (A) and abnormal (B) balance between smooth muscle contraction and relaxation on the entire erectile process. Normal smooth muscle tone during flaccidity and sufficient relaxation during tumescence permit the rise in intracorporeal pressure to the level needed for the full erection to occur. Any physiological perturbation that results in heightened contractility during flaccidity and impaired relaxation of the corporeal smooth muscle during tumescence will shift the delicate balance in favor of flaccidity over erection. I.C. pressure, Intracorporeal pressure. [Reproduced with permission from G. J. Christ: *Urol Clin North Am* 22:727-745, 1995 (39).]

factors that are believed to participate in regulation of male sexual desire.

Several lines of evidence in animal and human males support a role for central dopaminergic neurotransmission in mediating sexual behavior and erection (see Ref. 44 for review). Further, testosterone promotion of copulation appears to be mediated by an increase in dopamine release in the medial preoptic area, possibly via up-regulation of NO synthesis (45). A role for dopaminergic activation in stimulation of sexual behavior in the human is supported by the following observations: administration of the dopamine agonists apomorphine, bromocriptine, and pergolide mesylate frequently elicits spontaneous penile erection; use of the dopamine precursor levodopa is associated with increased libido (46), return of spontaneous erection (47), or onset of nocturnal emissions (48) in 20-30% of patients with Parkinson's disease who are treated with this agent; and use of pharmacological agents with antidopaminergic effects is associated with decreased libido and erectile dysfunction in up

to 50% of cases. However, caution must be exerted in interpreting some of these data for the following reasons: lack of consistency in the results of many investigations; pharmacological agents used may stimulate or inhibit other central neuromediator systems, including adrenergic, cholinergic, serotonergic, histaminic, and peptidergic systems; and many neuroleptics increase PRL secretion, which can decrease libido through inhibition of the hypothalamic-pituitary-gonadal axis or inhibition of 5 $\alpha$ -reductase activity (49).

Evidence for a role of androgens in regulation of sexual behavior in the human male has been reviewed by Moora-dian and colleagues (50). Higher serum testosterone appears to be associated with greater sexual activity in healthy older (51) but not younger (52) men. Further, higher testosterone levels may also shorten the latency of erection stimulated by the exposure to erotic material (53), and testosterone replacement in hypogonadal males restores sexual interest (54), shortens latency, and increases frequency and magnitude of nocturnal penile tumescence (NPT) (55). Conversely, with-

TABLE 1. Male sexual function: relationships among the phase of sexual response cycle, neural pathways, end-organ and hemodynamic changes, and genital functional responses

Phase of sexual response cycle	Neural pathways	End-organ changes	Penile hemodynamic changes	Genital functional responses
Excitement	Inputs from external sensual (visual, auditory, tactile, olfactory) and internal psychic stimuli to the limbic system resulting in activation of sacral parasympathetic and inhibition of thoracolumbar sympathetic pathways	Relaxation of smooth muscles and helicine arterioles of corpora cavernosa	Increase in arterial blood flow without change in intracavernous pressure	Penile filling (latency) Tumescence
Plateau	As above plus: Activation of the sacrospinal reflex	As above plus: Contraction of ischiocavernosus muscle. Stimulation of corpus spongiosum. Stimulation of accessory glands (Cowper's and Littre's)	Rise in intracavernous pressure to 85% of systolic and decrease in arterial inflow Rise in intracavernous pressure to above systolic and further decrease in arterial inflow	Full erection and dilatation of urethral bulb Rigidity and secretion of fluid from accessory glands
Orgasm	As above plus: Activation of the thoracolumbar spinal reflex  Neuronal discharge to somatic efferent pudendal nerve Activation of CNS orgasmic sensations	As above plus: Contraction of vas deferens, ampulla, seminal vesicle, and prostate Contraction of bulbocavernosus and pelvic floor muscles	Maintenance of intracavernous pressure above systolic	Emission  Ejaculation
Resolution	Activation of thoracolumbar sympathetic pathway	Contraction of smooth muscles and arterioles of corpora cavernosa	Increase in venous return Arterial and venous blood flow returns to minimum	Detumescence Refractoriness and flaccidity

drawal of androgen therapy in hypogonadal males leads to a decline of libido in 3–4 weeks (56), and unreplaced hypogonadal men have impairment in spontaneity of erection (56, 57). Despite these androgen deficiency-related abnormalities, hypogonadism does not appear to compromise the ability to achieve erection in response to viewing of erotic films (55, 58).

**2. Erection.** Erection is the ultimate response to multiple psychogenic and sensory stimuli from imaginative, visual, auditory, olfactory, gustatory, tactile, and genital reflexogenic sources, which effect several neurological and vascular cascades that lead to penile tumescence and rigidity sufficient for vaginal penetration. Further, erection is associated with significant psychological and physical changes, including heightened sexual arousal, full testicular ascent and swelling, dilatation of the urethral bulb, an increase in glans and coronal size, cutaneous flush over the epigastrium, chest, and buttocks, nipple erection, tachycardia and elevation in blood pressure, hyperventilation, and generalized myotonia (40, 59). The local penile changes are effected by a vasodilating parasympathetic discharge subsequent to the central nervous system (CNS) inputs or as a result of reflex action in response to local afferent stimulation of the sacral parasympathetic nuclei.

New data implicating gonadal androgens in modulation of penile erection through local regulation of NO secretion and/or action need to be emphasized. Experiments that have

shown castrated rats to have reduced penile tissue NOS content and androgen replacement to restore NOS production and action (60) have cast doubt on the older dogma that androgens act only centrally to modulate sexual libido. Data in which androgens were shown to influence the frequency of nonerotic or "reflex" erection support a role for peripheral androgen actions in the human (61). Moreover, a recent study in rats by Lugg and colleagues (62) implicates dihydrotestosterone and not testosterone as the local modulating androgen of the NO-cGMP pathway. However, the fact that androgens can enhance NPT, but not erection in response to erotic stimuli (61), may suggest the presence of both androgen-sensitive and androgen-insensitive central pathways for erectile control.

**3. Ejaculation.** The ejaculation phase is controlled by sympathetic innervation of the genital organs and occurs as a result of a spinal cord reflex arc. There is a considerable voluntary inhibitory control over this phase of the sexual response, which consists of two sequential processes. The first process is called emission and is associated with deposition of seminal fluid into the posterior urethra. Simultaneous contractions of the ampulla of the vas deferens, the seminal vesicles, and the smooth muscles of the prostate (43, 63) mediate emission. The second process is the true ejaculation and results in expulsion of the seminal fluid from the posterior urethra through the penile meatus.

Evidence reviewed by Segraves (44) suggests that seroto-

nergic neurotransmission has an inhibitory effect on male sexual function and ejaculation. The inhibitory action of serotonin neurotransmission on ejaculation is likely to be mediated by the serotonergic tracts in the medial forebrain bundle.

4. *Orgasm.* Both physiological and psychogenic elements contribute to genesis of the orgasmic phase (43, 64). Afferent stimuli that transmit via the pudendal nerve induce the following physiological events: smooth muscle contraction of the accessory sex organs; buildup and release of pressure in the posterior urethra; sensation of the ejaculatory inevitability; contraction of the urethral bulb and perineum; rhythmic contractions of the pelvic floor muscles; semen emission and ejaculation; and finally, the reversal of the generalized physiological changes and sexual tension. Sensory cortical neurons perceive these events as pleasurable. Factors that influence the subjective sensation of orgasmic pleasure include the degree of sexual excitement, recency of sexual activity, and the psychosexual makeup of the individual. It is possible for orgasm to occur without being preceded by the previous two phases of erection and ejaculation. Conversely, contractions of pelvic musculature and ejaculation could occur in the absence of orgasmic sensations.

5. *Detumescence.* During this phase the penis returns to the flaccid state. Vasoconstriction of the arterioles and reversal of events within the contractile corporeal units divert the blood away from the cavernous sinuses and allow an increase in the venous drainage of their contents. Initially, the rate of blood outflow increases by about 10-fold, followed by a progressively decreasing rate until it reaches the pretumescence level (63) and a period of inhibition to resumption of erectile and ejaculatory functions. The length of this refractory phase is dependent upon many variables including age, physical state, and psychological environment (43, 63, 64). However, the traditional view that assumes male orgasm is instantly followed by detumescence and refractoriness has recently been challenged by reported observations in which some men were multiorgasmic, and the phenomenon of repeated orgasms without intervening detumescence and refractoriness was actively learned by some males (65). Local penile  $\alpha$ -adrenergic receptor activation is the most important neuromediator effecting detumescence. Interference with this function through the  $\alpha$ -1 receptor blockade may lead to the development of priapism (66).

#### E. Penodynamic changes during the male sexual cycle

The evidence reviewed above suggests that a fall of resistance within the corporeal vascular bed and the subsequent increase in arterial inflow are the major vascular events leading to erection of the penis (Figs. 4 and 5) (39, 63, 67). A dramatic increase in penile arterial blood flow to about 25 to 60 times that of the flaccid state occurs during the rapid period of tumescence (63). Pulse Doppler analysis studies with intracavernous vasoactive drug injections have established that a peak cavernosal artery systolic flow greater than 25 ml/sec is required for erection to occur (68–71). At full rigidity, an increase in penile length of 7.5 cm usually requires the entrapment of 80–115 ml of blood. As the penile

volume increases to near maximum (from <10 ml in the flaccid state to ~60 ml in the erect state), the arterial influx declines and plateaus at a level that is sufficient to keep the penis in the rigid (full erection) state. Dynamic infusion cavernosometry and cavernosography (DICC) studies have shown that a fluid flow rate between 5 and 40 ml/min is required to maintain a normal penis in the erect state (72, 73). Further, at these minimum flow rates of full erection, the cavernosal artery occlusion pressure (CAOP) equilibrates with the intracavernous pressure.

The intracorporeal pressure during the flaccid state is between 10 to 15 mm Hg. Intrapenile pressure changes are modest during the initial phase of the sexual cycle and remain so until near-maximum changes in circumference and volume are attained. As the penis becomes erect, the penile body pressure increases rapidly to about 90 mm Hg. Perineal muscle contraction results in further increase in penile body pressure to greater than 120 mm Hg (suprasystolic pressure), which results in full rigidity and elevation of the penis to greater than 90 degrees from the plane of lower extremities (63, 67). After orgasm, penile body pressure declines rapidly and the penile volume returns to the flaccid size. The aforementioned DICC studies suggested that the intrapenile pressure normally drops at a rate of less than 1 mm Hg/sec during detumescence, as reflected by the rate of drop in intrapenile pressure when fluid infusion is discontinued.

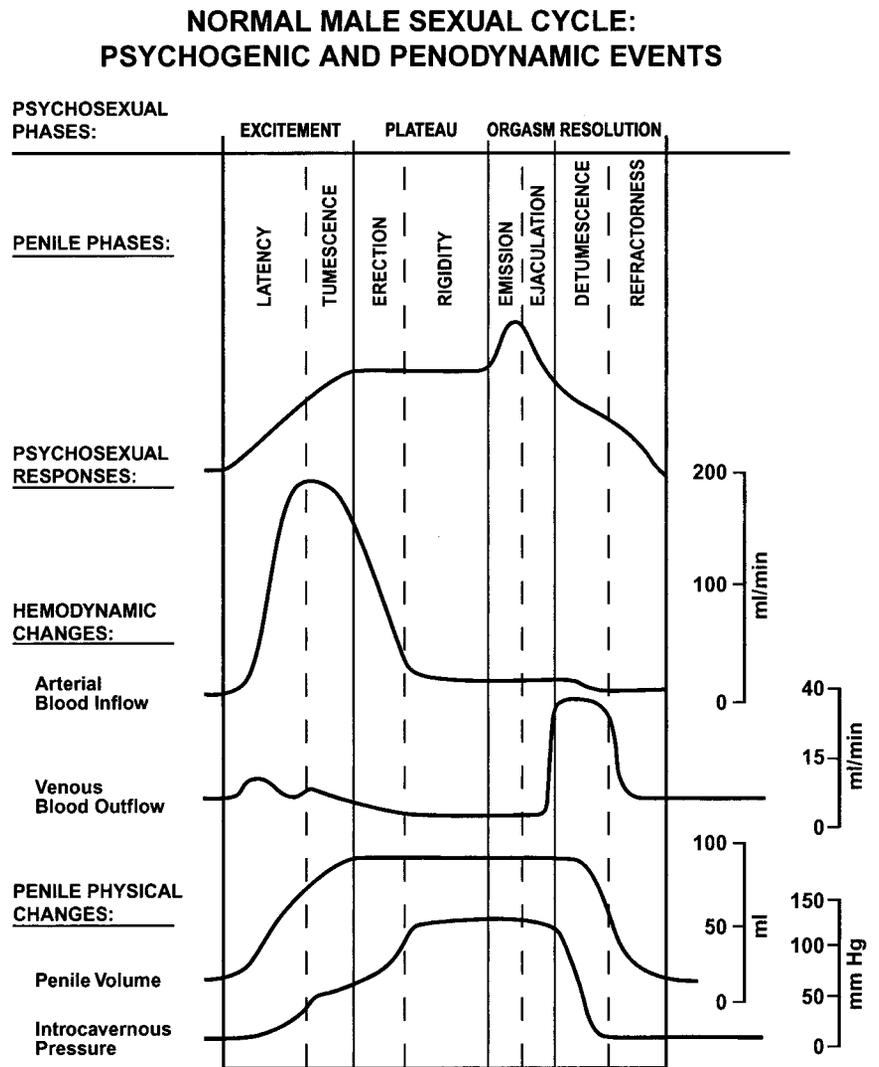
#### F. Nocturnal penile tumescence (NPT)

NPT refers to spontaneous penile erections that occur during the rapid eye movement (REM) stage of sleep. The phenomenon occurs four to five times per night at 90-min intervals, and each episode lasts 30–45 min. Total NPT time ranges between 90 and 180 min per night and accounts for 20–25% of the total sleep time (67, 74–76). Ninety percent of REM sleep episodes are associated with penile tumescence, with maximum changes in circumference and about 70% of full rigidity. The number of erectile and maximum tumescence episodes decreases with age, from 6.8 and 4 per night at age 13 yr, to 3.5 and 1.7 per night at age 70 yr, respectively. As a result, total tumescence time decreases by about 25% between these two ages. Most dreams associated with NPT are not associated with erotic content. Erections on waking usually represent NPT associated with the last episode of REM sleep and are not related to bladder fullness (see Ref. 75 for review).

Serum androgen concentrations may have a role in regulation of NPT (54, 55, 58, 77). In addition, studies during waking and sleep in normal males and in men with erectile insufficiency suggest that  $\alpha$ -2 antagonists enhance central arousability of the kind that is androgen dependent. These studies also suggest that more than one norepinephrine-mediated system is involved in this process, with possible contrasting and counteracting effects (77, 78).

A small number of studies have reported on the effect of pharmacological agents on NPT. Antidepressants and antihypertensives are the most investigated classes of drugs for their effect on NPT. Trazodone, an antidepressant with complex pharmacological effects including serotonin reuptake inhibition, prolongs NPT while it decreases REM sleep du-

FIG. 5. The psychogenic and penodynamic events of the normal male sexual cycle. The psychosexual response cycle has 4 major phases: excitement, plateau, orgasm, and resolution. They are represented by the *solid vertical lines* and by the top diagram. Each of the psychosexual phases comprises two interrelated physical events, which are represented by the vertical dashed lines. The penile hemodynamic changes associated with the sexual cycle (arterial and venous flow rates) are depicted in the middle portion, and the penile physical changes (volume and intracorporeal pressure) are depicted in the lower portion of the graph. Arterial blood inflow rate increases dramatically during latency, tumescence and early stages of erection. This increase in arterial inflow is accompanied with an earlier increase in venous return, and results in gradual expansion of the cavernous tissue, increase in intracorporeal pressure, obliteration of emissary veins, and ultimately restriction of the venous return. The rise in intracavernous pressure, in turn, leads to a progressive decline in the arterial inflow to a temporary cessation during the full penile rigidity. Venous drainage also completely ceases with full penile rigidity. As the corporeal smooth muscle cells begin to contract in late ejaculation, venous return increases sharply and remains high during the detumescence phase until the entrapped blood is fully drained and the intracorporeal pressure declines to its baseline level, which is maintained during the flaccid state. Penile volume expands maximally during late erection and intracavernous pressure rises maximally during full rigidity. Data are compiled from several sources referenced in the text.



ration (79). In contrast, amitriptyline (a tricyclic antidepressant) and mianserin (a tetracyclic  $\alpha$ -2 receptor blocker) decrease both the amplitude and duration of NPT (80). Varying effects on NPT have been seen with different members of the  $\beta$ -blocker family (81–83).

#### G. Male sexual function and aging

Males reach peak sexual capacity in the late teens. With advancement of age, a gradual decrease in sexual responsiveness occurs (84), characterized by a prolongation of the time required to achieve full erection and decrease in the effectiveness of psychic and tactile stimuli. The plateau phase is also prolonged, and the maintenance of erection requires continuing direct genital stimulation. Orgasm and the feeling of ejaculatory inevitability frequently become less intense. Penile detumescence occurs more rapidly and the refractory period is more prolonged. The ejaculatory volume also decreases with age. Recent studies in rats have shown that advanced age is associated with a decrease in the number of NOS-containing penile nerve fibers, erectile response to apomorphine stimulation, and maximum intracavernous pres-

sure. It is not clear at present whether some of these changes are related to the age-associated decline in serum testosterone concentrations.

The effects of age on male reproductive physiology have recently been reviewed (85). Aging is associated with decreased total serum and bioavailable testosterone concentrations, decreased testosterone to estradiol ratio, increased sex hormone-binding-globulin (SHBG) leading to increased plasma protein binding of circulating testosterone and decreased testosterone clearance, decreased LH pulse frequency, and diminished accumulation of  $5\alpha$ -reduced steroids in reproductive tissues. Some of these changes are related to the increased incidence of idiopathic hypogonadotropic hypogonadism (86) and/or a decline in serum levels of GH, insulin-like growth factor-1 (IGF-1), and dehydroepiandrosterone sulfate (DHEA-S) (85). Normally, IGF-1 enhances the Leydig cell response to LH, and DHEA-S provides a precursor for testosterone production.

Recent studies, such as the Massachusetts Male Aging Study, showed that between the ages of 40 and 70 yr, serum levels of both free- and albumin-bound testosterone decrease annually by about 1% (87). Several studies have confirmed

the role of obesity in the decline of androgen levels in aging men (88). Both age- and obesity-related reduction in gonadal hormones are caused by a parallel decline in the functional capacity of the hypothalamic-pituitary axis (88). A decrease in number of testicular Leydig cells (82) and in their secretory capacity for testosterone in response to hCG injections (89) in aging men has also been shown. Recent studies have implicated leptin (the obese *ob* gene product) in the development of some of these abnormalities. Decreased testosterone production with age could be due to a decrease in dehydroepiandrosterone (DHEA) and DHEA-S formation (90) as a result of a differential decrease in the side chain cleavage (17,20-lyase activity) rather than in the 17 $\alpha$ -hydroxylation of the cytochrome P450<sub>C17</sub> enzyme system. This decrease in 17,20-lyase activity restricts the metabolic conversion of 17- $\alpha$ -hydroxy progesterone to DHEA and its steroid derivatives, including testosterone (91).

Korenman and colleagues (92) have suggested that 90% of older men with reduced testosterone concentration have evidence of hypothalamic-pituitary dysfunction as reflected by a low-normal serum LH and reduced LH response to GnRH stimulation. A few other studies have also shown the absence of correlation between erectile dysfunction and testosterone concentration (93). However, since long-standing hypogonadal men usually complain of loss of sexual interest and activity, decrease in seminal emission volumes, loss of nocturnal and morning erections, and loss of energy and sense of well-being, and, since testosterone replacement is associated with improved self-reported libido, sexual potency, and both subjective (56, 57) and objective measures of nocturnal erections (94), severe testosterone deficiency is likely to be the primary cause of sexual dysfunction in many cases of combined hypogonadism and erectile dysfunction.

### III. Disorders of Male Sexual Function

Sex disorders of the male are classified into disorders of sexual function, sexual orientation, and sexual behavior. Disorders of sexual orientation and disorders of sexual behavior are believed to be entirely due to psychological etiologies; hence, they are discussed elsewhere (95).

The National Institutes of Health (NIH) Consensus Development Conference (96) advocated that "erectile dysfunction" be used instead of "impotence" to describe disorders of male sexual function and defined the new terminology as the "inability to achieve an erect penis as part of the overall multifaceted process of male sexual function." However, use of the term "erectile dysfunction" to refer to all aspects of male sexual dysfunction would be inappropriate.

Major advances have been made in the last few years toward understanding the nature of various forms of male sexual dysfunction and the possible underlying organic and psychological factors. Table 2 lists the clinical manifestations and the most common etiological categories for sexual dysfunction in the male. Identification of the sexual response component central to the dysfunction can significantly reduce the number of investigations required to characterize the underlying etiology(s) (97). However, the exact contribution of each etiological category to the genesis of a given

dysfunction may be difficult to establish, but the knowledge of its presence is essential to treatment planning.

#### A. Disorders of desire

The Diagnostic and Statistical Manual-IV (DSM-IV) (98) defined hypoactive sexual desire (HSD) as persistently or recurrently deficient (or absent) sexual fantasy and desire for sexual activity leading to marked distress or interpersonal difficulty. It is generally estimated that more than 15% of adult men and 30% of adult women have HSD. The diagnosis of primary desire loss in men can only be made after eliminating the presence of factors known to affect the sexual function. These include major psychological disorders, chronic medical conditions, intake of contributing pharmacological agents, or substance abuse. The most common causes of secondary disorders of sexual desire are psychogenic etiologies and androgen deficiency (99, 100).

Psychogenic conditions leading to a desire deficiency state in men (previously termed desire inhibition) include psychiatric illnesses such as depression or psychosis, preoccupation with life crisis or grief, maternal transference to sexual partners, gender identity conflicts, and aging-related psychological issues (57, 97, 101). Another form of secondary desire disorder caused by psychological factors is termed "excitement inhibition" and is seen in patients who have sexual drive but cannot maintain excitement. It is commonly seen in patients with performance anxiety due to the fear of sexual failure and the vigilant preoccupation with erection during lovemaking (57, 101). Traumatic employment or marriage-related issues may contribute to diminished self-image and heightened anxiety leading to male sexual dysfunction. A substantial number of patients with affective disorder, chronic depression, and obsessional personality may also develop a desire disorder. A high frequency of sexual dysfunction was also reported in males with schizophrenia (102).

Patients with a primary CNS disease such as partial epilepsy (103), Parkinsonism (104), poststroke (95), and adrenoleukodystrophy (105) may have diminished sexual arousal. The pathogenesis of desire insufficiency in these disorders appears to be multifactorial in origin and includes disease-related hormone abnormalities, physical restrictions, and reduced general well-being.

A critical level of blood androgens is required for the maintenance of normal sexual desire, NPT, and nonerotic penile erections in most men. A certain concentration of androgens is required for initiation and maintenance of spermatogenesis and for maximum stimulation of growth and function of the prostate and seminal vesicles (43, 67). The amount of androgens required for these latter effects is greater than that needed for maintenance of libido.

Not all studies that have examined the relationship between serum testosterone and sexual desire in aging men have reported a robust relationship. Therefore, total or free-testosterone levels may not be an adequate measure of sexual drive, at least in some populations.

A number of pharmacological agents or drugs of addiction could potentially induce libido dysfunction, including anti-hypertensives (chlorthalidone, guanadrel, guanethidine, methyl dopa, reserpine, and spironolactone), psychiatric

TABLE 2. Causes of sexual dysfunction in the male classified by clinical manifestation

Clinical manifestation	Most common causes
Disorders of desire	
Hypoactive sexual desire (HSD)	Psychogenic ( <i>e.g.</i> , depression, marital discord leading to desire deficiency, performance anxiety leading to excitement inhibition) CNS disease (partial epilepsy, Parkinson's, poststroke, adrenoleukodystrophy) Androgen deficiency (primary or secondary), androgen resistance Drugs (antihypertensives, psychotropics, alcohol, narcotics, dopamine blockers, antiandrogens)
Compulsive sexual behaviors	Psychogenic (obsessive-compulsive sexuality, excessive sex-seeking in association with affective disorders, addictive sexuality, sex impulsivity)
Erectile dysfunction	Psychogenic Drugs (antihypertensives, anticholinergics, psychotropics, cigarette smoking, substance abuse) Systemic diseases (cardiac, hepatic, renal, pulmonary, cancer, metabolic, postorgan transplant, pelvic irradiation) Androgen deficiency (primary or secondary), androgen resistance, other endocrinopathies Vascular insufficiency (atherosclerosis, pelvic steal, penile Raynaud's, venous leakage) Neurological disorder (Parkinson's, Alzheimer's, Shy-Drager, encephalopathy, spinal cord or nerve injury) Penile disease (Peyronie's, priapism, phimosis, smooth muscle dysfunction, trauma)
Disorders of ejaculation	
Premature ejaculation (primary or secondary)	Psychogenic (neurotic personality, anxiety/depression, partner discord or other situational factors) Organic (increased central dopaminergic activity, increased penile sensitivity)
Absent or retarded emission	Sympathetic denervation (diabetes, surgical injury, irradiation) Drugs (sympatholytics, CNS depressants) Androgen deficiency (primary or secondary), androgen resistance
Postejaculation pain	Psychogenic
Orgasmic dysfunction	Drugs (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, substance abuse) CNS disease (multiple sclerosis, Parkinson's, Huntington's chorea, lumbar sympathectomy) Psychogenic (performance anxiety, conditioning factors, fear of impregnation, hypoactive sexual desire)
Failure of detumescence	
Structural penile disease	Penile structural abnormalities (Peyronie's, phimosis)
Priapism (primary or secondary)	Primary priapism: idiopathic Priapism secondary to disease: hematologic (sickle cell anemia, leukemia, multiple myeloma), infiltrative (Faber's disease, amyloidosis), inflammatory (tularemia, mumps), and neurologic diseases, solid tumors, trauma Priapism secondary to drugs: phenothiazines, trazodone, cocaine, intrapenile vasoactive injections

[Adapted with permission from R. S. Swerdloff and F. R. Kandeel. In: *Textbook of Internal Medicine*, Lippincott Co., 1992 (187).]

medications (fluoxetine, barbiturates, clomipramine, and fluphenazine), and others (danazol, digoxin, ethinyl-estradiol, ketoconazole, methadone, niacin, alcohol, diazepam, and marijuana) (99, 100, 106–108).

Several mechanisms of action exist for drugs commonly associated with male sexual dysfunction. Drugs that create HSD can have sedating effects and/or produce a central neurogenic blockade. Testosterone deficiency and antagonism may also lead to HSD. Medications that produce an elevation in PRL or induce parasympatholysis can manifest erectile dysfunction. Absence of emission and/or retrograde ejaculation can be found in men using antihypertensives, monoamine oxidase (MAO) inhibitors, or antipsychotics due to sympatholysis. Lastly, delayed ejaculation and/or orgasmic dysfunction may occur with selective serotonin reuptake inhibitors (SSRI) usage due to serotonergic agonist effects.

Another group of desire disorders with psychological bases is known as compulsive sexual behaviors (CSBs) (109, 110). CSBs constitute a wide range of complex sexual behaviors that have strikingly repetitive, compelling, or driven qualities. They usually manifest as one or more of several aberrant sexual behaviors, including obsessive-compulsive sexuality (*e.g.*, excessive masturbation and promiscuity), excessive sex-seeking in association with affective disorders

(*e.g.*, major depression or mood disorders), addictive sexuality (*e.g.*, attachment to another person, object, or sensation for sexual gratification to the exclusion of everything else), and sexual impulsivity (failure to resist an impulse or temptation for sexual behavior that is harmful to self or others such as exhibitionism, rape, or child molestation). Detailed discussion of these disorders is beyond the scope of this review and can be found elsewhere (109, 110).

### B. Erectile dysfunction

This is best defined as persistent failure to generate sufficient penile body pressure to achieve vaginal penetration and/or the inability to maintain this degree of penile rigidity until ejaculation (63). Although the exact prevalence of erectile dysfunction in the United States male population is not known, estimates have ranged from 12% of males above age 18 in the report of Furlow (111) to 25–30% of men between ages 60 and 70 in the surveys of Kinsey and colleagues (59), Schiavi and colleagues (112), and Diokno and colleagues (113), and to 52% in the Massachusetts Male Aging Study (93).

The current literature on the relationship between sexual dysfunction and psychiatric disorders in men is not exten-

sive, and much of the older literature is limited by methodological flaws. However, several new studies have established some association between sexual dysfunction and psychological disorders. In the Massachusetts Male Aging Study, male erectile dysfunction was found to be associated with depressive symptoms (odds ratio 1.82) (114). Similar results were reported by at least one other study in which depressed patients with erectile dysfunction had lower libido and were more likely to discontinue treatment for their erectile problem than other patients without depression (115). Further, in the cross-sectional Massachusetts Male Aging Study the incidence of moderate to complete erectile dysfunction was estimated to be nearly 90%, 60%, and 25% in men with severe, moderate, and minimal depression, respectively (114). In addition, older studies have estimated that approximately one-third of all patients with untreated depression have reported sexual dysfunction (116). The association between male erectile dysfunction and panic disorder (117) and perfectionism (118) has also been reported.

Many commonly prescribed pharmacological agents can adversely influence sexual function of the male (107, 108). Antihypertensives, anticholinergics, psychotropics, and many other agents are common causes for erectile dysfunction. The percentage of men with complete erectile dysfunction in the Massachusetts Male Aging Study who were taking hypoglycemic agents (26%), antihypertensive drugs (14%), vasodilators (36%), and cardiac drugs (28%) was significantly higher than the 9.6% observed for the sample as a whole (93). The cause of erectile dysfunction in many of these patients may not be related to the intake of the pharmacological agent but to the underlying disease. Another possibility in the case of antihypertensives is the reduction of blood pressure in the face of penile arterial atherosclerosis (119).

Mechanisms by which medications can induce erectile dysfunction may include central and/or peripheral neurological blockade or stimulation of PRL secretion. Hyperprolactinemia may reduce testosterone concentration and action through a variety of mechanisms including disruption of the anatomic integrity of the hypothalamic-pituitary axis, decreased GnRH expression (120), interference with GnRH action on the pituitary (121), inhibition of gonadotropin secretion (122), and reduction of testosterone conversion to the more active metabolite dihydrotestosterone (123). Hypogonadism has recently been shown to be associated with decreased NO formation and action in the penis, thus reducing erectile capacity (124, 125). Priapism as a mechanism for erectile dysfunction may be invoked by the intake of phenothiazines (*e.g.*, thioridazine and chlorpromazine) (107) or the newer antidepressant trazodone (107, 108). At present, it is not clear whether drugs of addiction such as alcohol, methadone, and heroin reduce sexual potency by influencing the secretion and metabolism of androgens or by the associated deterioration in the general physical and psychological status of the addict (43, 107).

There is convincing evidence that smoking is a major risk factor for the development of erectile dysfunction (93, 126). Recent statistical studies have shown that the relative risk of developing arterial atherosclerosis in the penis, and subsequent erectile dysfunction, is 1.31 for each 10 pack-years

smoked (127), and that 86% of smokers have an abnormal penile vascular evaluation (128). Long-term smoking has also caused ultrastructural damage to the corporeal tissue in impotent men (129). Acute vasospasm of penile arteries in response to cigarette smoking, possibly subsequent to excessive release of catecholamines, has also been reported (130). Nicotine and conitine were shown to inhibit steroidogenesis in mouse Leydig cells (131), and long-term passive smoking in the rat has been shown to cause an age-independent moderate hypertension as well as considerable decrease in penile NOS activity and neuronal NOS content (132). Thus, smoking impairs erection through a variety of mechanisms, including enhancing atherogenesis, reduction in testosterone production, inappropriate adrenergic stimulation, and inhibition of local vasodilator(s) release.

The organic causes of erectile dysfunction can be grouped into systemic diseases and endocrine, neurological, vascular, or local penile disorders (43). A variety of advanced states of systemic diseases are associated with sexual dysfunctions (97), including chronic liver disease (133), renal failure (134), chronic obstructive pulmonary disease (135), sleep apnea (136, 137), cancer (138, 139), and postorgan transplantation (140). Hepatic cirrhosis and renal failure adversely affect androgen production and/or metabolism.

In addition to deficiency of androgen secretion and/or action that has already been addressed in the preceding section, diabetes mellitus has increasingly been recognized as a major cause for erectile dysfunction (141, 142). Surveys by various investigators suggest that erectile dysfunction occurs in about 50% of diabetic males (97), which is twice the incidence in nondiabetic normal males (111). Moreover, the frequency of erectile dysfunction in diabetics increases with age, from about 25% at age 35 to greater than 70% after age 60, and among diabetic patients with autonomic neuropathy.

Vascular insufficiency is probably the most common cause of organic male sexual dysfunction (67, 143–147). Atherosclerosis of the large pelvic arteries (common iliac, hypogastric, or pudendal) can lead to inadequate perfusion of the penis. In some instances of unilateral disease, erection is achievable while the patient is in the supine position but is lost upon initiation of active pelvic movements. Shunting of blood from the penis to the hip muscles constitutes the pathogenic mechanism for this “steal” phenomenon (144). Other examples of large vessel disease are Leriche syndrome (143) and penile Raynaud’s phenomenon (147). In the former condition, impedance of penile blood supply occurs as a result of obstruction of the distal aorta and presents with claudication of lower back, buttocks, and thighs, whereas the latter condition is due to a vasospastic disorder superimposed on borderline penile arterial flow. Alternatively, obliteration of the small vessels of the cavernous tissue is frequently implicated in the diminution of erectile rigidity in aged men and in men with diabetes (67, 141, 148, 149).

Erectile dysfunction secondary to excessive venous leakage is being reported with significant frequency in clinical studies (72, 73, 150). However, studies in animal models and the low success rate of venous ligation surgery in humans (28–73% of patients recover their erectile function after surgery) suggest that the primary defect is likely to be related to an abnormal function (incomplete relaxation) of trabecular

smooth muscle cells of the corpora cavernosa rather than due to a pathological process inflecting the penile veins themselves (151).

Erectile dysfunction can accompany a variety of acute and chronic central and peripheral nervous system diseases (67, 74, 152–154). Spinal cord injuries deserve a special comment. Loss of erectile or ejaculatory functions in these conditions depends upon the level and extent of the damage. Upper motor neuron lesions diminish the erectile response to psychogenic stimuli but leave the reflexogenic erections intact. The degree of diminution in psychogenic erections is directly related to the extent of the lesion. In contrast, lower motor neuron lesions abolish the reflexogenic response without altering the psychogenic erections except when the lesion is complete. When the latter occurs, psychogenic erections diminish in about 75% of patients (153, 155).

Penile diseases, such as congenital malformation (156), Peyronie's disease (157), priapism (158–161), phimosis (162), and, rarely, cold abscess (163), may interfere with erectile function. Sporadic reports of congenital anomalies, such as absent communication between the corpora cavernosa (isolated cavernous bodies), corporeal venoocclusive dysfunction, and/or hypoplastic cavernous arteries leading to primary erectile dysfunction, have also been reported (156, 164). Lack of circumcision in older men was reported to be associated with a higher incidence of sexual dysfunction (165).

Genitourinary trauma that results in rupture of the corpora cavernosa or the encapsulating connective tissue sheaths, formation of traumatic occlusion of multiple arteries, posttraumatic aneurysmal dilatation with arteriovenous fistulae, resection of the cavernosal nerves during pelvic surgery, penile schwannoma, or pelvic irradiation can all be causes for erectile dysfunction (158–162). Radiation exposure has been shown to decrease the number of NOS-containing nerves in the rat penis (166), and regeneration of penile NOS-containing nerves was shown to coincide with the recovery of erectile function in animals with unilateral cavernous nerve injury (167). Such observations suggest that NO pathway abnormalities are involved in the pathogenesis of erectile dysfunction after unilateral cavernosal nerve injury or pelvic radiation in man (10).

### C. Disorders of ejaculation

There exists a spectrum of disorders of ejaculation ranging from mild premature to severely retarded or absent ejaculation. Normally, by age 17 or 18 yr, 75% of men are able to control their ejaculation (168). Premature ejaculation is the most common male sexual dysfunction (169). Several surveys among different populations estimate its prevalence at 29%, with a range between 1% and 75% depending on the population and criteria used to define the condition (see Refs. 169–171 for review). The DSM-VI (98) defines the diagnostic criteria for premature ejaculation as follows: 1) persistent or recurrent ejaculation with minimum sexual stimulation that occurs before, upon, or shortly after penetration and before the person wishes it; 2) marked distress or interpersonal difficulty; and 3) the condition does not arise as a direct effect of substance abuse, *i.e.*, opiate withdrawal. Premature ejaculation and sexual desire disorders were the frequent re-

ported problems in young adult males with adverse familial relationship to attachment figures (172). Premature ejaculation was also found to be associated with anxiety in a recent survey of 789 men in England (173). Table 2 delineates other common causes of disorders of ejaculation.

Several classifications for premature ejaculation have been reported. In one, premature ejaculation was classified into primary and secondary disorders (170). Primary premature ejaculation describes persons who, since the beginning of sexual experience, have never been able to control the ejaculatory function, whereas secondary premature ejaculation describes individuals who develop the condition after years of satisfactory sexual activity.

Painful ejaculation has been reported as a side effect of tricyclic antidepressants in at least two patients (174). Psychogenic postejaculatory pain syndrome (PEPS) is a rare sexual disorder of male dyspareunia that was first described in 1979 (175) as a persistent and recurrent pain in the genital organs during ejaculation or immediately afterward. Detailed descriptions of clinical features, pathogenesis, and treatment of this syndrome have recently been reviewed by Kaplan (176).

Ejaculatory pain in the testicular region may result from epididymal congestion after vasectomy (177) or from duct obstruction and/or infection (178), testicular torsion, mass lesion, or prostatitis (179). In some cases, specific etiological factors other than psychological stress cannot be identified (180).

### D. Disorders of orgasm

Male orgasmic disorder is defined as a persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase during sexual activity (98, 181). The disorder is relatively rare, occurring in 3–10% of patients presenting with sexual dysfunction (181). Table 2 delineates the most common causes of orgasmic dysfunction.

### E. Failure of detumescence

Priapism is a prolonged (>4 h duration) and extremely painful erection unaccompanied by sexual desire and is often preceded by usual sexual stimuli. The condition is self-perpetuating and is characterized by diminished perfusion of the corporeal bodies. When chronically present, corporeal fibrosis and erectile dysfunction occur.

At least two classifications of priapism have been described (158). The first is etiologically based and classifies the condition into primary (idiopathic) and secondary priapism. The latter condition could be precipitated by causes listed in Table 2. Of particular note, drug-induced priapism lasting for more than 48 h frequently leads to the development of corporeal fibrosis (182), and cocaine-induced priapism can be refractory to treatment (183). The second classification is pathophysiologically based and depends on measurement of penile blood gases and pressures. It classifies priapism into low-blood flow (ischemic) and high-blood flow (nonischemic) conditions. In the majority of ischemic priapism cases, erection probably starts with a normal or high-blood flow state (particularly in cases induced with intrapenile drug

injection) and ischemia ensues when a large number of emissary veins become occluded. Recent studies in rabbits (184) showed that acidosis impairs trabecular smooth muscle contractility, probably secondary to the interference of  $[H^+]$  with the intra- and extracellular mechanisms that regulate homeostasis of  $[Ca^{2+}]$ . Since acidosis is an early complication of ischemic priapism, it was thought that the reduced contractility of trabecular smooth muscle is a significant factor in the perpetuation of the ischemic state (184). A variant of high-flow priapism that is caused by perineal or penile trauma occurs as a result of arterial-lacunar fistula. In this condition, blood bypasses the helicine artery and passes directly into the lacunar spaces. Characteristically, there is no pain or tenderness in this form of priapism, and the penis is incompletely but constantly rigid with a focal area of high-flow turbulence on color-flow Doppler ultrasound examination and high-oxygen tension (160). Sexual stimulation may cause a further increase in penile rigidity.

#### IV. Diagnostic Assessment of Sexual Dysfunction in the Male

Evaluation of male patients with sexual dysfunction requires not only the thorough understanding of the anatomical and the physiological bases of human male sexual dysfunction but also the ability of the physician to collect and properly interpret the patient's history and physical findings. Along with others, we (43, 67, 96, 185–187) have previously advocated such an approach in diagnostic assessment of male sexual dysfunction.

##### A. History

Medical, psychological, and sexual histories are extremely helpful in providing clues to the underlying cause of the dysfunction and they reduce the need for an expensive investigation to rule out all possible etiologies.

1. *Medical history.* Historical events related to the presence of chronic disease (*e.g.*, diabetes, hepatic failure, renal failure, cardiac failure, advanced pulmonary disease, tabes dorsalis, multiple sclerosis, cerebrovascular accident), use of pharmacological agents (*e.g.*, antihypertensives, antihistamines, antipsychotics, anticholinergics), endocrine disorders (gonadal failure, pituitary tumors, thyroid disease, adrenal disease), prior surgeries (prostatectomy, proctectomy, vascular surgery), and trauma (temporal lobe and spinal cord lesions, blunt pelvic trauma) should all be carefully evaluated. Further, vascular risk factors such as family history of cardiovascular disease, hypercholesterolemia, hypertension, diabetes, cigarette smoking, and pelvic radiation therapy should be inquired about, and, if present, vascular etiology should be highly suspected. Potentially irreversible pathology should be anticipated in patients with evidence for other microvascular disease (peripheral neuropathy, retinopathy, and nephropathy). Patients with neurological disease should be questioned about the temporal relationship between the development of the sexual dysfunction and that of the neurological disorder. Patients suspected for hypogonadism should specifically be assessed for family history of the dis-

ease, deviation of adolescence from normality, recent changes in secondary sexual characteristics, symptoms of pituitary dysfunction, history of orchitis, testicular trauma, infertility, or exposure to radiation or cytotoxic agents. Patients should also be assessed for symptoms of thyroid and adrenal diseases.

2. *Psychological history.* Psychological factors associated with male sexual dysfunction have recently been classified into three categories (95, 188): predisposing factors, precipitating factors, and maintaining factors. Restrictive upbringing, disturbed family relationships, traumatic early sexual experiences, inadequate sexual information, and insecurity in the psychosexual role are among the frequently encountered predisposing factors. Unreasonable expectations, random failure, discord in the relationship, dysfunction in the partner, infidelity, reaction to organic disease, or depression or anxiety are some of the factors that could precipitate the onset of sexual dysfunction. Performance anxiety, guilt, poor communication, loss of attraction between partners, and impaired self-image are among the factors that lead to maintenance of the sexual dysfunction. Affective disorders or character pathology can lead to both precipitation and maintenance of sexual problems. Evidence for the presence of any of these psychological or situational conditions should be carefully assessed. Moreover, it should not be forgotten that the existence of an organic disease does not preclude the possibility of a coexisting psychogenic factor. Such omission could lead to diagnostic difficulties as well as to therapeutic failures.

3. *Sexual history.* One of the first goals of the differential diagnosis during history taking is to ascertain the nature of the sexual dysfunction. The patient should be asked to describe his problem, the time and manner of onset, its course, its current status, and any associated medical or psychological problems.

Decreased libido should alert the clinician to three probable causes: endocrinopathy, affective disorder, or relationship discord. A history of frequent strong erections under any circumstances (during foreplay, fantasy, or masturbation, with another partner or upon awakening) indicates that the endocrine, vascular, and neurological systems are probably intact and that the erectile dysfunction is predominantly psychogenic. Conversely, historical data indicating the presence of decreased erectile turgidity in noncoital activities are highly suggestive of an organic etiology. Moreover, a report of firm sustained erections during foreplay that are lost after intromission or upon initiation of pelvic movements might suggest either a psychogenic etiology or a vascular problem (pelvic steal syndrome). A history of delayed or retrograde ejaculation is suggestive of a neuropathy or an adverse drug effect. Premature ejaculation, on the other hand, is more compatible with a psychogenic dysfunction. Finally, it must be remembered that absence of orgasmic sensations in patients with normal erectile and ejaculatory functions is almost always due to psychogenic etiology, whereas failure of detumescence is usually organic in nature, which should direct the investigations toward ruling out local penile, neurological, and hematological etiologies. Table 3 lists other

TABLE 3. Features differentiating predominantly psychogenic from predominantly organic erectile dysfunction

Parameter	Psychogenic	Organic
Onset of disorder	Situational with defined onset	Insidious
Precipitating event	Psychogenic condition	Debilitating disease, vascular insufficiency or CNS abnormality, penile trauma or interfering drugs
Erectile function before intromission	May be present	Usually absent except in patients with pelvic steal phenomenon
Erectile function after intromission	Variable with different partners	Usually absent
Erectile response to other sexual stimuli	Usually present	Usually absent
Nocturnal or morning erections	Initially present and full, lost in long-standing dysfunction	Absent or reduced in frequency and intensity
Course of disorder	Episodic or transient loss of erection	Persistent and progressive erectile dysfunction
Associated ejaculatory disorder	Premature ejaculation and intermittent loss of ejaculation	Retrograde or absent ejaculation
Nocturnal penile tumescence		
Total time	>90–180 min/night	<60 min/night
Circumferential change	>2 cm	<2 cm
Penile-brachial index (PBI)	>0.70	<0.60
Bulbocavernosus reflex latency	<35 msec	>40 msec

[Adapted with permission from R. S. Swerdloff and F. R. Kandeel. In: *Textbook of Internal Medicine*, Lippincott Co., 1992 (187).]

historical events most useful in differentiating predominantly psychogenic from predominantly organic erectile dysfunctions.

### B. Physical examination

When detailed history is coupled with a careful physical assessment, clues to the underlying pathology are frequently obtained. Thus, every effort should be made to elicit physical signs of suspected pathology. General chronic diseases (hepatic, renal, cardiovascular, granulomatous, neoplastic) must be ruled out, and, if present, state of disease control must be determined. Similarly, presence of chronic illnesses such as diabetes, hypertension, thyroid disease, adrenal disease, or hematological disorder, and any degree of complications, must be sought. For example, if diabetes is found, evidence for peripheral neuropathy, autonomic neuropathy, and macro- and microvascular complications should be assessed. In addition to the general and systemic evaluations, detailed assessment of gonadal function, vascular competence, neurological integrity, and genital organ normalcy should be performed on every patient.

Patients suspected of hypogonadism should be assessed for evidence of muscle development, size and structure of the penis (normal adult penis is >6 cm in length in the unstretched flaccid state, 3 cm or more in width, has normal urethral opening, and no evidence of hypospadias) and size and consistency of the testes and the prostate. Patients with moderate hypogonadism including some with Klinefelter's syndrome and many patients with gonadotropin deficiency usually exhibit a decrease in testicular volume from a normal size of 15–30 cm<sup>3</sup> to a size of 6–12 cm<sup>3</sup> (2.9–3.7 cm length, 1.8–2.3 cm width) (189). Patients with severe hypogonadism and many with Klinefelter's syndrome usually have infantile size testis of 2–4 cm<sup>3</sup> (2.0–2.5 cm length, 1.2–1.5 cm width) (8).

A careful vascular assessment should include the palpation of ankle, femoral, and dorsal penile arteries. Penile systolic blood pressure should be determined with a 3-cm blood pressure cuff placed around the base of the penis and a

Doppler stethoscope positioned over each cavernosal artery (67, 99, 143, 185, 186). The penile systolic occlusion pressure is then obtained and compared with that of a brachial artery, and a penile brachial index (PBI) is derived (190–193). Values greater than 0.7 are considered normal (192, 193). Studies by Chiu and colleagues (193) suggested that PBI is highly diagnostic in patients with evidence for peripheral vascular disease but no other risk factors such as diabetes or current intake of medications with potential adverse effects on the erectile function. The PBI is less predictive in patients with peripheral vascular disease and diabetes, and least predictive in those without peripheral vascular disease, diabetes, or current drug intake. Repeating the measurements after 3–5 min of gluteal muscle exercise (186) may enhance sensitivity of the test. Reduction in PBI by more than 0.15 is suggestive of redistribution of the blood supply and its shunting away from the arterial penile bed to the gluteal region. Such a phenomenon is characteristic of patients with steal syndrome (144). Further, the significance of a low PBI may go beyond aiding the diagnosis of vasculogenic erectile dysfunction. This is suggested by a prospective study in 130 impotent patients that were followed for 24–36 months in which a low PBI (0.65 or less) was shown to predict occurrence of a future major vascular event (myocardial infarction or cerebrovascular accident) (194). Physical signs of muscular atrophy, pallor, and/or loss of hair growth of the lower extremities are also consistent with vascular pathology.

Neurologically, the patient should be evaluated for the presence of motor deficits, changes in deep tendon reflexes, loss of sphincter tone, or decrease in light touch or pinprick sensations, particularly in the genital area. Penile temperature sensation testing could also be performed with the use of alcohol swabs (3). In addition, the bulbocavernosus reflex should be elicited by squeezing the glans penis and assessing the evoked contractions of external anal sphincter or bulbocavernosus muscles (186, 195). This reflex response is clinically detectable in 70% of normal males (186). The more sensitive penile vibration perception threshold testing (3, 152, 185, 186, 196, 197) may be performed to confirm results

of the bulbocavernosus reflex. Testing of penile vibration perception threshold is performed by sequentially placing a tuning fork on the glans and bilaterally on midshaft of the penis. Vibration amplitude is then increased until the patient perceives the stimulus. The vibration perception threshold testing is the most predictive sensation testing procedure, but others can also help in evaluating a loss of somatic innervation. The penis should also be examined for evidence of masses or plaque formation, angulation, unprovoked persistent erection, or tight unretractable foreskin.

### C. Selective investigations for male sexual dysfunction

A detailed patient history is important in the evaluation of male sexual dysfunction as it can help suggest the underlying etiology and narrow the scope of the required investigation for selecting an appropriate modality of treatment. A thorough physical examination and brief office-based investigation with assessment of PBI and real-time penile tumescence may also be sufficient to corroborate the nature of the problem and to suggest an etiological basis in most male patients with sexual dysfunction. Once detailed history and physical examination are completed, focus of the medical investigation can then be shifted toward confirming the underlying pathophysiological abnormalities and devising a treatment plan.

Patients with desire disorder, premature ejaculation, and/or postejaculatory pain require a careful assessment of drug use, possible underlying hypogonadism, or presence of psychological or psychiatric conditions (Table 2). Patients with HSD and absent or retarded emission or anorgasmia may need to be evaluated for the presence of CNS disease. Patients with prolonged or painful erection should be evaluated for the possibility of primary penile disease, hematological disorder, or other systemic diseases associated with penile complication, or the intake of pharmacological agents or drugs of addiction that could potentially cause failure of detumescence.

There remain the majority of patients with sexual dysfunction who present with problems related to erectile insufficiency. The availability of erectogenic agents such as oral sildenafil or intrapenile vasoactive drugs (*e.g.*, PGE1) tempts many treating physicians to use them as a primary therapeutic modality without conducting any specialized investigations. Although this may be suitable for a significant fraction of patients with erectile insufficiency, potential complications from these modalities could be life threatening (in the case of sildenafil when taken together with nitrates), and the possibility of finding a potentially correctable disorder (*e.g.*, psychosexual problem, hypogonadism, treatable chronic illness and/or correctable vascular insufficiency) indicate the need to perform the appropriate investigations. Such investigations are needed for patients at high risk for complications and those who may have experienced complications from the intake of these newly approved erectogenic agents (*e.g.*, changes in vision on sildenafil, systemic symptoms from intraurethral prostaglandin, or penile priapism or fibrosis from intrapenile vasoactive injections) to establish the underlying pathophysiology, and hence to select the proper therapeutic interventions. However, before

commencement of such detailed investigations, patients with a clear evidence of chronic organic disease should be evaluated and treated for their primary illness. Those on drug therapy that is likely to be responsible for their erectile problem should have their medications changed or discontinued for a trial period while assessing for the return of potency. Discontinuation of substance abuse before a full diagnostic workup is also required. The remaining group of patients in whom history and physical examination are not conclusive in identifying any specific etiology require an organized multidisciplinary approach involving psychological, endocrine, vascular, and neurological investigations to search for treatable etiological factors. The investigation may also help in counseling patients with uncorrectable etiologies such as microvascular disease or neurological deficits.

*1. Psychological evaluations.* All male patients presenting with sexual dysfunction should be evaluated for psychological factors, even in the presence of an obvious organic etiology. Conversely, the presence of psychogenic conditions, such as anxiety, anger, guilt, or marital discord, should not be construed as evidence for a sole primary causation (101). Initial evaluation can be done by administering a detailed sexual history questionnaire exploring current sexual interactions, social and sexual discords, history of sexual abuse or trauma, gender identity conflicts and preferences, state of mood and affect, and cultural and religious influences. Such questionnaires are helpful in identifying psychological contributions to erectile dysfunction. The coexistence of more than one condition is a frequent occurrence (97). A well structured psychosocial interview with the patient alone, and if possible conjointly with his partner, should follow the administration of any sexual questionnaire to ensure the most complete understanding of all possible predisposing, precipitating, and/or maintaining psychological factors. Features differentiating predominantly psychogenic from predominantly organic dysfunctions are summarized in Table 3 (67).

Several well established and validated self-administered psychosocial questionnaires have been developed and used to assess the frequency and nature of sexual dysfunction in men, and some have been used to assess the adequacy of response to therapeutic modalities. The questionnaires useful in clinical practice include the Derogatis Interview for Sexual Functioning-Self Report (DISF-SR) (198), International Index of Erectile Function (199), and Florida Sexual History Questionnaire (200). For research purposes, the Derogatis Sexual Functioning Inventory (DSFI) (201) and Leiden Erectile Dysfunction Questionnaire (202) are useful. A general criticism of these inventories is the small number of patient samples used to validate them. Other limitations include the lengthy time required for completion of the questionnaire and lack of accuracy in distinguishing psychogenic from organic causes of sexual dysfunction. They are, however, helpful in assessing the presence of problematic personality features, comorbid affective disorders, and situational factors that may be important in predisposing, precipitating, and/or maintaining the disordered sexual function.

*2. Measurement of reproductive hormones.* Patients with a history of decreased libido, diminished secondary sexual char-

acteristics, developmental disorder, anosmia, headache, visual disturbance, and drug ingestion, or patients with physical signs consistent with hypogonadism or androgen resistance, such as abnormal secondary sexual characteristics, decreased testicular size, or abnormal testicular consistency, should have bioavailable serum testosterone and LH measured. Figure 6 describes an algorithmic approach to the work-up and treatment of patients with hypogonadism.

Circulating blood testosterone exists in three states: free, albumin-bound, and SHBG-bound (203). While it is generally considered that SHBG-bound testosterone is not available for uptake by tissues, opinion is mixed as to whether the biologically active testosterone is restricted to the small quantity of the hormone that is free (~2%) or includes the larger amount of albumin-bound hormone (20–80%). Recent investigations suggest that both free and albumin-bound testosterone are biologically available (204). However, measurement of total testosterone levels should be performed only if the patient is free of conditions influencing serum SHBG and/or albumin concentration or binding activities. The free testosterone level calculated from the total testosterone level and the level of SHBG is an alternative approach, and the correlations among this calculated index of bioavailable testosterone and the measured free testosterone by equilibrium dialysis are high (205).

Patients with primary hypogonadism may provide a history of orchitis or exposure to radiation or toxins or may exhibit phenotypic signs of inherited disorders. These patients will have high LH and low bioavailable-testosterone concentrations (206). Patients with androgen resistance will present with varying degrees of hypoplastic genitalia, lack of secondary sexual characteristics, and/or gynecomastia and feminization. Such conditions are heralded by an elevation in both total (or bioavailable) testosterone and LH (206). In subtle cases of androgen resistance, genital skin biopsy for assessment of receptor number and enzyme activities (5 $\alpha$ -reductase and 3  $\alpha$ -ketoreductase) may be required to establish the diagnosis (207).

Patients with secondary hypogonadism and some men with obesity, advanced age, or reduced testosterone binding to carrying proteins may have low total testosterone and LH serum concentrations (Fig. 6) (61, 87, 88, 208–210). Aging is associated with an increase in SHBG and consequently a greater reduction in bioavailable than in total testosterone (87, 90, 92), whereas obesity and certain conditions of abnormal binding proteins may be associated with more suppression in total testosterone than in bioavailable or free testosterone (211). Androgen replacement therapy is usually not required in conditions associated with normal bioavailable or free but depressed total testosterone. Serum PRL

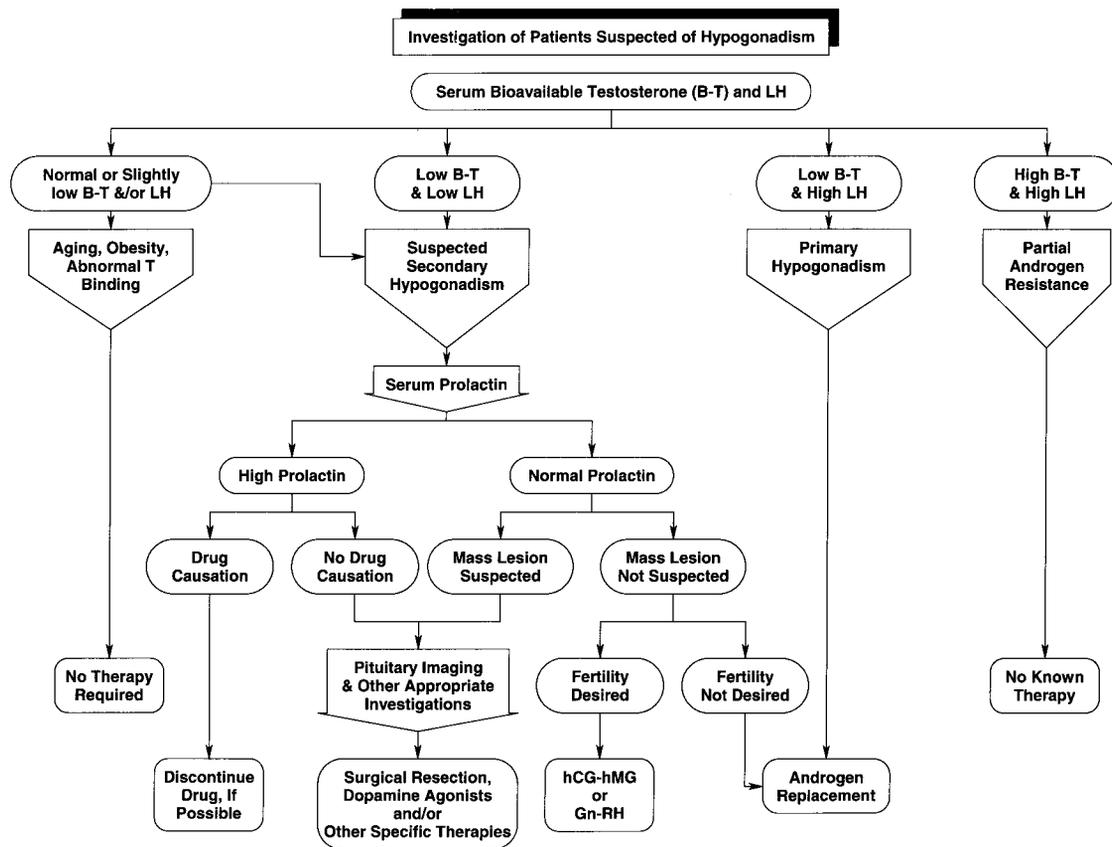


FIG. 6. Algorithmic approach to investigation and treatment of men suspected to have hypogonadism. Elevated levels of serum bioavailable testosterone (B-T) and LH concentrations identify patients with androgen resistance, whereas elevated LH and suppressed B-T identify patients with primary hypogonadism. Low normal or slightly suppressed levels of B-T and/or LH may be found in many subjects with obesity, aging and/or abnormal testosterone (T) binding. Clearly suppressed B-T and LH concentrations identify patients with secondary hypogonadism. In such cases measurement of serum PRL should be obtained to identify patients with hyperprolactinemia. Treatment option should be selected based on the underlying pathology and subject's need, as outlined.

concentration differentiates between hyperprolactinemia and other disorders of the hypothalamic-pituitary axis. In the latter cases PRL is normal or low, but both testosterone (total or non-SHBG-bound) and LH are usually below their respective normal ranges. PRL concentrations in excess of 100 ng/ml are frequently associated with PRL-producing adenomas, whereas lower concentrations may be seen in drug-induced or in idiopathic hyperprolactinemia (206). Other conditions of secondary hypogonadism are characterized by normal or low serum PRL concentration. Further workup of these patients should be directed toward identification of the primary site of deficiency (pituitary *vs.* hypothalamus) since this may influence the selection of treatment modality.

A recent study reviewed the reproductive hormone parameters in 508 men with sexual dysfunction (212). A normal free fraction of testosterone saved an unnecessary endocrine evaluation in 50% of patients with low total testosterone.

**3. Investigation of structural abnormalities of the penis.** Several techniques are available for evaluation of structural and functional integrity of the penile tissue. The following is a brief description of some of these experimental methods and their application.

*a. Penile imaging.* Structural abnormalities of the penis can be evaluated by a variety of methodologies based on the nature of the suspected lesions. Peyronie's disease and its effect on penile vascular competence can be evaluated with color duplex sonography (213). Arteriovenous malformations and lymphohemangiomas can be assessed for lesion extent and involvement of adjacent structures with MRI (145). MRI can also be used to assess for penile ruptures and tears of the tunica albuginea (214).

*b. Penile biopsy.* Percutaneous core biopsy, using 19- and 20-gauge coaxial automatic devices under local anesthesia, has been developed as a safe and technically easy procedure to perform (215). In addition, computerized image analysis techniques of smooth muscle and elastic fibers of the corpus cavernosum tissue samples from normal and impotent men have been developed.

Corporeal fibrosis may develop secondary to abnormalities in the regulation of normal collagen synthesis and degradation, most likely as a result of chronic ischemia (216). Changes in oxygen tension have been shown to affect human corpus cavernosum smooth muscle cell expression of TGF- $\beta$ 1 and synthesis of PGE-1 (217). Oxygen tension consistent with blood PO<sub>2</sub> observed in flaccidity (30 mm Hg) induce TGF- $\beta$ 1 expression and suppress PGE-1 synthesis (217, 218). TGF- $\beta$ 1 is a pleiotropic cytokine that induces connective tissue synthesis and inhibits growth of vascular smooth muscle cells (218), the two principal changes observed in corporeal fibrosis (129).

*c. Cavernosal electrical activity.* Single potential analysis of cavernous electrical (SPACE) activity has been measured in normal subjects and in patients who had pelvic surgery (including prostatectomy), spinal cord injury, and long-standing insulin-dependent diabetes with presumed autonomic neuropathy, as well as smooth muscle dysfunction (219). This study is done by placing two coaxial electrodes into the corpora cavernosa, with the tip of one electrode being placed

centrally into each corporeal body. The neutral electrode is placed on the body surface. The patient is allowed to rest to reduce stress-induced sympathetic overtone, and single potential signals are processed using electrophysiological instruments.

**4. Penile tumescence monitoring.** A variety of procedures are available to assess the involuntary, unconscious penile tumescence that occurs during the REM stage of sleep or the cognitively induced erection that occurs during the exposure to sensual (audio, audiovisual, or fantasy) and/or local tactile (penile vibration) sexual stimuli, which can be used to differentiate between organic and psychogenic erectile dysfunction. Monitoring of penile tumescence after intracorporeal injection of vasoactive drugs has also been used to assess the response to local pharmacological therapies. Changes in penile circumference can be measured in one (midshaft) or two (proximal to the glans and at the base of the penis) locations, using mercury strain gauges (75, 220), electronically controlled constrictive loops (218, 220, 221), Snap Gauges (Timm Medical Technologies, Eden Prairie, MN) consisting of pressure-sensitive plastic strips (222), or simple strips of postage stamps (223). Penile rigidity is assessed either directly using specially designed manual tonometers to measure the pressure required to "buckle" the penis (axial rigidity) (74), or indirectly using electronic dynamometers (224) or constrictive loops (cross-sectional rigidity) (221) during maximum tumescence. Penile rigidity can also be inferred from breakage of three plastic strips incorporated into the Snap Gauge device. The three elements break at degrees of tension corresponding to intracorporeal pressures of approximately 80, 100, and 120 mm Hg, respectively (76, 185, 222). Basic assumptions and limitations of each of these methods are described below.

*a. Nocturnal penile tumescence (NPT) monitoring.* This procedure evaluates the presence or absence of the involuntary unconscious erections, which normally occur during the REM stages of sleep, during 1–3 nights (74–76). Normal nocturnal tumescence has been defined as a total night erection time greater than 90 min and an increase in penis circumference in excess of 2 cm. A change in circumference of 16 mm or 80% of a full erection is thought to reflect a sufficient degree of penile rigidity for vaginal intromission (74, 185). Subsequently, a penile buckling pressure of 100 mm Hg using the manual tonometer, or 100 Penrig (unit used for the electronic dynamometer), was found to provide a more accurate assessment of the degree of penile rigidity required for vaginal penetration than the percentage change in circumference. A buckling pressure less than 60 mm Hg is thought to be inadequate for vaginal penetration (74). Formal NPT testing is performed in a sleep laboratory and includes monitoring the penile circumference and axial rigidity at or near the time of maximum tumescence, and should be reserved to investigate difficult cases, *e.g.*, males in whom psychological factors are strongly suspected but in whom organic factors are questionable or the intake of pharmacological agents are not identified. An electronic home device (Rigiscan monitoring device, Timm Medical Technologies) (225) has been developed to provide continuous recording of NPT and rigidity (76, 221, 226). The system uses two loops, placed around the base and tip of the penis proximal to the coronal

sulcus, to measure penile circumference in millimeters. Radial rigidity as measured by the Rigiscan device was found to correlate with the axial rigidity as measured by the buckling pressure, and both were related to the intracorporeal pressure (76). Recently, Rigiscan data analysis software, in which a 20% increase in base circumference lasting for 3 min or more is counted as an erectile event, has been described by Levine and Lenting (76).

Very recently, a new electrobioimpedance device was used to determine the number and duration of erectile events and the percentage increase in penile blood venous changes during these events (227). The NEVA System (Urometrics, Inc., St. Paul, MN) consists of a small recording unit that attaches to the upper thigh, and three small adhesive electrode pads that are placed over the hip and on the penile base and glans. A constant nondetectable alternating current is delivered to the tissue, and a potential difference is then measured between the electrodes and converted to impedance. Since impedance changes with variation in blood flow, penile volumetric changes can be calculated from the changing measurement of impedance.

Several pitfalls associated with NPT monitoring, which limit the value of using this investigation as an initial screening test, have been discussed extensively by Levine and Lenting (76) and by Schiavi (228). These pitfalls include 1) the paucity of NPT norms for men older than 65 yr; 2) the lack of validation by an independent method other than NPT monitoring itself for the basic assumption underlying this investigation; 3) the lack of clear objective measures to relate the quality of sleep-associated penile erections to those occurring during usual sexual activity; 4) the presence of psychological factors (*e.g.*, anxiety, depression, or loss of sexual desire) or dreams with anxiety content may influence the occurrence of NPT; 5) the first-night effect that may occur on the first night of sleep laboratory monitoring; 6) sleep abnormalities such as apnea, periodic leg movement, and nocturnal myoclonus can adversely influence the quality of NPT recording; 7) the identification of NPT events is dependent on the arbitrary criterion of the minimum erection time required for an erection episode; and 8) the formal sleep laboratory testing is very costly and involves waking the patient when he has 80% of a full erection to measure the buckling pressure of the penis.

*b. Daytime penile tumescence monitoring.* Several adaptations for NPT monitoring were described to reduce the cost of nocturnal sleep laboratory testing and/or to improve the diagnostic efficiency of tumescence monitoring. These include monitoring during the following: 1) morning naps preceded by modest sleep deprivation (229, 230); 2) audio-visual and/or fantasy stimulation (231–233); 3) erectile response to intracavernous vasoactive drug administration with or without audio-visual enhancement (230); 4) pulse Doppler analysis of penile arteries with audio-visual enhancement of the erectile response (234, 235); 5) erotic audio-visual enhancement of the erectile response to vibrotactile stimulation (236); and 6) affective and cognitive response to erotic audio and fantasy stimulation (237). However, several pitfalls of real-time tumescence and rigidity testing in its present form exist and need to be addressed before a suitable

adaptation for general screening can be recommended. These include the following: 1) real-time response to erotic stimuli may be adversely influenced by the psychological factors underlying the dysfunction or those related to the testing environment itself; 2) content of the audio-visual material used may not be consistent with the subject's preference, leading to a reduced or absent erectile response; and 3) criteria for normal tumescence and rigidity response to real-time erotic stimulation have not been established or validated.

A careful medical history and physical examination with basic laboratory tests is currently the recommended initial investigation. The availability of sildenafil may also provide an inexpensive and practical first line of therapy, regardless of etiology, and preclude the need to seek more elaborate testing for many males with erectile dysfunction. However, this testing procedure could have a significant role in evaluating some patients with sexual dysfunction, particularly when psychological factors are suspected as the cause of the problem. Such patients could initially be evaluated with either a Snap Gauge band over 1–3 nights, daytime nap monitoring, or erotic audio-visual/tactile/fantasy stimulation monitoring (Fig. 7).

*5. Vascular investigations.* Patients suspected of having vascular lesions, based on history, physical signs, or abnormal PBI, and those with abnormal tumescence monitoring, may undergo more detailed vascular evaluation of the penile vasculature to determine whether a surgically correctable factor(s) underlies the dysfunction. Earlier studies have used indirect measures to infer arterial blood supply to the penis, such as intraurethral temperature recording during gluteal exercise (31) and simultaneous graphic tracing of finger and penis pulse volume changes (plethysmography) before and after temporary occlusion of blood flow in both organs (postocclusive reactive hyperemia) (146). More recently, several tests were developed to directly evaluate penile inflow and outflow vasculatures.

*a. Pharmaco-penile duplex ultrasound (PPDU).* A duplex scanner with color-flow imaging capability coupled with spectral-displaying system and 7.5-mHz linear-array transducer is the optimal instrument for performing this study (68–70, 146). Using B-mode ultrasonography and color-image guidance, the device can assess the penile soft tissue for the presence of structural abnormalities of the tunica albuginea such as fibrous plaques or calcifications. It can also define the arterial tree, measure the diameter of the cavernosal arteries, and display the Doppler spectrum waveform of blood flow in the cavernosal arteries. Figure 8 describes an algorithmic approach to the interpretation of results of the PPDU investigation.

The diagnostic classification based on PPDU testing is difficult in up to 20% of patients. Other secondary data that could be obtained from the PPDU examination may help to improve the diagnostic yield of vascular abnormalities. For example, Fitzgerald and colleagues found that the combination of persistent dorsal vein flow and elevated end diastolic velocity (EDV) resulted in 93% accuracy in diagnosing venous leakage when correlated with cavernosographic findings, even though the determination of dorsal vein flow

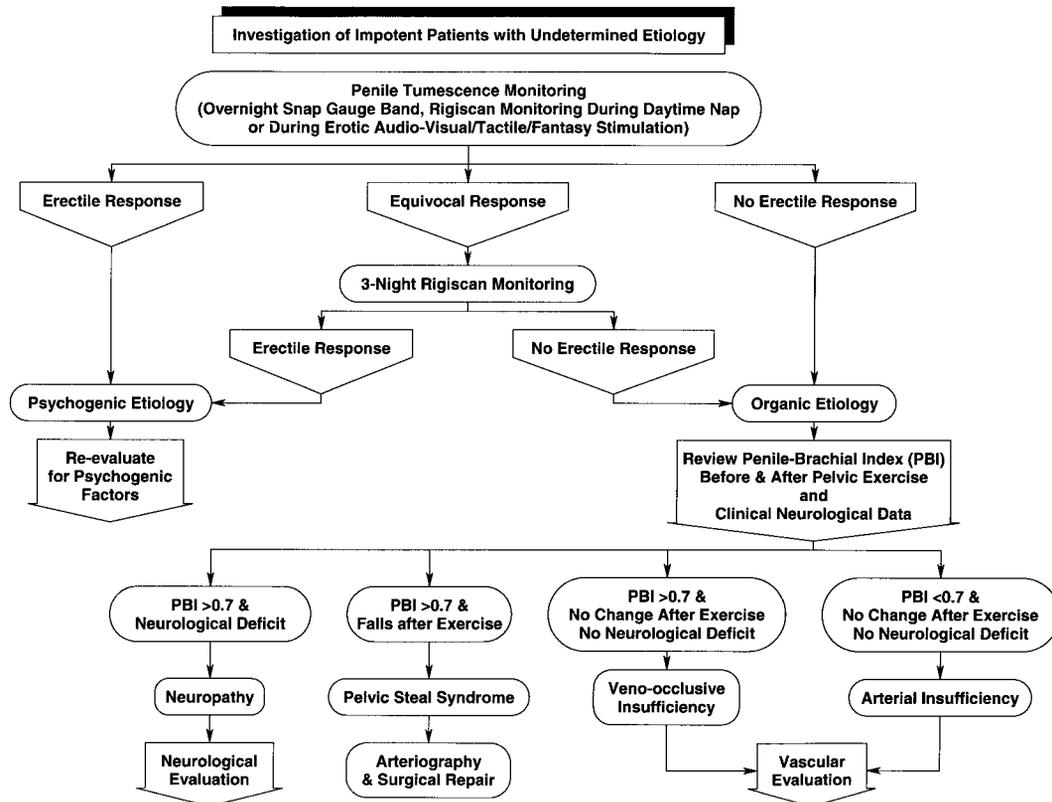


FIG. 7. Algorithmic approach to the investigation of impotent men without hypogonadism or a clear indication for other underlying etiologies. Penile tumescence monitoring with an overnight snap gauge band, or tumescence monitoring during daytime nap or during erotic audio-visual, tactile, and/or fantasy stimulation may provide cost effective screening methods of distinguishing between a primarily organic from a primarily psychogenic dysfunction. Adequate normative data for these procedures are currently needed and should be established for each individual laboratory. A formal 3-night Rigiscan monitoring of NPT should be reserved for patients with inconclusive screening test results. Subjects suspected of organic impotence should have the penile-brachial index (PBI) measured before and after pelvic exercise, and neurological history and physical examination findings reviewed. Normal PBI before ( $>0.7$ ) but not after pelvic exercise suggests a pelvic steal syndrome, a phenomenon that could be treated with surgical revascularization. Abnormally low PBI ( $<0.7$ ) before and after pelvic exercise suggests arterial insufficiency. Normal PBI before and after exercise argues against arterial insufficiency and suggests venous leakage/smooth muscle dysfunction. Patients suspected for vascular insufficiency should undergo the appropriate vascular investigation (see Fig. 8). Presence of neurological deficits by history or on physical examination may help to identify subjects suitable for the further neurological evaluation.

velocity by itself did not prove to be useful in making such a diagnosis (68). PPDU examination may also provide significant information about the existence of significant congenital vascular anomalies and functional or structural abnormalities with the helicine arteriolar system. Knowledge of these types of findings may be of benefit in determining whether surgical intervention is possible or needed.

Several pitfalls exist in the interpretation of data provided by the PPDU investigation (70, 146, 238). Some of these pitfalls may be eliminated by meticulous attention to technique, use of color Doppler scanning, and correlation of results with the degree of penile rigidity. Repeated vasoactive drug injections (239) or exposure to visual erotic stimuli may also help to induce complete relaxation of trabecular smooth muscle, and hence, reduce the overestimation of corporeal structural disease. Also, sufficient erectile response, as assessed by a self-reporting instrument (a postinvestigation questionnaire), may help to reduce the false-positive diagnosis of venoocclusive dysfunction by as much as 50% (240). Venoocclusive dysfunction due to smooth muscle dysfunction or venous incompetence can be ruled out using this approach.

*b. Dynamic infusion cavernosometry and cavernosography (DICC).* This is a four-phase investigation in which corporeal body pressure at equilibrium is determined after injection of vasoactive agents (commonly 45–60 mg papaverine and 1–2.5 mg phentolamine) into one corpus cavernosum to relax the corporeal smooth muscles (phase I). Cavernosometry is then performed by infusing the penis with heparinized saline to raise the corporeal body pressure to 150 mm Hg and observing the fall in pressure over 30 seconds after cessation of infusion (phase II). Cavernosal artery systolic occlusion pressure is measured from the reappearance of the Doppler signal in the cavernosal artery during the decline in intracorporeal pressure following the termination of saline infusion (phase III). Finally, cavernosography is performed by infusing a radiocontrast material into the corporeal tissue and obtaining radiographic images of the penis and perineum (phase IV).

DICC is widely accepted as the reference diagnostic technique for evaluation of venoocclusive dysfunction (72, 73, 146). Intracavernous and systemic brachial blood pressure and penile circumference are monitored continuously throughout. Valid DICC testing is dependent upon a com-

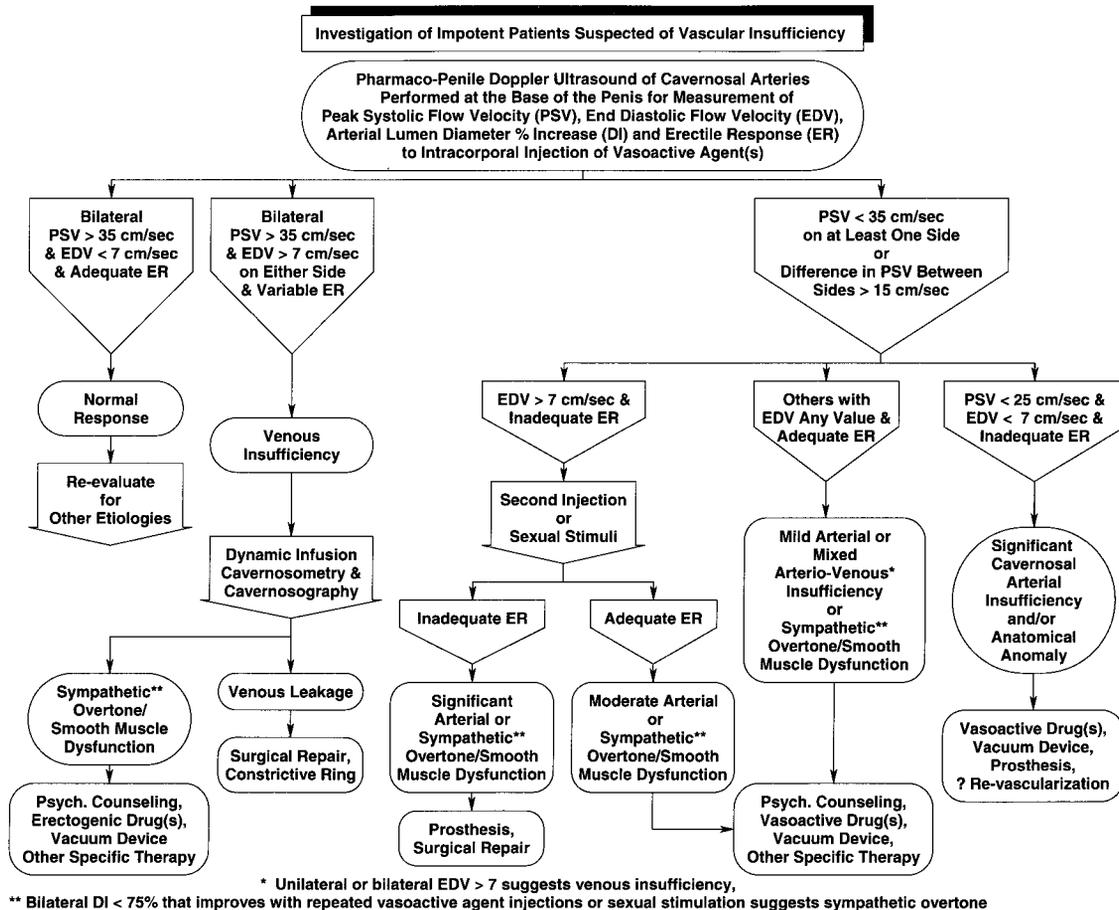


FIG. 8. Algorithmic approach to the investigation and treatment of impotent men suspected of having vascular insufficiency. PPDU of cavernosal arteries with intracorporeal administration of 10  $\mu$ g PGE-1 is suggested as the initial step of the vascular investigation. Subjects with bilaterally normal response should be evaluated for other causes of impotence. Patients with normal PSV but elevated EDV are likely to have veno-occlusive dysfunction. DICC, and in some instances other tests (see text for details), may be required to identify patients with true venous leakage who may benefit from venous ligation surgery. Patients with abnormal PSV, on at least one side, are likely to have arterial insufficiency with or without veno-occlusive dysfunction or sympathetic overtone. The degree of abnormality in PSV in one or both cavernosal arteries, presence or absence of a normal EDV, and the degree of erectile response to one or more vasoactive drug injection(s) or other adjunct sexual stimuli may help to identify the nature and the degree of underlying pathophysiology.

plete relaxation of penile smooth muscles with vasoactive drug administration. Failure to achieve such a state due to the patient's anxiety, an inadequate dose of vasoactive agent(s), or intrinsic smooth muscle dysfunction may yield false-positive results. False-positive results can also occur with psychogenic erectile dysfunction and in normal controls.

At least two other variations of cavernosometry have been described, including pump and gravity cavernosometry (146). In the latter method, an intravenous infusion set is used instead of the pump, and complete corporeal smooth muscle relaxation is induced with local vasoactive drug(s) injections with or without audio-visual sexual stimulation. Gravity cavernosometry has been considered by several investigators to be more physiological, safer, and cheaper than DICC or pump cavernosometry.

*c. Penile angiography.* This study is usually performed in selected patients before reconstructive vascular surgery. These patients are usually young men with a history of blunt perineal trauma leading to a blockage at the origin of the cavernosal artery. Penile arteriography is not indicated in

older men due to low success rates for penile revascularization among this population. Selective pudendal angiography is helpful in defining the site of arterial block and thus in planning the appropriate surgery (241). The sensitivity of procedures for detecting arterial lesions is in the order of 95%. The value of arteriography in microvascular disease is limited, as microsurgical reconstruction is not always feasible. Further, the many variations of arterial supply to the penis and lack of normative data may make the interpretation of the study difficult. Lastly, anxiety related to this procedure may lead to excessive adrenergic discharge with arterial vasoconstriction and increased potential for false-positive results.

*d. Radionuclear scintigraphy.* Several radionuclear scintigraphy techniques have been described in the last three decades (see Refs. 242 and 243 for review). Radionuclide techniques can objectively measure the whole organ blood flow and continuously monitor penile blood volume changes from flaccidity through various phases of erection. Radio-

nuclide techniques that continue to evolve include dynamic penile scintigraphy and dual-radioisotope.

*e. Cavernous oxygen tension.* Measurement of oxygen tension of corporeal blood during flaccidity and during penile tumescence has been suggested as a method for characterization of cavernous perfusion, and thus corporeal vascular dysfunction. Aoki *et al.* (244) reported a sudden increase in cavernous oxygen tension at the onset of penile tumescence during visual sexual stimulation. Others (38) have reported an increase in the corpus cavernosum oxygen tension from 25–40 mm Hg in the flaccid state to 90–100 mm Hg in the erect state of the penis. More recently, Knispel and Andresen (245) correlated changes in cavernous oxygen tension during PGE-1-induced penile tumescence to peak systolic velocity (PSV) during Doppler ultrasonography. They found some impotent men to have low cavernous oxygen tension (measured by new, unbreakable, small-caliber oxygen-sensitive probes, and defined arbitrarily as <65 mm Hg) despite normal blood velocity (defined as >25 cm/sec). Thus, a decrease in oxygen tension may occur as a result of arterial insufficiency and lead to a decrease in trabecular smooth muscle dysfunction (decrease in vascular smooth muscle cells and an increase in connective tissue formation, leading to corporeal fibrosis) in some men with erectile dysfunction. Such changes are probably mediated by an increase in TGF- $\beta$ 1 with a simultaneous decrease in PGE-1 concentrations in corporeal tissue (see discussion in *Section IV.C.3.b*).

*6. Neurological investigations.* A significant amount of research has been performed over the last few decades to define the role of neurological factors in the genesis of male sexual dysfunction. However, much of the earlier work was restricted to studies of the somatic innervation of the penis. Only recently has significant attention been directed to the role of autonomic disorders in the development of sexual dysfunction. Still, many of the newly developed investigative procedures provide only indirect evidence for the presence of autonomic disturbances, and therefore, these procedures may not accurately reflect the abnormality in autonomic nervous system control of the penis. Presence of autonomic dysfunction in organ systems such as the cardiovascular or urological may signal a similar abnormality in the erectile mechanism of the penis. However, most of the tests have not been adequately validated.

*a. Somatic innervation of the penis.* The somatic sensory innervation is important in the development and maintenance of normal erection, and the somatic motor innervation plays an important role in the control of ejaculation. The following provides a brief summary of available methods for testing the integrity of these innervations:

i. *Vibration perception threshold (biothesiometry):* The test provides a biothesiometric screening method for abnormality within the penile sensory afferent pathway. It is performed with a portable hand-held electromagnetic vibration device that has a fixed frequency and variable amplitude of vibrations (3, 197). The loss of, or an abnormal decrease in, vibratory sensation suggests the presence of a peripheral neuropathy.

ii. *Dorsal nerve conduction velocity:* A sensory deficit of the dorsal nerve may reduce the ability to sustain erections during coitus. The decrease in sensory transmission from the penis is also often associated with ejaculation difficulties (197). Since the penis is a distensible structure and the dorsal nerve of the penis is serpiginous at rest, gentle stretching with a one-pound weight is usually performed to straighten the coiled nerve and permit optimal and more accurate measurement of the conduction velocity (246).

iii. *Bulbocavernosus reflex (sacral reflex arc) latency:* Bulbocavernosus reflex latency testing determines the time interval required for a reflex arc that utilizes the dorsal penile/pudendal afferent pathway, the S2–S4 spinal cord segment, and the pudendal/perineal efferent pathway. The test may be helpful in documenting suspected sacral nerve root, cauda equina, or conus medullaris lesions (S2–S4) caused by multiple sclerosis, spinal cord trauma, spinal cord tumors, and herniated intervertebral discs. Since parasympathetic sacral neurons are anatomically close to the central portion of the pudendal pathways, insults to the somatic innervation at these sites may also cause parasympathetic dysfunction (246). The diagnostic sensitivity of the bulbocavernosus reflex latency measurement has been compared with other testing procedures in several studies (247, 248).

iv. *Pudendal nerve somatosensory (genitocerebral)-evoked potential:* This test allows the evaluation of the peripheral and suprasacral afferent pathways by stimulating the pudendal nerve at the penis. The evoked waveforms are recorded at various sites within the CNS, but most typically over the conus medullaris and parietal cortex (3, 152). Patients with sacral lesions (distal to the sacral recording electrodes) caused by multiple sclerosis, spinal cord trauma, or tumor may demonstrate prolonged peripheral and total conduction times. However, patients with suprasacral lesions (cephalic to recording electrodes) caused by transverse myelitis, cervical disc disease, tumor, or trauma may have prolonged total conduction time and central conduction time, but normal peripheral conduction time (196). Further, performing both the bulbocavernosus and the pudendal nerve somatosensory-evoked potential testing may allow the evaluation of the different components of the pudendal nerve.

v. *Perineal electromyography:* The test identifies disturbances in pudendal motor pathways, which may be associated with metabolic or toxic disorders such as diabetes and alcoholism (152). Structural abnormalities of the perineal striated muscles also give rise to abnormal electromyographic recordings. The information obtained can help in assessing the presence of neuropathic defects, the ability to contract the bulbocavernosus muscle voluntarily, and the degree of motor-unit action potential recruitment during a bulbocavernosus reflex or cough (3).

*b. Autonomic innervation.* As previously discussed, the parasympathetic efferent pathways involve the spinal S2–S4 segments and pelvic nerve (Nervi Erigentes), and the sympathetic efferent pathways involve spinal cord segment T12–L2 and the hypogastric nerve. Many of the available autonomic testing procedures provide an indirect measure of the functional state of the autonomic control of the erectile function. However, autonomic parasympathetic [various

forms of cystometry, heart rate variability, and pupillary light reflex latency (249)], and autonomic sympathetic [pupil size adaptation, histamine and acetylcholine skin tests (250, 251)] innervations hold the promise for diagnosing various types of autonomic neuropathy that contributes to erectile dysfunction.

## V. Treatment

Significant advances have been made in the fields of psychosexual counseling, pharmacological therapy, nonsurgical device design and availability, and in surgical techniques. Since some of the pharmacological agents that are currently being used or evaluated for treatment of desire and ejaculatory disorders have a variety of central and peripheral effects, the term "erectogenic drugs" will occasionally be used to more accurately reflect the varying modes of action. Table 4 outlines the current therapeutic options available for each form of sexual dysfunction in men.

### A. Hypoactive or deficient sexual desire

1. *Psychological and behavioral counseling.* At least two recent reviews have addressed the treatment of HSD in males (252, 253). It is generally agreed that desire disorders have a substantially poorer response to psychotherapy (<50%) than other forms of sexual dysfunction (~70%) (175). In addition, the course of therapy tends to be more difficult (175) and the conventional sex therapy techniques (*e.g.*, sensate focus) have generally been inadequate (175, 181). As a result, many psychosexual therapists have adopted a more flexible and individualistic approach to treatment. Others have included cognitive-behavioral therapy, systems approach, script modification, clinical hypnosis, guided fantasy exercises, and sexual assertiveness training (181, 253). Cognitive-behavioral therapy emphasizes the role of thought patterns and beliefs in perpetuating maladaptive behavior and is useful when beliefs held by the patient or couple about norms or responses are contributing to the sexual problem (188). The "systems" approach, on the other hand, targets couple dynamics and allows sex therapists to assess the extent of using sexual dysfunction by the couple to maintain a "sexual equilibrium" within the relationship (*i.e.*, the way sexual dysfunction is used to regulate intimacy or to allow the share of blame between partners for the failure of the relationship) (254). Indicators of poor treatment outcome include lack of spouse motivation, younger age, poor quality of marital relationship, significant symbolic use of sexual symptoms as a defense against the underlying conflict(s), presence of homosexual tendencies, and the presence of major psychopathology and/or hidden medical problems. Accurate diagnosis of desire inhibition, on the other hand, was found to improve treatment outcome.

### 2. Drug therapy.

*a. Hormone replacement.* Several studies have examined the effect of androgen replacement on sexual responsiveness. Studies in hypogonadal men have clearly demonstrated significant improvement in libido factors (*i.e.*, sexual motivation/interest) and spontaneous erections with testosterone

replacement even in the absence of desire deficiency disorders (54, 255–257). However, the results of androgen therapy of men with desire disorder without hypogonadism have been limited and inconclusive (see Refs. 252 and 253 for review).

Male sexual dysfunction caused by insufficient androgen levels can be treated by testosterone replacement therapy. Intramuscular injection of long-acting testosterone esters in oil has been the mainstay of androgen replacement therapy in the United States for decades. The two available preparations are testosterone enanthate (Delatestryl, BTG Pharmaceuticals, Iselin, NJ) and testosterone cypionate (Depo-Testosterone, Pharmacia & Upjohn, Peapack, NJ). Although achieved serum testosterone levels are not physiological (high values for several days after the injection and a decline to low values after 10 days), most males with sexual dysfunction obtain therapeutic effects following injection of 100 to 200 mg at 2- to 4-week intervals since administration of these agents every 4 weeks does not maintain serum testosterone levels within normal range for the entire 4 weeks. Hence, other longer-acting testosterone esters, such as testosterone buciclate and microencapsulated testosterone, which potentially could provide more physiological, long-lasting testosterone levels, continue to be evaluated.

Excessive androgen intake may cause a substantial rise in hematocrit levels, especially in men with chronic obstructive lung disease and heavy smokers. It also decreases the serum concentration of high-density lipoprotein (HDL) cholesterol. Both of these complications could increase the risk for coronary artery disease. Another potential hazard of androgen therapy is the increase in serum prostatic specific antigen (PSA) levels and in prostate volume (see Ref. 258 for review). It is currently not known whether these changes are associated with an increased risk for prostate cancer, although several cases of prostate cancer have been diagnosed after initiation of exogenous testosterone treatment (259). It is important, therefore, that patients undergoing testosterone therapy have baseline rectal examination and baseline PSA measurement performed, and that both studies be repeated at regular intervals.

Testosterone may have a role in the treatment of male frailty with hypogonadism. With careful monitoring because of its potential risks, testosterone supplementation may be considered for improving specific physical and cognitive outcomes in this population.

*b. Other pharmacological agents.* Other pharmacological approaches have included the use of various centrally acting agents (see Refs. 44, 106, 252, and 260 for review). However, controlled studies on the use of these agents in treatment of isolated HSD have not been widely reported, and many of the currently available drugs are not selective and can alter the neurotransmission of more than one receptor type. Generally, administration of the dopamine agonists apomorphine, bromocriptine, and pergolide, or the dopamine precursor levodopa (44, 45, 48, 106, 261), have been associated with increased libido. Cabergoline (Dostinex, Pharmacia & Upjohn) is a new long acting dopamine agonist (262) that is expected to have a similar effect. Also, the antidepressants bupropion and nomifensine have been shown to increase

TABLE 4. Therapeutic approaches to male sexual dysfunction

Sexual disorder	Etiologic factor	Therapeutic options
I. Hypoactive sexual desire	Psychogenic	Psychosexual counseling Drug therapy (trazodone, yohimbine, bupropion) (Table 5)
	Androgen deficiency Primary or secondary hypogonadism	Testosterone replacement for primary and dopamine agonist or other appropriate intervention for secondary hypogonadism
II. Erectile dysfunction	Androgen antagonism	Change inciting agent, if possible
	CNS disease	Depends on nature and extent of disease
	Psychogenic	Psychosexual counseling
	Drug therapy	Discontinue drugs with parasympatholytic or sympathomimetic activities, if possible
	Systemic disease	Treat primary disease including endocrine disorders
	Arterial insufficiency	
	Large artery disease	Vascular reconstruction (Table 6)
	Small artery disease	Vacuum device (Table 6)
		Erectogenic drugs (primarily local vasoactive agents) (Tables 5 and 6)
		Revascularization, if possible
		Prosthesis (Table 6)
		Surgical ligation (Table 6)
	Vacuum device (Table 6)	
	Erectogenic drugs (primarily local vasoactive agents) (Tables 5 and 6)	
	Prosthesis (Table 6)	
	Tissue/molecular engineering (? in the future)	
	Psychosexual counseling	
	Pelvic floor muscle training	
	Constrictive ring or vacuum device (Table 6)	
	Erectogenic drugs (local or systemic agents including $\alpha$ -receptor blockers) (Tables 5 and 6)	
	Surgical reconstruction, if possible (Table 6)	
	Initial trial of systemic (vitamin E, Potaba, colchicine, tamoxifen) or local (collagenase, calcium channel blocker) medical therapy for Peyronie's disease	
	Vacuum tumescence	
	Erectogenic drugs (primarily local vasoactive agents) (Tables 5 and 6)	
	Prosthesis (Table 6)	
	Surgical reinnervation, if possible	
	As per venoocclusive dysfunction, plus	
	Erectogenic drugs (local or systemic agents including $\alpha$ -receptor blockers) (Tables 5 and 6)	
III. Disorders of ejaculation	Premature ejaculation	Psychosexual counseling Drug therapy (local or central acting agents including serotonergics, $\alpha$ -receptor blockers, and anesthetic creams) (Tables 5 and 6)
	Absent or retarded emission	Discontinue sympatholytic drugs, if possible Sympathomimetics, tricyclic antidepressants Vibratory stimulation
Postejaculation pain	Androgen deficiency Psychogenic	Androgen replacement Psychosexual counseling
IV. Orgasmic dysfunction	Drug therapy Psychogenic CNS disease	Discontinue psychotropic agent, if possible Psychosexual counseling Treat inciting disease, if possible
V. Failure of detumescence	Primary penile disease	Surgical correction (Table 6)
	Secondary penile disease	Treatment of inciting systemic disease
	Cavernosal vasoactive drug therapy	Adjustment of agent dose Change to a different agent(s) or a different method of erection enhancement therapy (Tables 5 and 6)

libido in some studies (263). A noradrenergic mechanism of action has been advanced to explain the libido-enhancing effect of bupropion (260). Studies with the serotonergic

agents trazodone (264), venlafaxine (265), and fenfluramine (266) have also shown an increase in sexual desire, and in the case of trazodone, there was no correlation between the im-

provement in libido and the changes in mood. Venlafaxine and its metabolite *O*-desmethylvenlafaxine are potent inhibitors of norepinephrine and serotonin reuptake but weak inhibitors of dopamine reuptake (267). More specific serotonergic agents, however, are generally considered to have an inhibitory neurotransmitting effect in the control of sexual drive (see Refs. 44, 106, and 260 for review).

3. *Other specific therapies.* It has been recognized increasingly that men with primary CNS diseases such as partial epilepsy (103, 268), Parkinsonism (104), poststroke (269), and adreno-leukodystrophy (105) have diminished sexual arousal. Proper counseling and rehabilitation of patients with strokes may lead to an improvement in libido and other sexual disorders (269). Thus, although desire disorders in primary CNS disease may be multifactorial in pathogenesis, treating the primary CNS disease, by itself or in conjunction with other treatment modalities, may well help to recover the sexual libido.

### B. Partial or complete erectile dysfunction

Treatment of male erectile dysfunction should be individualized and in all instances directed at the identified etiologies (Tables 4, 5, and 6). The majority of patients do have systemic diseases and therefore should receive effective treat-

ment for their primary illness and proper counseling regarding the causal relationship, if any, between the underlying disease and the manifestation of erectile dysfunction. The United Kingdom Prospective Diabetes Study Group (270) found that the proportion of type 2 diabetic patients with impotence did not differ at 12 yr across intensive therapy and conventionally treated groups. However, a more recent study has shown that hemoglobin A1c levels, which measure long-term glycemic control, to be an independent predictor of erectile function even after adjusting for peripheral neuropathy in a group of type 2 diabetic males (271). In comparison with men with good metabolic control, Fedele *et al.* (272) found the odds ratios for erectile dysfunction were 1.7 and 2.3 in diabetic men with fair and poor glycemic control, respectively. Generation of superoxide anions and inactivation of NO are involved in the pathophysiology (273).

Discontinuation or substitution of medication may also be required if a temporal relationship between intake of drugs and genesis of the erectile dysfunction is suspected. In addition, the appropriate psychosexual counseling, local or systemic drug therapy, use of nonsurgical erection-enhancement devices, and/or surgical repair of local disease and/or amenable vascular insufficiency should be considered based on the identified pathophysiology. Lastly, surgical implant-

TABLE 5. Pharmacological agents currently used to treat erectile failure

Drug	Drug type	Dose	Comment
Sildenafil (Viagra)	Specific type 5 cGMP phosphodiesterase inhibitor	Oral agent, 25–100 mg in a single daily dose	A very promising agent (effective in up to 87% of patients at 1 yr follow-up) Side effects include headache, facial flush, and indigestion More specific phosphodiesterase type 5 inhibitors are being developed or tested
PGE-1 (alprostadil, Caverject, Edex/Viridal, MUSE pellet)	PGE	Intracorporeal injection, 2.5–40 $\mu$ g Intraurethral pellet, 125–1,000 $\mu$ g	Higher erectile response (74%) than papaverine, with less priapism (0.1%) Least incidence of systemic side effects or corporeal fibrosis, most natural, but often painful (20–40%) Can be supplemented with papaverine and/or phentolamine
Papaverine	cAMP phosphodiesterase inhibitor and $\alpha$ -1 receptor blocker	Intracorporeal injection, 10–80 mg	Potent local vasoactive agent produces usable erections in 30 to 60% of patients Associated with a high incidence of priapism and corporeal fibrosis (up to 20%) Often supplemented with phentolamine and/or PGE-1 (erection rate of 60–90%) Combination preparations of papaverine (5–20 mg) and five other vasoactive drugs are available in Europe (Cerinject)
Phentolamine (Regitine)	$\alpha$ -Receptor blocker (mainly $\alpha$ -1 but has $\alpha$ -2 activity)	Intracorporeal injection, 5–10 mg	Short lived penile rigidity if used alone, commonly used to supplement other vasoactive agents to increase effectiveness and to reduce incidence of side effects A mixture with VIP (Invicorp) is now being evaluated A new oral preparation (Vasomax) is being evaluated
Yohimbine	$\alpha$ -2 Receptor blocker	Oral agent, 6–36 mg per day	Mostly ineffective except in some patients with psychogenic impotence May increase blood pressure and sympathetic nervous outflow in hypertensive patients and those taking tricyclic antidepressants May be effective in treating SSRI-induced sexual dysfunctions May have a synergistic effect when given with Trazodone (100–200 mg at bedtime)

TABLE 6. Comparison of erection-enhancement therapies

Method	Advantage	Disadvantage
I. Oral erection enhancement agents	Ease of administration	Specific phosphodiesterase-5 inhibitors are effective, but many other classes are ineffective High rate of systemic side effects
II. Local vasoactive agents		
A. Papaverine intracorporeal injections	Effective in >90% of neurogenic and psychogenic impotence and in 60–80% of other conditions	Risk of infections, bruises, fibrosis, deformity, priapism, and orthostatic hypotension Variability of dose required
B. PGE-1 intracorporeal injections and intraurethral pessaries	As for papaverine Intraurethral application does not involve self-injection	Burning sensation, priapism
III. Constrictive ring and vacuum-induced tumescence	Relatively inexpensive Constrictive ring may treat venous leakage Vacuum device efficacy is comparable to papaverine injection	Requires patient dexterity and strength to apply and remove Risk of injury during application or tissue ischemia with prolonged use Not suitable for patients with primary or secondary penile disease, blood clotting disorder, or pelvic infection
IV. Surgical corrections		
A. Large artery revascularization	Likely to succeed if isolated lesion	Low rate of success if associated with diffuse atherosclerosis and small vessel disease
B. Small artery revascularization	Attractive permanent treatment option	Technically difficult with low rate of success
C. Venous ligation	Attractive permanent treatment option	High rate of failure and recurrence
D. Repair of penile anomalies (congenital deformity, traumatic rupture, curvature, abnormal size)	Good surgical correction of trauma, curvature, penoscrotal webbing, or penile lymphoedema, particularly in the young Apparent gain of 1 inch with forward displacement phalloplasty, and 1–2 inches with girth-increase phalloplasty	Peyronie's disease may have immunologic basis and could reoccur Recurrent penile shortness, loss of sensation, and impotence after prolongation phalloplasty Graft-site fat absorption, loss of sensation, and hideous appearance after dermal-fat graft
E. Penile prosthesis		
1. Semirigid or nonarticulating malleable implant	Simple construction that provides straight penis in most patients with curvature Easy to insert with fewer complications Least expensive	Constant erection May be difficult to conceal Fixed, relatively small penile girth Not suitable for patients with poor sensations or with history of distal erosion
2. Self-contained articulating or inflatable implant	Relatively easy to insert Suitable for patients with narrow phallus Patient controls state of erection with spring-activated and inflatable devices May mimic natural process of rigidity and flaccidity	Spring-activated and inflatable devices require manual dexterity to operate Inflatable break down more frequently than semirigid or malleable devices Not suitable for patients with poor sensations or with history of distal erosion Some spontaneously deflate with penile bending during intercourse All with fixed, relatively small penile girth Expensive
3. Two or three pieces fully inflatable implant	Mimics natural process of rigidity and flaccidity Patient controls state of erection Two-piece device is suitable for patients with previous pelvic surgeries Three-piece device produces maximum girth and length expansion, and thus suitable for the large phallus Suitable for patients with impaired sensation	Extensive surgical procedure Earlier versions had highest rate of mechanical failure (fluid leakage, tubing obstruction, cylinder ballooning), newer devices are more reliable Two piece device has limited fluid reservoir which makes it suitable only for patients with short or narrow phallus All require high degree of dexterity Expensive

ing of a penile prosthesis may have to be considered if other medical or surgical therapies are not effective.

1. *Psychological and behavioral counseling.* In the past, behavioral and psychodynamic sex therapies and psychoanalysis have been employed as the sole therapeutic intervention in patients with a predominant psychogenic condition. More recently, however, many of these psychological treatments

were proposed as adjunct therapeutic interventions together with specific medical treatment in patients with predominant organic disease (274). Conversely, in certain well chosen cases of psychogenic erectile dysfunction, medical therapies (Table 4) may effectively be used as an adjunct to sex therapy. As discussed earlier, the psychological treatments comprise a wide range of theoretical and practical approaches that have been advocated and used (188, 252). However, there

appear to be no clear-cut differences among the different types of therapy, with most producing positive results lasting for at least 6 months (275). Core elements of the Masters-Johnson psychoeducational approach to sex therapy (276) have been retained by many newer schools because of the higher incidence of patient misinformation about sexual function (277). Psychotherapy has been provided to the male patient alone or more effectively to the couple. A young age of onset of sexual dysfunction for the man, a young age of his partner, a shorter duration of the relationship together, and not being married are all associated with a higher acceptance of couple psychotherapy (278). Treatment of single men frequently reveals intense performance anxiety that prevents them from getting involved in intimate relationships (188). The cognitive strategies are especially useful with single men because of their high degree of dysfunctional attitude toward the problem, and because of their willingness to accept a rational, informative approach without focusing on feelings (279). Treatments that address the patient's interpersonal difficulties result in a significantly better outcome than approaches that focus on problems in sexual functioning alone (280). Recent evidence suggests that sexually dysfunctional couples are generally more distressed than sexually satisfied couples, and the sexually dysfunctional couples appear to address relationship conflicts with somewhat polarized roles characterized with an "avoid *vs.* engage" pattern (281). Thus, significant relationship conflicts may require the adoption of more individualized treatment approaches. Favorable treatment outcome is likely to depend upon many factors, including absence of concurrent psychopathology, minimal partner discord, willingness of partner to participate in therapy, high motivation, short duration of impairment, and lack of gender identity conflicts or homosexual tendencies. Psychosexual techniques that include setting of realistic couple goals, periodic psychosexual therapy follow-up, continual utilization of nonintercourse pleasuring sessions, and initiating intimacy dates have been advocated as relapse prevention strategies (282). Further, two recent studies suggested that behavioral techniques such as pelvic floor muscle rehabilitation with physical exercises and electrical stimulation may help in regaining the erectile function in patients with and without venoocclusive disease (283, 284). Physiotherapy may be particularly effective in treating patients with venoocclusive disease due to dysfunctional corporeal smooth muscle fibers, such as that due to sympathetic over-tone. Hypnosis, but not acupuncture, was also shown to be superior to placebo in treating patients with sexual dysfunction and no detectable organic etiology (284).

## 2. Drug therapy.

### a. Systemic medications.

i. Reproductive hormones: Treatment of hypogonadism should depend upon its etiology and whether or not fertility is desired. Several dopamine agonists are currently available for treatment of patients with hyperprolactinemia not caused by drug ingestion, including the widely used relatively short-acting bromocriptine (Parlodel, Sandoz Pharmaceuticals, East Hanover, NJ) (206), and the more recently approved short-acting pergolide mesylate (Permax, Eli Lilly and Co., Indianapolis, IN) (285) and the long-acting cabergoline (Dostinex, Pharmacia & Upjohn) (262) preparations. Patients with primary or secondary hypogonadism should be treated

with androgen replacement except when fertility is desired (257, 286). Patients with pituitary hypogonadism who desire fertility may be treated with gonadotropin replacement (hCG-hMG) (287), whereas those with hypothalamic hypogonadism may have the option of treatment with GnRH as well (288). Patients with other endocrine dysfunctions should be treated for their primary disease, as androgen therapy has no role in these conditions.

ii. cGMP PDE inhibitor: Sildenafil (Viagra) is a novel oral agent with selective inhibiting activity of PDE-isozyme-5, the major isozyme responsible for clearance of cGMP from human cavernous tissue (13). Such an effect potentiates erections during sexual stimulation. The overall efficacy of sildenafil, estimated from the responses obtained in more than 3,000 men who participated in clinical trials, is approximately 70%. Patients with diabetes mellitus (289) and some of those with neurological dysfunction (289), spinal cord injuries (290), prostatic surgery (291), and pelvic irradiation (292) may have lower response rates, between 35% and 67%. Several other studies have reported on the safety and efficacy of this agent in treating male erectile dysfunction (289–297). Safety and tolerability data from a series of double-blind, placebo-controlled studies and from 10 open-label extension studies of sildenafil in the treatment of erectile dysfunction were analyzed by Morales and colleagues (295). The most commonly reported adverse events were headache, flushing, dyspepsia, and priapism (298); however, the rate of drug discontinuation due to adverse effects was comparable to that of placebo (295).

Sildenafil has a potential for drug-drug interaction with nitrates and NO donors and could cause a drop in systemic vascular resistance and hypotension (299). For example, significant interaction has been observed in clinical studies with a drop in systolic pressure >25 mm Hg in subjects receiving sublingual glyceryl trinitrate (500  $\mu$ g) and sildenafil (25 mg, three times daily) (300). Physician-prescribing guidelines issued by the American College of Cardiology/American Heart Association (ACC/AHA) have recommended extreme caution with the use of nitrates within 24 h of sildenafil ingestion and recommended that sildenafil not be used within 24 h of taking a nitroglycerin preparation; in addition this drug should not be used by men with certain cardiovascular conditions, liver or kidney disease, and by those taking medications that may prolong sildenafil's half-life (*e.g.*, erythromycin or cimetidine) (301). Males with known or suspected coronary artery disease may benefit from an exercise test to determine whether resumption of sexual activity with use of sildenafil is likely to be associated with an increased risk of myocardial ischemia (301). However, retrospective analysis of the concomitant use of antihypertensive medications ( $\beta$ -blockers,  $\alpha$ -blockers, diuretics, angiotensin-converting enzyme inhibitors, and calcium antagonists) in patients taking sildenafil did not indicate an increase in the reports of adverse events or significant episodes of hypotension compared with patients treated with sildenafil alone (302). Thus, the available data support the view that oral sildenafil significantly improves erectile function and is well tolerated in appropriate patients with erectile dysfunction and ischemic heart disease who are not taking nitrate therapy (302).

Sexual activities are likely to be associated with increased cardiac risks in patients with ischemic heart disease due to the increase in cardiac work load, as reflected by the increase in heart rate and blood pressure. Analysis of the adverse events related to sildenafil use posted by the Food and Drug Administration (FDA), as of early 1999, revealed that 70% of 128 patients in question had one or more risk factors for cardiovascular or cerebrovascular disease, including hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, obesity, or previous cardiac history (298). Thus, caution should also be taken if sildenafil is to be used by patients with prior cardiac history or patients with one or more cardiac risk factors, and by those who are taking multiple antihypertensive medications (297). When appropriate, a symptom-limited maximal exercise electrocardiogram examination may be performed to predict patients at risk for ST segment depression during coitus (296). This cautious approach is warranted, particularly in view of the reported case of acute myocardial infarction that occurred 30 min after ingestion of sildenafil in a patient with no clear risk factors for ischemic heart disease (303).

Sildenafil also has a weak inhibiting effect on PDE-6 in the retina. Since long-term human data on retinal changes in patients receiving sildenafil is not yet available, caution is also recommended in prescribing this agent to patients with significant preexisting retinal abnormalities or inherited retinal disease such as retinitis pigmentosa.

Studies using other type 5 PDE inhibitors in animals (Zaprinast, Rhone Poulenc Rorer, France) (304) and humans (IC351/Cialis, Lilly-Icos LLC, Indianapolis, IN) (305) are appearing. Conclusions regarding the specificity and efficacy of these agents are currently awaited.

iii. Vasodilator agents: Although the interest in the use of vasoactive agents in management of erectile dysfunction has surged recently, evidence for the effectiveness of these agents in patients with etiologies other than psychological factors remains tenuous. With the exception of yohimbine most of the available studies were performed on a small number of patients, with ill-defined etiologies. The studies underscore the need for development of new selective receptor modulators. The following is a brief description of available agents.

Yohimbine: Yohimbine (*e.g.* Yocon, Palisades Pharmaceuticals, Tenafly, NJ; Yohimex, Kramer Laboratories, Inc., Miami, FL) is an indole alkaloid obtained from the bark of the African tree, *Pausinystalia yohimbine*. Since it has an  $\alpha$ -2 adrenoceptor blocking action, it was initially thought to facilitate erectile function via a sympatholytic effect, similar to its chemical relative reserpine. More recently, it was suggested that yohimbine facilitates erections by blocking central  $\alpha$ -2 adrenoceptors and produces an increase in sympathetic drive and firing rate of neurons within the brain's noradrenergic nuclei (306). It has also been suggested that yohimbine is active at other CNS receptors, including some serotonergic and dopaminergic subtypes (306). However, several new studies (see Ref. 307 for review) have shown yohimbine to induce a rise in blood pressure and plasma norepinephrine, suggesting that it also exerts peripheral adrenergic actions. Placebo-controlled studies have suggested the effectiveness of yohimbine (usually in doses of 4.5 to 6 mg three times daily) in treating erectile insufficiency due to psycho-

genic or mild organic etiology. The return of complete or partial erections in these studies ranges from 33–71% (308). A recent meta-analysis study of seven therapeutic trials with yohimbine found it to be superior to placebo in treatment of erectile dysfunction (309). However, poor therapeutic effects of yohimbine were reported in several other studies, particularly in patients with clear organic etiology (310, 311). The combination of yohimbine with other agents such as trazodone produced higher response rates in patients with psychogenic impotence, with 56% of patients continuing to draw clinical benefit after 6 months of treatment (312). Delquamine is another new agent with a selective  $\alpha$ -2 adrenoceptor antagonist property that shows promising therapeutic effects in treating impotence. It is currently undergoing evaluation in multicenter trials (313).

Phentolamine: Phentolamine (Vasomax) induces relaxation of corpus cavernosum erectile tissue by direct antagonism of both  $\alpha$ -1 and  $\alpha$ -2 adrenergic receptors and by indirect functional antagonism via a nonadrenergic, endothelium-mediated effect, possibly through NO synthesis activation (314). To date, phentolamine has been used mainly as an adjuvant to other intracavernous vasoactive agents (see below). However, recent limited studies have suggested the possibility of its oral or sublingual use for management of erectile insufficiency. Systemic administration of phentolamine may exert a central antianxiety effect in addition to the local vasodilatation effect on the corpus cavernosum. Alcohol abolishes the effect of buccal administration of this agent, which should also be avoided in patients with severe ischemic heart disease (306).

Isoxsuprine: Isoxsuprine (Vasodilan, Geneva Pharmaceuticals, Broomfield, CO) is a  $\beta$ -2 adrenoceptor agonist that causes vasodilatation by direct stimulation of vascular smooth muscle. It is commonly used as an adjuvant therapy for patients with peripheral vascular disease. Further studies are needed to clarify the role of agents with  $\beta$ -2 receptor stimulation properties in the treatment of male erectile dysfunction.

Pentoxifylline: Pentoxifylline (Trental, Hoechst-Roussel, Somerville, NJ) is a xanthine derivative agent that is widely used in management of intermittent claudication. Pentoxifylline has two major therapeutic effects: an increase in flexibility of red blood cells and a vasodilatation property. Korenman and Viosca (315) used oral pentoxifylline (400 mg three times daily) in a double-blind placebo-controlled study of 18 impotent men with mild to moderate penile vascular insufficiency. Fourteen men were able to reestablish the erectile function on pentoxifylline therapy. Further, the majority of patients had significant improvement in penile-brachial index. Patients with advanced diabetes mellitus, however, did not respond to pentoxifylline.

Other agents: Limited new studies have attempted the use of an oral PGE-1 derivative (Limaprost, Ono Pharmaceuticals, Japan) (316), and the NO donor L-arginine (317) to treat patients with erectile insufficiency with a subjective response rate ranging from 30–45%. In a study examining the effect of dietary supplementation of L-arginine on penile erection and penile NOS content and activity in the aging rat, serum and penile levels of L-arginine were found to increase by 64–148% in treated animals as compared with controls.

A number of herbal remedies have been used by native healers, mostly in Eastern countries, as oral treatment for erectile dysfunction and have recently been reviewed (318). Placebo-controlled clinical trials examining the efficacy and safety of these agents are currently scarce, and much of the available evidence is unsubstantiated. Careful scientific studies examining the safety and efficacy of these naturally occurring remedies in animals and human subjects must be performed and evaluated before the use of any agent can be accepted.

iv. Centrally acting drugs: The use of centrally acting agents to target specific neuronal centers responsible for regulation of the erectile function provides an attractive therapeutic option, particularly for treating patients without local vascular disease or significant peripheral neuropathy. However, the studies are hampered by the lack of clear identification of the various receptor subtypes participating in regulation of erectile function, the relative contribution of each to the overall functional mechanisms, agent selectivity for the receptor subtypes, and the small number of patients involved in the reported studies. The following is a brief summary of recently described agents.

**Trazodone:** Trazodone (Desyrel, Mead Johnson Pharmaceuticals, Evansville, IN) is a triazolopyridine derivative that influences  $\alpha$ -adrenergic, dopaminergic, and serotonergic functions and indirectly stimulates corporeal smooth muscle relaxation. Its therapeutic use for management of erectile function remains controversial, since two recent controlled studies have failed to show a significant improvement in erectile function above that of placebo (319, 320). A retrospective study, however, suggested that trazodone produces significant improvement in the erectile ability in 78% of patients less than 60 yr of age who have no known risk factors for erectile dysfunction. It is likely that major therapeutic effects of trazodone on libido and erectile function is mediated by a central effect through inhibition of serotonin reuptake and an increase in serotonin stimulation of 5-HT-1c receptor (321). This appears to be at variance with the loss of libido induced by serotonin interaction with other receptor subtypes (322). Additional evidence suggests that trazodone may aid erectile function through  $\alpha$ -adrenoceptor blockade and the subsequent reduction in the sympathetic tone (323). Improved libido, improved erectile function, prolonged erection, and priapism have been reported in about 200 patients who were treated for depression with trazodone (323, 324). As a single agent, it may restore erectile function in up to 60% of patients and is superior to placebo (325). A simultaneous use of trazodone with yohimbine has been advocated by some (312, 313).

**Apomorphine:** Apomorphine (Spontane/Uprima, TAP Pharmaceuticals, Deerfield, IL) alkaloids are naturally occurring dopaminergic agonists that may have been responsible for the psychotropic effects of waterlily tubers reported by the ancient Egyptians and the Maya (306). When administered subcutaneously, apomorphine induces bouts of yawning and penile erection in animals and humans (313). It has been used clinically to induce emesis, sedation, and more recently to treat refractory on-off oscillations in Parkinson's disease. In some of these instances a significant improvement in the erectile function was noted (326). Its effects on sexual function appear to be due to central dopa-

minergic activities that lower the response threshold for erectile and ejaculatory reflexes (306) and, at least in rats, are mediated by the sacral parasympathetic and thoracolumbar sympathetic pathways (327). Administration of apomorphine (0.25 to 1.0 mg sc) in placebo-controlled studies was shown to induce erection in approximately 60% of men with psychogenic impotence (328). Its effect on erectile function may be potentiated by visual sexual stimulation (329). A new sublingual controlled absorption preparation of apomorphine (at doses of 3 and 4 mg) was shown to induce erection in about 65% of a small sample of 12 patients with erectile insufficiency not due to organic etiologies (330). Bromocriptine, a dopamine receptor agonist, may offer another therapeutic modality for apomorphine-responsive men (331).

**Naltrexone:** Naltrexone (ReVia, DuPont Pharmaceuticals Co., Wilmington, DE) is a long-acting opiate antagonist. Naltrexone (25–50 mg daily) was reported to produce a full return of erectile function in six patients (332). Further, in two other placebo-controlled studies, naltrexone (50 mg daily) was shown to increase the frequency of morning erection and successful coital attempts (333) and to completely restore the erectile function in 20% of patients (334). The combination of opioid receptor blockade with yohimbine may increase the rate of return of erectile function over that obtained with the use of opiate antagonists alone (335).

**Fluoxetine:** Fluoxetine (Prozac, Dista Products Co., Indianapolis, IN) is a highly selective serotonin reuptake inhibitor that produces sexual side effects in up to 16% of patients receiving the agent for treatment of depression (336). However, case reports of priapism have been reported with the use of fluoxetine. Mechanisms proposed to explain the conflicting sexual stimulation and inhibition effects of fluoxetine and other SSRIs include selective blockade of 5-HT receptor subtypes, partial agonist/antagonist neurotransmission, and/or receptor down-regulation with subsequent activation of central serotonin release (306). As a significant lengthening of the ejaculatory reflex is commonly seen with SSRIs, these agents are better suited for treatment of premature ejaculation (see below).

#### b. Local vasoactive agents.

i. Intracavernous injections: Intracavernous injection therapy of male erectile dysfunction with vasoactive agents has recently been extensively reviewed (306, 322, 326, 337, 338). The following is a brief summary of the pharmacological effects and the reported clinical experience with these agents (also see Table 5).

**Papaverine:** Papaverine is an opium alkaloid without the clinically recognized narcotic effects. It has a direct relaxing effect on smooth muscle tone via the nonselective inhibition of cyclic nucleotide PDEs, which results in the accumulation of cAMP and cGMP (339). It also blocks the voltage-dependent calcium channels, reduces calcium influx, and inhibits the release of intracellular calcium stores. These effects may directly relax the corporeal arterioles, sinusoids, and veins (322, 337). Papaverine is acidic in solution (may precipitate at pH >5), is slowly cleared from the corporeal tissue, has a plasma half-life of 1–2 h, and is metabolized by the liver (337). Injections of papaverine alone produce a full erection in about 35–57% of patients, depending on dose used and the

underlying pathology (see Ref. 337 for review). Papaverine has been used at doses ranging from 3 mg to more than 100 mg, with the onset of response occurring at 10 min to 30 min, and the duration of erection ranging from 30 min to more than 240 min. Patients with underlying arterial disease tend to require higher doses and have a low rate of erectile response. In contrast, patients with neurological disease require small amounts and experience a more lasting response, on occasion requiring corporeal drainage (159, 161, 340).

Side effects associated with papaverine injections are both systemic and local (322, 337). Systemic effects may include peripheral vasodilatation, hypotension, reflex tachycardia, and elevation in liver enzymes. Hemodynamic complications may be more pronounced in patients with venoocclusive dysfunction and are reported to occur in 1% to 8% of patients. Local adverse effects include fibrosis and priapism. Fibrosis occurs in up to 20% of patients and is thought to result from repeated local shear trauma or repeated chemical injury from the low pH of injected solution. Priapism has been reported with more frequency in patients with neurological or psychological etiologies than in patients with vasculogenic impotence. In addition, papaverine-induced erection was found to decrease penile sensitivity as assessed by the perception of vibratory tactile stimulation at two different locations on the underside of the penis (341). Since many of these patients have reduced penile sensitivity at base line (possibly subsequent to neuropathy), intracavernous papaverine injection may augment such an abnormality.

**PGE-1:** PGE-1 (alprostadil) is a metabolite of arachidonic acid and is found in high concentrations in the seminal vesicle and seminal plasma. Injectable PGE-1 is available as a sterile solution (Prostin VR Pediatric, The Upjohn Co., Kalamazoo, MI) or as sterile powder (Caverject, Pharmacia & Upjohn; and Edex/Viridal, Schwarz Pharma, Inc., Milwaukee, WI) (342). Only the latter formulation is currently FDA-approved for management of erectile dysfunction. It is available in 10-, 20-, and 40- $\mu$ g dose-level packaging. PGE-1 is a potent smooth muscle relaxant and vasodilator in man. It also has an  $\alpha$ -2 adrenergic blocking effect and hence has the potential of reducing sympathetic overtone in patients with psychogenic erectile dysfunction. Local metabolism of PGE-1 within the corporeal tissue has also been suggested (343). Systemic blood levels of PGE-1 and its metabolites are significantly lower between 7 and 20 min after its intracavernous injection in patients who exhibit an erection as compared with those who do not (344), suggesting that retention of PGE-1 and its metabolites within the corporeal tissue is an important factor in the development of erectile response. The overall erectile response to prostaglandin intracorporeal injections is about 70% (345). Pain is the most common side effect, occurring in 13–80% of patients and is dose-related. Possible causes of pain include high acidity of solution, local secretion of other vasoactive substances, and/or direct activation of pain receptors by PGE-1 (306). Reduction in the perception of pain could be achieved by adding 7.5% sodium bicarbonate or procaine 20 mg to the injected solution (346, 347), and by slow administration (348). Other side effects associated with PGE-1 injections include local corporeal hematoma or ecchymosis (8%), prolonged erection to between

4 and 6 h (5%), priapism of greater than 6 h (1%), penile edema (2%), and fibrosis (2.3%) (349).

Long-term efficacy and safety of PGE-1 intracavernous self-injection were determined in several studies (350–352). The rate of dropout from treatment was 47% after 3 yr (351) and 67% after 4 yr (350). Patient satisfaction with their erection increased from approximately 23% without injections (351) to 67–91% with injections (351, 352). Reported side effects in one 4-yr study (352) were as follows: prolonged erection >6 h occurring during the first year in 1.2% of subjects; penile pain caused by the injected agent in 29% of subjects during year 1, declining to 12.1% by year 4; hematomas in 33.3% of subjects in year 1 that also declined to 12.1% by year 4; and fibrotic penile alteration (nodules, plaques, deviations) in 11.7% of subjects with spontaneous healing in 48%.

**Phentolamine:** Phentolamine is an  $\alpha$ -1 and  $\alpha$ -2 adrenoceptor blocker. It has a weak erectile-promoting effect when used alone. However, when used in combination with papaverine and/or PGE-1, it potentiates their erectile effects (353–355). By blocking the  $\alpha$ -receptors, phentolamine helps to reduce the vasoconstrictive effects of the sympathetic innervation of the corporeal arteries, and thereby aids in the erectile response. Adverse effects related to its use include orthostatic hypotension and tachycardia.

**NO donors:** Linsidomine (SIN-1) is a metabolite of the antianginal drug molsidomine and acts by releasing NO from the endothelial cells nonenzymatically. It also hyperpolarizes the cell membrane through influencing the sodium-potassium pump and thereby rendering it less responsive to adrenergic stimulation (322). Linsidomine injection at a dose of 1 mg produces usable erection in about 70% of patients (356) and full erection in up to 50% of patients (357). Linsidomine does not appear to be associated with priapism (306).

**Other agents and vasoactive drug mixtures:** Administration of moxisylyte (Mox or Thymoxamine, a competitive postsynaptic  $\alpha$ -1 receptor-selective antagonist), has been shown to produce an adequate erection in 85% of patients, with very low incidence of side effects (358). In comparative studies, PGE-1 was shown to be more effective in producing full penile rigidity than moxisylyte. Very recently, nitrosylated  $\alpha$ -adrenergic receptor antagonists, SNO-moxisylyte (NMI-221) and SNO-yohimbine (NMI-187), were shown to relax endothelin-induced contraction of human and rabbit corpus cavernosum strips in organ chambers to a greater extent than their respective parent compounds (359). Thus, nitrosylated  $\alpha$ -adrenergic receptor antagonists may have a therapeutic role in the treatment of erectile dysfunction by acting as NO donors as well as  $\alpha$ -receptor blockers (359).

VIP is a potent vasodilator and smooth muscle relaxant. However, its injection as monotherapy in man was not shown to produce adequate erection (340). Combined VIP and phentolamine preparations (*e.g.*, Invicorp, formerly known as Vasopotin, Senetek PLC, Napa, CA) have recently been shown to produce a response rate ranging from 66.5% to 75% compared with 12–18% for placebo.

CGRP leads to cavernous smooth muscle relaxation and penile erection (306, 360). It has been used as an addition to other vasoactive agents, such as PGE-1, to treat patients not

responding to a papaverine-phentolamine combination (360).

Trazodone is an antidepressant associated with priapism as a side effect (324). Intracorporeal administration of trazodone was shown, like other  $\alpha$ -blocking agents, to be much less effective in initiating penile erections than direct smooth muscle relaxants (361).

The mixture of papaverine with phentolamine has been extensively used to induce therapeutic erection since 1985 (362). It has been shown to be superior to papaverine alone in inducing erection (65% *vs.* 36%), particularly in geriatric patients (363) and in those with organic dysfunction (362). However, both of these populations tend to require larger quantities (50% or more) of these vasoactive agents than the younger population or those with psychogenic or neurogenic impotence (see Refs. 322 and 337 for review).

Another popular mixture of vasoactive drugs includes papaverine (15–30 mg/ml), phentolamine (0.5–5.0 mg/ml), and PGE-1 (8.33–500  $\mu$ g/ml) and is used in quantities ranging from 0.1 ml to 0.75 ml per injection. In some instances, atropine (3 mg/ml) and/or normal saline (up to 2.4 ml) is added to the tri-mixture (306, 322, 337, 364, 365). The clinical efficacy of the tri-mixture has been documented in several studies. For example, Goldstein and colleagues (365) used a mixture of papaverine, 22.5 mg/ml, phentolamine, 0.83 mg/ml, and PGE-1, 8.33  $\mu$ g/ml, to salvage 62% of nonresponders to either PGE-1 monotherapy or therapy with a mixture of papaverine and phentolamine. Several other studies showed rates of response ranging from 66–92% (see Refs. 306, 322, and 337 for review). Lower incidence of prolonged erection was also reported for the tri-mixture as compared with papaverine alone, papaverine-phentolamine combination, but not for PGE-1 monotherapy.

Several other complications have been reported in patients receiving intracavernous vasoactive drugs. Fibrotic nodules seem to occur more frequently with papaverine monotherapy [5.4% of 1,573 patients from different series reviewed by Junemann and Alken (340)] than with PGE-1 [ranging from occasional cases of Peyronie's-like plaque in up to 3% (366), and Upjohn Co.], or with the tri-mixture [none to 4.2% (367, 368)]. Higher incidence of nodules with increasing duration of therapy with any vasoactive agent has also been suggested (364). The trauma from the repeated administration of vasoactive drugs is more likely to be responsible for the local fibrotic reaction of the tunica albuginea than the drug causing a generalized corporeal fibrotic effect (337). Other rare complications of intracavernous vasoactive injections include local infections (369), hepatotoxicity with the use of papaverine/phentolamine mix in patients with history of alcohol abuse (370), penile shaft hypopigmentation with the use of PGE-1 (371), and accidental breakage of needles in the penile shaft (372).

Home therapy programs of intracavernous vasoactive drugs require careful patient education and training on the use of the lowest effective dose. The latter should be determined by the treating physician and allied in a careful dose titration investigation. Of patients who start on a home-injection therapy program, only 50–80% continue to use it long-term. Frequently cited reasons for the dropout include loss of efficacy, loss of interest, fear of complications, lack of

sexual spontaneity, resumption of spontaneous erections, and favoring other forms of therapy (337, 338). The most likely cause for the resumption of spontaneous erection is the resolution of performance anxiety. In addition, an increase in arterial peak flow velocity may occur in some patients (373).

Several other agents were evaluated for local induction of penile erection either alone or with one or more of the well established drugs. These agents include atropine (374), adenosine (375), enprodyl tartrate [available in France as a separate agent or as a mixture with papaverine under the trade name Vadilex (376)], and  $\alpha$ -melanocyte stimulating hormone analog (377). Additional data on the efficacy and safety of these compounds are currently awaited.

Two new, rather unusual, permanent delivery systems for intracavernous vasoactive drug therapy have been described. In the first, a small cannula is surgically inserted at the penile scrotal junction into the corporeal tissue, and a connected reservoir is placed in a small pouch between the testes. The reservoir is filled with a mixture of phentolamine and verapamil. The system was implanted in eight patients with organic impotence and was reported to be functional in all patients after an average follow-up duration of 13.3 months. In the second system, a 1-cm square window is created in Buck's fascia and tunica albuginea and covered with a piece of the deep dorsal vein of the penis. The penile skin overlying the window is marked with India ink and the patient is instructed to apply the vasoactive drug (nitroglycerin) to this area.

ii. Topical applications: The success in treating erectile dysfunction with intracavernous injection of vasoactive drugs has generated high interest in topical application of these substances. Vasodilating agents used include nitrates (nitroglycerin, isosorbide dinitrate), PGE-1, papaverine, minoxidil, aminophylline, and co-dergocrine (378–384). In general, achieving a functional erection with topical application of these agents has been limited, with more success in patients with psychogenic and neurogenic disorders than in those with vascular problems. Topical application of nitroglycerin has been reviewed by Anderson and Seifert (382). Reported data on the topical application of PGE-1 are limited (306, 385, 386). Kim and colleagues (380) examined the efficacy of 15% and 20% papaverine base gel applied to the scrotum, perineum, and penis in 20 men with organic impotence in a placebo-controlled nonblind study. Full clinical erection was observed in only 3 of 17 patients with mean duration of 38.7 min. The same patients developed erection after topical application of placebo, but with a mean duration of 8.0 min.

Major side effects reported by the patient and/or his sexual partner with the topical application of vasoactive agents include headache and a drop in blood pressure and heart rate. Several precautionary measures are suggested to reduce the incidence of such adverse effects, including careful selection of patients and treatment agents, limiting the topical application to 2–6 h before intercourse, intake of acetaminophen before the topical application, use of latex condom to protect the partner (see Ref. 382 for review).

iii. Urethral applications: Both PGE-1 (alprostadil) and PGE-2 (dinoprostone) are used as intraurethral treatments of erectile insufficiency. Transurethral alprostadil (MUSE, Vi-

vus, Inc., Mountain View, CA) treatment of men with erectile dysfunction is approved in the United States. The observation that approximately one-third of patients responding to transurethral PGE-1 in clinical setting fail to do so at home has been consistent among many studies (387, 388). When accounting for this, the overall in-home response rate for transurethral PGE-1 use is approximately 40%. Moreover, at least two studies have reported even more disappointing results with transurethral PGE-1 (389, 390).

### 3. Nonsurgical devices.

*a. Vacuum pump.* The first vacuum erection device was patented in 1917 and, with some minor modifications, still remains the prototype (391). The device usually consists of a wide clear plastic barrel that is placed around the penis and sealed against the pubic region. Air in the barrel is then vacuumed with the aid of a manual or a battery-operated pump attached to its free end. The vacuum causes expansion of the penis and reduction in the pressure within the cavernous sinusoidal spaces. With increased negative pressure within the barrel, penile blood inflow increases and the erect-rigid state is attained. Maintenance of the latter state is achieved by placing a constrictive rubber band at the base of the penis (some constrictive rings such as the "Soft Touch" by Mission need to be mounted first in advance of vacuuming). Vacuum is then released and the barrel is removed. Most devices incorporate a safety valve to prevent creation of high negative pressure, and consequently penile injury. Duration of erections induced by this method should not be extended beyond 30 min because of the development of ischemia. Generally, these devices are used as a noninvasive method of treatment for patients with vascular and/or neurological erectile dysfunction. Table 6 summarizes the advantages and disadvantages of these and other erection-enhancement therapies.

Several follow-up studies have attempted to evaluate the efficacy and the acceptability of this method of therapy for erectile dysfunction (392). The vacuum constrictive device was found to be particularly effective in patients with partial impotence (392). A few other follow-up studies corroborated these results and suggest a stable use of the device by more than 60% of patients who are able to apply it successfully (392, 393). Thus, the vacuum device is likely to be an effective treatment for erectile dysfunction in the majority of appropriately selected patients.

*b. Constrictive ring.* The few medical devices available are usually sold as part of the vacuum device kit. Intuitively, the constrictive ring is likely to be the only external device needed for management of erectile dysfunction in patients with mild to moderate venous leakage and no coexisting significant arterial insufficiency. Under adequate sexual arousal, such patients should have enough penile arterial inflow to achieve the erect state. As expected, however, the erection is not maintained due to lack of venous occlusion and the decline in the high arterial inflow associated with the initial phases of the erectile cycle. Thus, simple constriction of venous return after attainment of full penile erection may be all that is needed to treat a significant number of men with isolated venoocclusive dysfunction. Of available medical de-

vices, two rings deserve noting: the "Soft Touch" ring from Mission Pharmacal Co. (San Antonio, TX), and the "Pressure Point" ring from Osbon (Augusta, GA). The "Soft Touch" ring consists of a rubber plate with a narrow central neck protruding vertically approximately 0.5 inch. Using an application cone, the plate is placed against the male's body with the projecting neck portion wrapping around the base of the penis. The plate facilitates the removal of the ring without entangling the pubic hair. The "Pressure Point" rubber ring, on the other hand, includes a V-shaped section on the ventral segment to reduce the obstruction to flow of semen in the urethra. In addition, the ring incorporates two internally protruding portions at the dorsolateral junctions to exert more focal pressure at these locations and consequently restrict the venous outflow more efficiently.

Pervasive influence of shame and demoralization regarding erectile problems rather than the ineffectiveness of treatment can be a major cause for the failure of these therapeutic methods. Thus, careful, explicit, extensive, and concrete explanations and instructions of treatment options must be given to the patient at the time of treatment selection. In addition, patient education and training must be reinforced during several follow-up visits if these or any similar methods of treatment are to succeed.

### 4. Surgical treatment.

*a. Arterial revascularization.* About 40% of patients with impotence have evidence of abnormal arterial flow, and approximately 12% of these may have aortoiliac disease due either to aneurysms or occlusive disease (394). Generally, these conditions are amenable to surgical correction, and about 60% of these patients recover spontaneous erectile function postoperatively (394). Most men with major vessel disease, however, rarely present with impotence. Conversely, the majority of impotent patients with arterial disease have pathological changes in the small vessels of the penis. Technically, the corrective surgeries for such smaller vessels are challenging and reported outcome varies significantly (Table 6). Several recent reviews have indicated that the success of these operations depends upon correct patient selection as well as on correct choice of the operative technique (395, 396). Patients younger than 50 yr, with no history of diabetes, with less than two risk factors for atherosclerosis, and who are not tobacco users are more likely to have a higher rate of successful outcome (397). Complications of penile revascularization surgery include pain, altered sensation, shortening of penile length, glans hyperemia, and graft failure (396). The NIH Consensus Development Conference on Impotence, held in 1992, recommended that surgical revascularization of the penis be considered experimental and be performed only by expert surgeons and as part of clinical investigation (96).

*b. Venous ligation.* Initial recovery of erectile function (successful intercourse without adjunctive therapies) within the first 6 months of the surgery has been reported in 60% to 70% of patients (398–409). However, the long-term success rate of penile vein ligation is poor, with only about 20% of patients able to have normal intercourse more than 1 yr after surgery (410). Patients with distal penile shaft leakage (402), younger

age, and lack of concomitant arterial disease or significant crural leak appear to have a higher rate of lasting recovery (405). Thus, the recurrence is unacceptably high and occurs mostly within the first 24 months of surgery. This has led many investigators to conclude that psychological factors and not significant hemodynamic changes are responsible for much of the initial improvement reported after the venous ligation (395). Complications of this procedure include shortening of the penis, penile deviation, glans numbness, and wound infection. More thorough attention to the presence of functional venoocclusive disease and the use of other therapeutic modalities such as psychosexual counseling, pelvic-floor exercises, constrictive ring, and vasoactive drugs should be considered in managing patients with venous dysfunction.

*c. Repair of penile structural abnormalities and augmentation phalloplasty.* Common congenital structural anomalies of the penis include micropenis, hypo- and epispadias, and penile curvature (395). Micropenis and hypo- and epispadias are usually corrected with a penile-lengthening operation. In addition to infection and other common surgical complications, penile lengthening procedures have the potential for several specific problems, including recurrent penile shortening related to reattachment of ligaments; a hump deformity of genitalia due to advancement of the thick hair-bearing lower abdominal skin onto the dorsal shaft; injury to the corporeal bodies or the neurovascular bundle; loss of penile elevation during erection; and patient disappointment due to unrealistic expectations (411).

Webbing of skin at the penoscrotal junction can be congenital or may occur as a result of overresection of the ventral skin during circumcision. The web can be removed by performing a Z-plasty or V-Y advancement at the penoscrotal junction (411). Likewise, penile swelling due to lymphedema can occur with or without an associated lymphatic disorder of the lower extremities. Surgical excision of the lymphedematous tissue may be beneficial if treatment of the underlying cause is not successful in resolving the condition (395).

Penile curvature occurs as a result of the presence of congenital anomalies such as chordee, disproportionate length or elasticity of the tunica albuginea, short urethra, or subsequent to an acquired disorder such as Peyronie's disease or phimosis. Surgical removal of ellipsoid segments (Nesbit), removal of diamond-shaped segments (Nesbit-Kalami), double cross-over (plication), and horizontal closure of longitudinal incision (incisional) are some of the corporoplasty procedures used to correct penile curvature (412, 413). Lengthening of the shortened penis caused by Peyronie's disease using venous grafting and daily stretching with a vacuum erection device has recently been reported in four patients (414). Phimosis is usually adequately treated with circumcision regardless of the age of the patients.

Phalloplasty to increase the penile girth has been attempted by either injecting deposits of fat cells (obtained by liposuction) in the space between dartos fascia (the most superficial fascial layer) and Buck's fascia (a deeper, dense fascial sheath that anchors the penis to the symphysis pubis), or more effectively by inserting dermal-fat graft strips directly above the tunica albuginea (see Ref. 411 for review). Fat

cell injection is associated with uneven aggregation and lipolysis, frequently with only 30% of injected fat surviving after 1 yr. Dermal-fat grafts are more lengthy procedures but have the potential of producing a more lasting effect, frequently with circumference increase of 1 to 2 inches (Table 6).

*d. Phallic reinnervation.* The development of microsurgical techniques and free tissue transfers hold the promise of success for phallic reinnervation. At present this procedure is performed mainly as a part of the total phallic reconstruction in patients with severe micropenis, penile trauma, or those transsexuals undergoing female-to-male conversion (415). In these procedures, the major sensory nerve of the donor free flap is usually coapted to the pudendal nerve. Preliminary results in seven total phalloplasty patients, evaluated at one or more years postoperatively by Gilbert and colleagues (415), showed an encouraging return of tactile and erogenous sensibility despite the presence of high vibratory thresholds and slow bulbocavernosus reflexes.

*e. Penile prosthesis.* Penile prosthetic devices offer an acceptable therapeutic modality for patients who fail vasoactive drugs and vacuum-constrictive device therapies and who are not candidates for vascular reconstruction procedures. Devices are placed by creating an adequate space within the tissue of each cavernosal body, followed by implanting a prosthetic erectile element. When applicable, the two erectile elements are linked to a pump that is implanted into the scrotum, and a fluid reservoir that is implanted into the scrotum, the pelvis, or the abdominal cavity. More than 15 different devices have been marketed since the early 1970s and can be classified broadly into three categories (416–418): semirigid or nonarticulating malleable; self-contained articulating rod or unitary inflatable; and, two- or three-piece fully inflatable implants. Several factors must be considered when selecting a prosthetic device for a given patient, including penile size, presence of intracorporeal fibrosis, the patient's manual dexterity, and the expectation of the patient and his partner. An excellent review of the various models and the advantages and disadvantages of each penile prosthesis has recently been published by Mulcahy (416). A summary of features of each class of prosthesis is also presented in Table 6.

Long-term results of penile-prosthetic implants have recently been reviewed by several investigators (416–418). Generally, modern devices appear to have a long-term mechanical failure rate of approximately 5%. Patient satisfaction over long periods of follow-up approximates 80%, and that of the partner is slightly lower (between 60% and 80%). Many investigators reported enhancement of sexual and nonsexual relationships between the partners after placement of prosthesis. A common dissatisfaction is the lack of penile length. Proper patient and device selection and patient and partner counseling before surgery are of paramount importance if complications and patient dissatisfaction with results are to be kept at a minimum. Other complications associated with placement of penile prostheses, in addition to device failure, penile shortening, and patient dissatisfaction, include acute and delayed infections, destruction of the cavernosal tissue, and possible silicone particle migration to regional lymph

nodes. It should be emphasized, however, that so far there has been no immunological disease in men receiving this treatment that is proven to be related to placement of the implant.

5. *Tissue and molecular engineering in treatment of erectile dysfunction.* Several new observations are promising for new therapeutic modalities of erectile insufficiency using molecular biology techniques. Recently, a number of vascular endothelial mRNA isoforms were shown to be expressed in the rat and human penis (419). Enhancing the expression of this growth factor in the cavernous tissue may emerge as a form of gene therapy for vasculogenic erectile dysfunction. Similarly, seeding of human corporeal smooth muscle cells and endothelial cells on biodegradable polymer scaffolds has led to the formation of cavernosal tissue when implanted in the subcutaneous space of athymic mice *in vivo* (420). Such observation suggests the possibility of corporeal tissue reconstitution by tissue engineering technology. A creative way to grow an autologous penile implant was also reported by the same group of investigators (421). Penile reconstruction using engineered autologous chondrocytes, seeded on biodegradable polymers to create cartilage structures, has been attempted in the rabbit penis. Such technology may be used to create autologous penile prostheses, avoiding the complications associated with the use of foreign materials. Moreover, immunophilins (a group of cellular proteins that mediate nerve regeneration) were shown to promote the regeneration of NOS-containing penile nerves and erection recovery after cavernous nerve crush injury in rats (422), an observation that suggests a possible role for immunophilins in treating male erectile dysfunction associated with penile nerve injury or disease. Another approach to treatment of erectile insufficiency due to neuropathy may involve the use of K<sup>+</sup> channels somatic gene (naked pcDNA/hSLo cDNA) inoculation into the corporeal tissue. Such a possibility is suggested by experiments in which a single intracorporeal injection of this gene restored the streptozotocin-induced decline in erectile capacity in rats *in vivo* (423), and in which the expression of the transcript was largely confined to the original tissue of injection (the penis) at time points greater than 24 h after inoculation (424). Moreover, the isolation of prostaglandin receptors EP2, EP3I, EP3II, and TP (425) and the isolation of caveolin-1 and caveolin-3 (inhibitors of NOS activity) (426) in the human corporeal tissue may help in designing new therapeutic approaches for management of erectile insufficiency and priapism, respectively. Lastly, the use of recombinant human superoxide-desmutase may prove to be effective as a nonsurgical topically applied treatment for Peyronie's disease (427). Thus, these novel strategies hold great promise for the development of physiological management approaches for a very sensitive form of human male inadequacies.

### C. Disorders of ejaculation

#### 1. Premature ejaculation.

a. *Psychological and behavioral counseling.* An array of individual, conjoint, and group therapy approaches using various behavioral strategies has been used in psychosexual

treatment of premature ejaculation (Table 4). In 1956, Semans (428) described the basic procedure for the stop-start technique. With this method, a man is repeatedly brought to high levels of arousal and then stimulation is stopped just before ejaculation begins. Subsequently, Masters and Johnson (429) adapted this technique to a start-stop-squeeze sequence in which the penis is squeezed proximal to the frenulum, by the man or his partner, immediately upon stopping of stimulation. Both techniques are usually employed in a graduated fashion, starting with masturbation, to partner manual stimulation, vaginal containment without thrusting, and ultimately, active thrusting intercourse. Several other additions have been suggested to these techniques, including pulling down on the scrotum, or performing the Valsalva maneuver when approaching the ejaculatory inevitability (430). Psychosexual-behavioral therapy for premature ejaculation can also be delivered in group format (431), through bibliotherapy (432), or as a multimodal holistic framework therapy (433). In the latter method, therapy is formulated after evaluating the individual patient from different perspectives that include behavior, affect, genital sensation, imagery, cognition, interpersonal relationship, and use of drugs or biological modifiers in response to the sexual problem. The combined use of psychosexual-behavioral therapy and pharmacological agents (see below) has also been advocated for the difficult-to-treat cases in some studies (434). In addition, the use of pelvic-floor muscle rehabilitation with exercise training, electrostimulation, and biofeedback to help patients gain control of ejaculatory latency has also been advocated (435).

Although initial rates of success of psychosexual-behavioral therapy have been very high, more recent rates are more modest and range between 60% and 90% (436). Further, these rates are not sustainable and may fall to 25% 3 yr after therapy (436). Such observations are not surprising since many of the studies have pooled patients with different premature ejaculation categories (primary and secondary), age groups, levels of general and sexual anxiety, sexual experiences, and somatic vulnerabilities (such as tactile and/or CNS hypersensitivities) (436). Future therapeutic trials of patients with premature ejaculation should account for these factors and more thoroughly explore the effect of combined behavioral-pharmacological treatment.

#### b. Drug therapy.

i. Serotonergic antidepressants: Several recent scientific articles and reviews have addressed the use of serotonergic drugs in treating patients with premature ejaculation (106, 437, 438). Data earlier than 1995 on the use of clomipramine were reviewed by Althof (438) and by Harvey and Balon (106). These data indicate that clomipramine at doses from 25 to 50 mg is effective in prolonging intravaginal intercourse to at least 2 min in about 70% of men, compared with a 10% improvement in patients treated with placebo. Further, a study by Segraves *et al.* (439) suggested that the intake of clomipramine could be limited to the day of intercourse. The minimum time between drug ingestion and maximum ejaculatory control, however, has not yet been fully established. The mechanism(s) by which clomipramine retards the ejaculatory latency is not totally clear. Clomipramine is a tricyclic

antidepressant, which also acts centrally at the 5-HT-2 receptor to inhibit serotonin reuptake and thus promotes serotonin activities. However, some studies have suggested that it increases the sensory threshold for stimuli in the genital area (440), possibly through inhibition of the adrenergic receptors in the peripheral sympathetic system (441). The effect of clomipramine on sexual function is not always consistent, and both spontaneous orgasms and ejaculation (442) and anorgasmia (443) have been reported to occur in some patients. Painful ejaculation is another possible side effect of clomipramine (442).

Selective serotonin uptake inhibitors, including sertraline (Zoloft), fluoxetine (Prozac), and paroxetine (Paxil) have also been used to treat premature ejaculation (444–446). Similar to clomipramine, these agents also have the potential for inducing variable effects on sexual function, including spontaneous orgasms and ejaculation, anorgasmia, or painful ejaculation (see Refs. 260, 443, and 437 for review).

ii.  $\alpha$ -Adrenergic receptor blockers: The use of  $\alpha$ -adrenergic receptor blockers to delay premature ejaculation is based on the understanding that the sympathetic nervous system is responsible for the peristaltic movement of the seminal fluid through the male genital tract. Preliminary studies (447) suggest that the effectiveness of  $\alpha$ -blockers in treating premature ejaculation is close to that seen in the treatment of benign prostatic hyperplasia (448). However, the final assessment of the role of  $\alpha$ -receptor blocking agents in treating premature ejaculation must await the results of large well controlled trials to examine both efficacy and safety of long-term use.

iii. Local anesthetics: Very limited data are available on the use of topical anesthetic preparations in treatment of premature ejaculation. The onset, depth, and duration of dermal analgesia provided depend primarily on the duration of application. Generally, the topical anesthetic creams are applied to the glans penis and penile shaft under occlusive cover (condom) for at least one half-hour before the sexual encounter. Dermal analgesia reaches its maximum at 2–3 h, and persists for 1–2 h after removal.

## 2. Absent or retarded ejaculation.

a. *Modification of inciting drug therapy/other agents.* Retrograde ejaculation results from damage to the sympathetic innervation of the ejaculatory system and bladder neck. Such a condition may follow spinal cord or cauda equina injury, retroperitoneal lymphadenectomy, radical prostatectomy, or extensive abdominal surgery. It can also be associated with diabetic autonomic neuropathy or with intake of  $\alpha$ -adrenergic blocking agents. A nerve-sparing surgical technique or adequate control of hyperglycemia may guard against the development of such a complication. Moreover, patients in whom retrograde ejaculation is traceable to the ingestion of  $\alpha$ -adrenergic drugs may benefit from trial with alternate classes of medications. Similarly, patients with bladder neck incompetence due to injury may be considered for surgical reconstruction, although the success of this procedure is usually limited. The majority of patients with established dysfunction may not, however, have an existing modifiable condition. Such patients could be considered for therapy with either an  $\alpha$ -adrenergic agent (e.g., ephedrine or midodrine) or imipramine (a tricyclic antidepressant of the dibenzazepine

group of compounds). Generally, restoration of successful antegrade ejaculation with these agents is possible in approximately 30% of patients with diabetic neuropathy or postretroperitoneal lymphadenectomy (449–451).

b. *Electrostimulation and vibratory stimulation.* Courtois and colleagues (153) used physiological recording techniques to study the remaining sexual function in men with spinal cord injury. They found 100% of individuals with high spinal lesions maintained the erectile response to reflexogenic stimulation, and up to 90% of those with lower spinal lesions maintained the erectile response to psychogenic stimulation. Patients with lesions of the conus terminals also maintained 100% of natural emission in response to psychogenic stimulation. The results of this and other similar investigations (452) suggest that men with spinal cord injury frequently underestimate their sexual capacity. However, in many cases attained erections may not be adequately sustained for a successful intercourse to take place (452). Quantitation of organic and psychogenic contributions to the pathogenesis of sexual inadequacy in these patients may require detailed neurophysiological and psychometric studies (453) in order to develop an appropriate treatment strategy. Available treatment modalities include cognitive-behavioral psychotherapy, local or systemic erection-promoting drugs, vacuum devices, and penile implants.

3. *Postejaculation pain.* Since the etiology of postejaculation pain is primarily a psychogenic one, the treatment of this disorder relies entirely on psychosexual and behavioral intervention (176). Organic causes of postejaculatory pain, i.e., chronic prostatitis, should be ruled out before beginning behavioral intervention therapy. In the behavioral therapy approach, the patient is provided with insight into the cause of his disorder and assigned with specific behavioral protocol in which he attempts to ejaculate under conditions that are conducive to muscle relaxation. In addition, the patient is cautioned not to attempt to delay his ejaculation and is allowed to use erotic fantasy to distract himself from the obsessional focus on control of ejaculation. Patients who are severely anxious and unable to relax sufficiently in response to behavioral methods may benefit from a benzodiazepine agent such as diazepam (Valium, 2 to 5 mg, Roche, Indianapolis, IN) or lorazepam (Ativan, 1 to 2 mg, Wyeth-Ayerst, Philadelphia, PA) administered one half-hour before ejaculation to induce a state of muscle relaxation (176).

## D. Absence of orgasm

1. *Modification of inciting drug therapy/other agents.* Since the most common etiology of anorgasmia is the intake of pharmacological agents (such as the selective serotonin uptake inhibitors, the tricyclic antidepressants, or the monoamine oxidase inhibitors), regaining of the orgasmic sensation may be achieved with discontinuation of the inciting drug and, when possible, substitution with an alternate psychotropic (Table 4). Another therapeutic strategy is to discontinue intake of the inciting agent temporarily for 1 or 2 days of each week during which sexual activity could be contemplated, i.e., a drug holiday.

2. *Psychological counseling.* The objective of psychosexual treatment of orgasmic inhibition is to modify the patient's tendency for the obsessive focusing on his preorgasmic sensations and the fostering of pleasure-avoidance and erotic fantasy-abandonment behavior during sexual activity (40, 429). The objectives of therapy can be achieved through implementation of a multiple-step treatment plan. Treatment usually starts with instruction on self-stimulation to orgasm under conducive circumstances while being distracted from his usual obsessive self-observations by external inputs from audio, visual, or imagery sources. This first phase of therapy is aimed at reducing the shared-sex-induced anxiety. Once the patient becomes orgasmic with self-stimulation, presence and then participation of the partner are gradually introduced. Psychotherapy is also provided to help the patient resolve his underlying conflicts (40, 429).

#### E. Failure of detumescence (priapism)

1. *Modification of inciting intracavernous or systemic/other factors drug therapy.* Prolonged erection is a small but significant risk in patients treated with intracorporeal injections of vasoactive drugs. Patients receiving this form of therapy should be adequately counseled on the risk of priapism and advised on the use of minimum effective dose of chosen agent(s) (Table 4). Younger individuals, and patients with psychogenic and/or neurogenic impotence, usually exhibit a satisfactory erectile response to small doses of vasoactive drugs, and they are at higher risks for development of priapism than patients with vascular insufficiency (158, 159, 161, 340, 454). Mild cases of prolonged erection may be treated with oral intake of  $\alpha$ -receptor agonists such as pseudophedrine 30 mg once or twice at 30-min intervals. Also, the  $\beta$ -receptor agonist terbutaline has been used orally to treat priapism of less than 4 h in traumatic paraplegic patients (161). More severe cases of priapism extending for more than 4 h usually require corporeal aspiration and irrigation with a solution containing heparin (5,000 U/liter) and epinephrine (1 mg/liter) (337). Another method is to aspirate 10–20 ml of blood from the corpora with a 19-gauge needle, followed by injection of phenylephrine beginning with doses of 200  $\mu$ g every 5 min and increasing to 500  $\mu$ g if necessary. This appears to be effective in resolving erections of less than 12 h duration (337). Phenylephrine doses of 500  $\mu$ g in 2 ml saline have also been injected into the corpus cavernosum every 15 min without aspiration until detumescence is achieved (455). Other adrenergic agonists such as norepinephrine, ephedrine, and metaraminol have been used to stimulate corporeal vasoconstriction and to reverse priapism. All these agents can cause significant increase in blood pressure, and use of metaraminol was reported to cause death in two cases (456). Occasionally, prolonged priapism (usually of more than 36 h duration) due to vasoactive drug injection requires the surgical placement of an arterio-venous shunt (159, 161, 182, 340). This will cause a venous leakage and possible failure of response to future vasoactive drug injections.

Priapism that is associated with systemic drug ingestion such as phenothiazines and trazodone should be treated with drug dose reduction, or when possible with drug substitution. Patients who are on illicit drugs such as cocaine should

be counseled with rehabilitation programs. Cocaine-induced priapism can be a high-flow variant that is refractory to therapy. In some cases treatment of cocaine-induced priapism may require shunt placement or even partial penectomy (183).

Arterial high-flow priapism, which is caused by arterial-lacunar fistula and is characterized by delayed onset of a constant, painless, nontender erection after blunt trauma, can be treated with mechanical compression, surgical resection of the fistula, and ligation of the internal pudendal or cavernous arteries, selective internal pudendal arteriography with transcatheter embolization, or with watchful waiting. The latter two modalities have recently been reported to be associated with excellent rates of long-term resolution and restoration of erectile function (454, 457).

2. *Treatment of inciting systemic disease.* Management of priapism associated with systemic diseases such as sickle-cell anemia, leukemia, multiple myeloma, Faber's disease, or amyloidosis, and those associated with inflammatory conditions such as tularemia or mumps, should first be directed toward the primary disease. Patients with sickle-cell disease or trait should receive oxygen, hydration, alkalization, and if necessary, transfusion. Patients with malignancy infiltration of the penis may benefit from irradiation, and those with leukemia usually respond to chemotherapy. Systemic infection should be treated with the appropriate antibiotics (159).

3. *Medical treatment of Peyronie's disease.* Treatment of structural penile diseases depends upon the nature of the underlying disease. Peyronie's disease can be self-limiting in many cases and may not require therapeutic intervention. Medical treatment is suitable in the acute phase (<12 months) of the disease when the plaque is unstable. Oral therapeutic agents may include vitamin E, *p*-aminobenzoate (Potaba, Glenwood, Inc., Tenafly, NJ), colchicines, or tamoxifen. Generally, use of these agents could be useful in patients with mild to moderate disease and is associated with 30–50% reduction in plaque size and/or shaft deformity. In addition, erection-associated pain is reduced by 60% to 80% (see Ref. 458 for review). Other forms of medical therapy may include local or systemic glucocorticoids and the intralesional injection of a collagenase or a calcium channel blocker (*e.g.*, Verapamil). These locally administered agents appear to have approximately the same therapeutic effects as the systemic medications. Medical therapy may help patients with moderate disease, whereas surgical correction is the treatment of choice for those with severe penile deformity.

4. *Surgical repair of primary penile disease.* Excision of the plaque and grafting procedures (*e.g.*, Nesbit procedure, corporeal plication, synthetic material, or autologous grafting) are preferred in young patients with well defined Peyronie's plaques, and insertion of a penile prosthesis is best suited for older patients and those with extensive fibrotic changes (458). Treatment of priapism should be directed at the identifiable etiology. When indicated, surgical intervention may help to preserve the subsequent erectile function (459). Phimosis, balanitis, and balanoposthitis usually respond to local measures or circumcision (460).

#### *F. Effect of sexual dysfunction and its treatment on quality of life in affected men*

It was not until very recently that any investigation attempted to evaluate health-related quality of life in men with erectile dysfunction either before or after institution of any specific therapy. Quality of life measures of men were evaluated by the Massachusetts Male Aging Study and found to highly relate to their adequacy of sexual functioning (461). Loss of sexual function after radical prostatectomy was found to be more commonly perceived as a major health problem by 112 Australian men and was more likely than urinary incontinence to adversely affect health-related quality of life (462). A significant correlation between marital interaction and sexual function has also been observed in men with sexual dysfunction attending urology clinics (463).

Long-term prospective follow-up studies evaluating outcome and associated factors in men with erectile dysfunction are also emerging. A follow-up study of 4.1 yr of 107 patients that received either sex therapy (31 patients), self-injection of vasoactive drugs (34 patients), prosthesis implant (21 patients), or no therapy (28 patients) found that, despite an increase in overall rate of penetration, coital frequency did not change and many patients were dissatisfied with the quality of their sex life (464). However, the successful treatment of erectile dysfunction has been shown to be associated with improvement in quality of life. Such a conclusion is supported by several studies in which the Duke Health Profile was used to assess the effect of therapy with PGE-1 on health-related quality of life and found a clear impact of treatment on emotional well-being of the patients (350). Collectively, these studies support the contention that restoring normal erectile function has a positive impact on quality of life.

### **VI. Summary and Future Directions**

Significant advances have been made over the past three decades in the understanding of the physiology and the pathophysiology of male sexual function, starting with the pioneering work of Masters and Johnson. Several new advances in the understanding of desire deficiency and couple dynamic disorders have also been made. As a result, new flexible and individualistic approaches to therapy have been described, including techniques such as cognitive-behavioral therapy and sexual assertive training. In the arena of basic science research, significant advances in understanding the hemodynamic mechanisms of erectile function and the important role of corporeal smooth muscle cells in mediating penile erection have been made. Important neurochemicals regulating the function of the corporeal smooth muscle cells, such as NO and cGMP, have been successfully identified. In addition, several clinical trials are currently evaluating the efficacy of single and combined use of other oral agents in treatment of erectile dysfunction including a myriad of agents with varying peripheral and central activities. Moreover, significant physiological and pathophysiological data are currently accumulating on the role of central neuromediators in regulation of sexual drive, erectile control, and perception of orgasmic pleasure. It is hoped that this will lead

to the development of pharmacological agents that are highly selective in targeting these regulatory sites. The advent of nocturnal and day-time penile tumescence monitoring, intracorporeal injection of vasoactive drugs in association with pulse Doppler analysis, dynamic cavernosometry, and radionuclear penile scintigraphy have been pivotal in arriving at the current understanding of normal and abnormal hemodynamics of male erection.

The realization of the complexity of sexual physiology is increasingly dictating the interdigitation of the expertise of multiple disciplines, including endocrinology, radiology, neurology, urology, and psychology, to provide effective investigative and therapeutic interventions. The role of the primary care physician remains pivotal in determining the presence and magnitude of the sexual difficulties, undertaking some of the preliminary evaluations, and assisting in instituting suitable therapeutic interventions. Detailed hormonal, neurological, vascular, and psychometric evaluations and the subsequent specific hormonal, surgical, and/or psychological therapies should be deferred, however, to the multidisciplinary specialized centers that are capable of undertaking such tasks.

Lastly, much of the attention in the future should be directed to a number of developmental areas. These include characterization of the physiological importance of a number of vasoactive and neuroactive peptides and amines recently found in the penis; simplification and standardization of techniques used in assessing penile structure and function; and establishment of safety and efficacy of newly developed diagnostic and therapeutic drug interventions. The use of androgen supplementation of men with erectile difficulties and low-normal bioavailable testosterone should be reexamined, particularly in view of the new data implicating androgens in local regulation of penile NOS production and action. Moreover, more work is needed to advance and refine the development of new therapeutic approaches such as the use of topically applied vasoactive agents, more selective phosphodiesterase type-5 inhibitors, and gene therapy interventions in the treatment of erectile insufficiency.

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