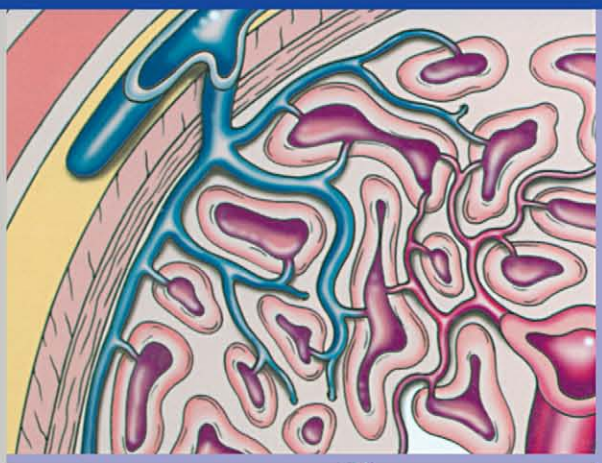
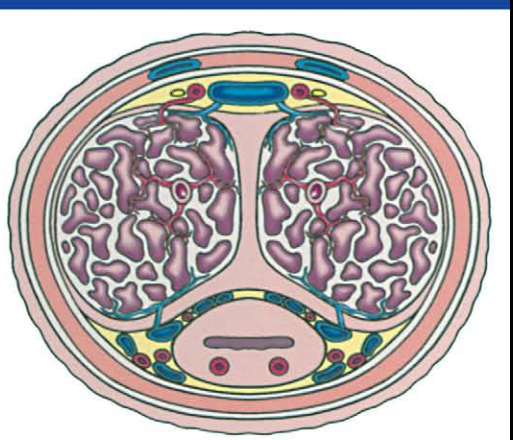
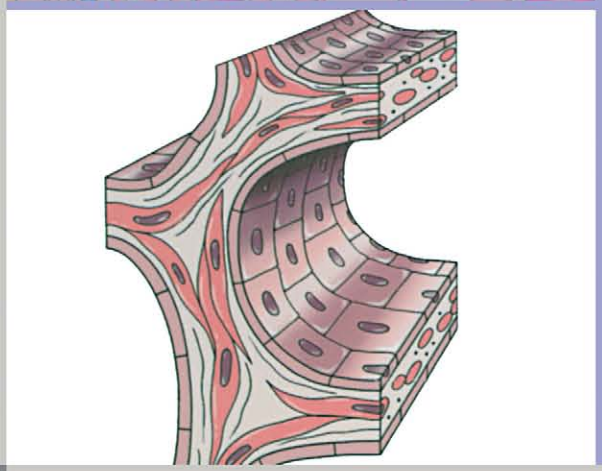
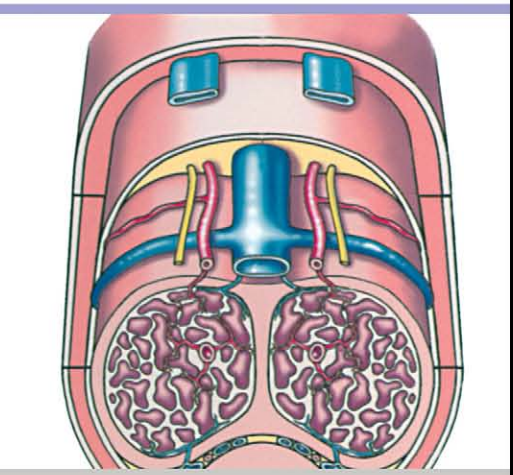
THE ENCYCLOPEDIA OF VISUAL MEDICINE SERIES

An Atlas of ERECTILE DYSFUNCTION

Second edition

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Second edition

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Foreword

It is a great pleasure for me to introduce this recently updated and beautifully constructed *Atlas of Erectile Dysfunction*. For many years, Roger Kirby has been a prolific author and researcher known for his simple and practical approaches to complex urological issues. This new endeavor is further proof of the bright ideas and talent that he possesses.

Over the last two decades, innovative basic research into the functional anatomy and physiology of the penis has vastly improved our understanding of erectile function and dysfunction. Working together, scientists, clinical researchers and pharmaceutical companies have brought on revolutionary changes in the diagnosis and treatment of erectile dysfunction, to the benefit of millions of men and their partners. These rapid changes in the understanding of the pathophysiology and management algorithm have also caused much confusion and debate among the medical community regarding the most appropriate and cost-effective approach to the management of erectile dysfunction. Therefore, it is with great admiration and appreciation of my dear colleague Roger Kirby that I acknowledge his tremendous achievement in putting together such an extensive, yet straightforward, book on the current state of the subject.

An Atlas of Erectile Dysfunction contains diagrams of basic anatomy mechanisms, pharmacology and neurophysiology that are clearly outlined and easy to understand. The chapter on diagnosis is streamlined to give the reader an excellent idea of which tests are needed in cases where more detailed examination is necessary. The discussions covering the various options are well written, especially the sections discussing the new oral agents. The illustrations of surgical treatments, such as revascularization, penile prosthetic surgery and reconstructive surgery for Peyronie's disease, are somewhat simplified but, nevertheless, illustrate the key steps involved in each technique.

Overall; this is an excellent reference book which is superbly illustrated by numerous drawings and photographs in color. The reader will not only appreciate the major progress in erectile dysfunction research and management, but will also enjoy the beautiful illustrations which make this atlas a must-read for anyone interested in this topic.

Tom F.Lue, MD
San Francisco

Preface

Good communication is the byword of our time. Visual images convey information more coherently and more effectively than words. With this in mind, I have put together an updated *Atlas of Erectile Dysfunction* to make available the latest state-of-the-art information as to the causes, diagnosis and treatment options for this highly prevalent and often distressing condition. Since both family and nurse practitioners are increasingly involved in the care of men suffering from erectile dysfunction, I have included some images of other conditions affecting the external genitalia; such as condylomata acuminata and penile carcinoma. These problems can occasionally surface and cause confusion in an erectile dysfunction clinic or the family practitioner surgery.

It has been estimated that overall one in ten men suffers from erectile dysfunction. Although never life-threatening in the usual sense of being fatal, erectile dysfunction may yet have major effects on quality of life by causing considerable loss of selfesteem and often putting important life relationships in jeopardy.

However, for the first time, we are now able to understand the causes, pinpoint the diagnosis, and initiate safe and effective therapy for the many sufferers with this disorder. Unfortunately, many doctors and other health-care professionals still become uneasy at the thought of a frank and open discussion concerning matters of sexual dysfunction. Much of this taboo is due to a lack of understanding of the causes and awareness of the remedies now available for the problem. It is my hoped-for intention that this second edition of the atlas will provide clinicians with easy access to the information that they require to bring up the subject with their patients and alleviate the often considerable anxiety and distress endured not only by the many men afflicted by erectile dysfunction, but by their partners as well.

Roger S.Kirby
London

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Introduction

Until recently, a man unable to develop or sustain an erection sufficient for penetrative sexual intercourse has been referred to as ‘impotent’. This term, however, has negative connotations which imply a general loss of prowess in other domains of mental and physical function. Thus, nowadays, the more specific term ‘erectile dysfunction’ is preferred.

Although the problem is most commonly the result of isolated malfunction of penile erection, diminished or absent libido and delayed or absent orgasm and ejaculation frequently coexist with erectile dysfunction, each in its own way contributing to the afflicted individual’s sense of failure and personal inadequacy.

Many millions of men world-wide are afflicted by erectile dysfunction. Although the ability to develop and sustain an erection may not always result in complete loss of sexual satisfaction, in most men, it creates a psychological stress that adversely affects the relationship with their partner. This, in itself; often compounds the physical problem. In men of all ages; erectile dysfunction diminishes the willingness to initiate or continue sexual relationships, not only because of loss of self-esteem, but also because of the fear of the humiliation associated with inadequate sexual performance and the risk of subsequent rejection.

Erectile dysfunction is frequently regarded as an inevitable part of aging and, thus, as a symptom simply to be accepted with stoicism. However; this assumption is often incorrect. Erectile dysfunction is not uncommonly the result of some other illness, such as diabetes mellitus or hypertension, or a consequence of the treatment of the latter disorder with antihypertensive agents.

The correct diagnosis of erectile dysfunction depends on an accurate and sympathetically elicited history which recognizes that the physical component may be only part of the problem. The psychological, interpersonal and wider social ramifications also need to be tactfully assessed. Careful physical examination and judicious stepwise use of investigations help to complete the picture.

Now, for the first time; an increasing range of safe and effective treatment options is available for men who suffer from erectile dysfunction. Many of these options, however, are poorly appreciated not only by patients; but also by health-care professionals, many of whom still feel too embarrassed to address this highly prevalent and distressing problem in a serious and sympathetic manner.

Erectile dysfunction often has a major impact on the self—esteem and quality of life not only of the man, but also of his partner. Thus, there are few areas in medicine where so much remains to be done and with so much potential to improve the outlook for the many millions of sufferers as well as for their partners.

Anatomy

The key structures mediating penile erection are the paired corpora cavernosa or ‘erectile bodies’ (Figure 1). These cylindrical structures form the bulk of the penis and fill with arterial blood under pressure at the time of erection. Fused distally for three-quarters of their length, they separate proximally to fuse with each ischial tuberosity of the pelvis. Each corpus cavernosum has a thick fibrous sheath, the so-called tunica albuginea, which surrounds the erectile tissue, made up of multiple lacunar spaces that are inter-connected and lined by vascular endothelium (Figure 2). The trabeculae constitute the walls of these spaces, and comprise smooth muscle and a fibroelastic framework of collagen in almost equal quantities.

The corpus spongiosum surrounds the urethra, which traverses the length of the penis within this structure, lying in the ventral groove formed by the paired corpora cavernosa in the pendulous portion. At its proximal portion, it expands to form the bulb, which curves upwards through the urogenital diaphragm to reach the apex of the prostate gland. Distally, the corpus spongiosum expands to form the glans penis (Figure 3). The spongiosum is composed of sinusoidal spaces of larger dimensions than those of the corpora cavernosa and with less smooth muscle. The tunica albuginea surrounding the spongiosum is flimsy compared with that of the corpora, but the spongiosum is nevertheless capable of an erectile response.

The corpus spongiosum in the bulbar region is surrounded by the bulbospongiosus muscles (Figure 4). These have two important functions: to facilitate ejaculation by their rhythmic contractions, and to empty the bulbar urethra after voiding, thereby preventing postmicturition dribble.

The skin overlying the penis is exceptionally mobile and expandable to accommodate the considerable increase in girth and length that occurs during erection. This lack of adherence makes it relatively susceptible to edema. In its distal portion, the penile skin extends forward to form the prepuce before folding backwards and attaching to the corona of the glans penis (Figure 5).

The pendulous portion of the penis is supported and stabilized by the suspensory ligament (Figure 6). Division of this structure makes the penis appear longer in its flaccid state, but this does not enhance the proportions of the organ when erect.

ARTERIAL BLOOD SUPPLY

The blood supply to each corpus cavernosum is derived mainly from the internal iliac artery, a branch of the atheroma-prone common iliac artery. In the pelvis, the internal pudendal artery passes beneath the sacrospinous ligament and over the sacrotuberous ligament, and gives off the perineal artery in Alcock’s canal, where it runs under the superficial transverse perineal muscle and the symphysis pubis (Figure 7). After giving off the perineal artery, it becomes the common penile artery (Figure 8). This vessel pierces the pelvic floor adjacent to the inferior ramus of the ischium near the bulb of the urethra and gives off the bulbar, urethral, dorsal and cavernosal branches before reaching the corpus cavernosum to form one element of the paired dorsal arteries (Figure 8).

The cavernosal artery on each side pierces the tunica albuginea at the hilum of the penis. It then runs distally in the center of each corpus while giving off numerous helicine branches. These corkscrewshaped muscular vessels open directly into the lacunar spaces (Figure 9). The tonic contraction of the smooth muscle walls (Figure 10) normally allows only small amounts of blood into the lacunar spaces, thereby maintaining penile flaccidity. Relaxation of the muscular walls of these vessels initiates the hemodynamic changes that result in penile erection.

VENOUS DRAINAGE

Blood leaves the penis via three venous systems: superficial, intermediate, and deep. The superficial system allows blood from multiple superficial veins to drain into the superficial dorsal vein, which itself drains into the left external branch of the internal saphenous vein. The intermediate venous system lies beneath Buck’s fascia and comprises the deep dorsal vein and the multiple circumflex veins. This system drains blood from the glans, corpus spongiosum and the distal two-thirds of the corpora. The deep dorsal vein runs in the groove dorsally between the corpora cavernosa. It enters the pelvis beneath the suspensory ligament, which suspends the corpora from the undersurface of the pubic arch and drains into the dorsal venous

complex at the urethroprostatic junction. The deep drainage system consists of the cavernosal and crural veins. Emissary veins in the proximal third of the penis join to form one or two cavernosal veins which pass between the bulb and crus of the penis to drain into the internal pudendal vein (Figure 11).

LYMPHATIC DRAINAGE

Lymph is drained from the penis by lymphatics which pass to the superficial and deep inguinal lymph nodes of the femoral triangle (Figure 12). In turn, these nodes, which may become secondarily involved in patients who have carcinoma of the penis (Figure 13), drain to the external and internal iliac lymphatic chains. Conditions that obstruct these lymphatic channels, such as metastatic prostate cancer, may result in gross penile and scrotal edema.

NEUROANATOMY

Three sets of peripheral nerves are involved in penile erection and subsequent detumescence: parasympathetic nerves from the second to fourth sacral (S2–S4) segments, sympathetic nerves from the tenth thoracic to the second lumbar (T10–L2) thoracolumbar outflow, and somatic fibers via the pudendal nerves (Figure 14).

The sympathetic nerves reach the corpora, as well as the prostate and bladder neck, via the hypogastric nerves, where they are susceptible to injury in retroperitoneal lymph node dissection performed for the treatment of metastatic testicular cancer. Postganglionic noradrenergic fibers pass posterolateral to the prostate in the so-called nerves of Walsh to enter the corpora cavernosa medially.

Parasympathetic nerves stem from the so-called sacral erection center and their cell bodies lie in the intermediolateral nuclei from S2 to S4. Exiting through the sacral foramina, these nerves pass forward lateral to the rectum as the nervi erigentes to reach the pelvic plexus. In this location, preganglionic fibers relay in ganglia, and postganglionic non-adrenergic, non-cholinergic (NANC) fibers pass in the cavernous nerves to the corpora cavernosa. These nerves are vulnerable during procedures such as abdominoperineal resection of the rectum and radical prostatectomy (Figure 15).

The pudendal nerves comprise motor efferent and sensory afferent fibers which innervate the ischiocavernosus and bulbocavernosus muscles as well as the penile and perineal skin. Pudendal motor neuron cell bodies are located in Onuf's nucleus of the S2–S4 segments. The pudendal nerve enters the perineum through the lesser sciatic notch at the posterior border of the ischiorectal fossa and runs in Alcock's canal towards the posterior aspect of the perineal membrane. At this point, it gives off the perineal nerve with branches to the scrotum and the rectal nerve supplying the inferior rectal region.

The dorsal nerve of the penis emerges as the last branch of the pudendal nerve. It then runs distally along the dorsal penile shaft lateral to the dorsal artery. Multiple fascicles fan out distally, supplying proprioceptive and sensory nerve terminals to the dorsum of the tunica albuginea and skin of the penile shaft and glans penis.

CENTRAL NERVOUS SYSTEM CONNECTIONS

Although reflex spinal erections may occur provided that the sacral reflexes are intact (for example, after cervical or thoracic spinal injury), central connections are paramount in engendering the normal male sexual response. These central pathways, however, are as yet incompletely understood.

A number of areas in the brain are involved in the modulation of erection, including the thalamic nuclei, rhinencephalon, limbic structures and paraventricular nucleus. Messages are integrated in the medial preoptic area where dopaminergic neurons are important. Norepinephrine (noradrenaline) and serotonin have also been identified as neurotransmitters in this region. Efferent pathways enter the medial forebrain bundle and pass caudally into the mid-brain tegmental region near the lateral part of the substantia nigra. Caudal to the mid-brain, the efferent pathway travels in the ventrolateral part of the pons and medulla, passing down to the sacral spinal centers via the lateral funiculus of the spinal cord. Activation of the parasympathetic neurons, located in the spinal cord, leads to intrapenile release of nitric oxide, mainly by neural terminations.

Superimposed on this hypothalamo-spinal circuit are higher centers, including the gyrus rectus, cingulate gyrus and hippocampus; these areas are all capable of modifying the erectile response, although their exact function has not yet been elucidated. Diseases specifically affecting these structures include Parkinson's disease, multiple system atrophy and stroke, all of which are often associated with erectile dysfunction.

Mechanisms of erection

Intracavernosal smooth muscle tone is by far the most important determinant of intracavernosal blood flow. Approximately half of the cavernosal volume is composed of smooth muscle, with the remainder consisting of either lacunar spaces or collagen. Collagen fibers are largely responsible for the passive mechanical properties of cavernosal tissue. In contrast, active contraction of cavernosal smooth muscle is dependent upon a number of factors, including the level of agonists (neurotransmitters, hormones and endothelium-derived factors), adequate expression of receptors, integrity of transduction mechanisms, calcium homeostasis, interaction of contractile proteins, and intimate intracellular communication between smooth muscle cells (gap junctions).

Cavernosal smooth muscle cells contain abundant amounts of the contractile proteins, actin and myosin. Following phosphorylation of myosin by adenosine triphosphate (ATP), attachments (crossbridges) form between the light chains of these two proteins and these attachments provide the mechanism for contractile tone of smooth muscle. The expenditure of energy for maintaining this state of tone is almost zero, but there is an absolute requirement for a high concentration of cytoplasmic free calcium.

Adequate calcium homeostasis is, therefore, fundamental to the normal regulation of smooth muscle tone. Three major mechanisms are involved:

(1) Influx of extracellular calcium through voltageregulated channels;
(2) Activation of membrane-bound receptors which allow extracellular calcium to enter through receptor-operated channels;
(3) Activation of signal pathways which allow intracellular release of calcium from the sarcoplasmic reticulum.

Relaxation of cavernosal smooth muscle may be thought of as ‘resetting’ the contractile machinery. This is mainly accomplished by lowering intracellular calcium. There are a number of mechanisms by which this may be achieved but, in general, all pathways depend on either the accumulation of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP), or the activation of potassium channels with consequent hyperpolarization of the cellular membrane (Figure 16).

Nitric oxide, produced from its precursor L-arginine by nitric oxide synthase (NOS), appears to exert two effects within the corpora (Figure 17):

(1) Activation of potassium-channel ATPase, resulting in hyperpolarization of the smooth muscle cell membrane. This hyperpolarization prevents the opening of voltage-dependent calcium channels, thereby reducing intracellular calcium;
(2) Activation of guanylate cyclase which catalyzes the conversion of guanosine triphosphate (GTP) to cGMP. This triggers relaxation by lowering intracellular calcium.

Other muscle relaxants act via cAMP-dependent mechanisms and include prostaglandin (PG) E_1 and vasoactive intestinal polypeptide (VIP). These substances react with membrane receptors coupled to a G protein which stimulates adenylate cyclase to produce cAMP, thus lowering intracellular calcium. The presence of two distinct and separate pathways to induce intracorporeal vasodilatation is probably a reflection of the importance of the erectile mechanism in the perpetuation of the species.

The breakdown of cGMP, accomplished mainly by phosphodiesterase type 5 (PDE5), raises cytoplasmic free calcium levels and reverses smooth muscle relaxation. Compounds such as papaverine and the recently discovered, more selective, molecule sildenafil inhibit intracorporeal PDE5, thereby increasing the intracellular half-life of cGMP and, thus, promoting and prolonging smooth muscle relaxation and erection.

REGULATION OF INTRACAVERNOSAL SMOOTH MUSCLE CONTRACTILITY

Two principal mechanisms control the tone of penile smooth muscle cells:

(1) Neurogenic control, in which adrenergic, cholinergic and NANC fibers all play a role; and
(2) Endothelial control, by neurotransmitter substances released by the endothelium lining the helicine arteries and lacunar spaces.

ADRENERGIC VASOCONSTRICTOR MECHANISMS

Catecholamine-containing adrenergic nerves have been demonstrated in the cavernosal and helicine arteries as well as in cavernosal smooth muscle of humans. Norepinephrine is released from dense-core vesicles of sympathetic nerve terminals to interact with α-adrenoceptors located on cavernosal smooth muscle membranes (Figure 18). The main mediator of penile smooth muscle contraction appears to be the α_1-adrenoceptor, all three subtypes (α_{1A}, α_{1B} and α_{1D}) of which have been detected in the human corpus cavernosum. There is some evidence that the (α_{1A} subtype is functionally predominant. The interaction of norepinephrine with the α_1-adrenoceptor results in an increase in intracellular calcium via a guanidine nucleotide-binding protein (G protein) mechanism amplified through inositol phosphate (IP3) and diacylglycerol (DAG) pathways (Figure 19). Sympathetic nerve activity is therefore involved in both inducing detumescence and active maintenance of intracavernosal smooth muscle tone when the penis is in its normal flaccid state. This is the basis for the clinical effectiveness of drugs such as phentolamine (Vasomax®).

CHOLINERGIC MECHANISMS

Erection is initiated by increased neural activity in the parasympathetic nerves originating from the S2–S4 spinal segments. The preganglionic neurotransmitter is acetylcholine, but the postganglionic nerve endings mediating vasodilation are NANC. Acetylcholine may, however, modulate noradrenergic vasoconstrictor tone by acting upon prejunctional muscarinic receptors on adjacent sympathetic nerve endings.

NON-ADRENERGIC NON-CHOLINERGIC MECHANISMS

The principal neurotransmitter mediating trabecular smooth muscle relaxation is NANC. Originally, the 28 amino-acid peptide VIP was put forward as the candidate molecule, but it is now recognized that nitric oxide (NO) is the most important molecular mediator of erection. NO synthase is present in the pelvic nerves (Figure 20) and in the peripheral autonomic nerve endings innervating the corpora (Figures 21 and 22). Release of NO leads to the accumulation of cGMP within trabecular smooth muscle cells and hyperpolarization of the cell membrane. The resultant reduction in intracellular calcium leads to smooth muscle cell relaxation which, as already mentioned, spreads rapidly from cell to cell through so-called gap junctions. Vasodilatory responses are terminated by degradation of cGMP, mainly by the enzyme PDE5.

ENDOTHELIAL MECHANISMS

Endothelium-derived relaxation factors were first described in the rabbit aorta by Furchgott in 1980. A similar mechanism in which lacunar endothelium releases a substance that relaxes trabecular smooth muscle also occurs in the corpora. Again, the main relaxing factor is NO, produced by NO synthase, which exerts an effect by stimulating the activity of guanylate cyclase, resulting in an accumulation of cGMP and a decrease in cytoplasmic free calcium.

Other molecules play a part in tumescence and detumescence, including endothelin-1, which has a powerful vasoconstrictory effect. In contrast, the action of PGE_1 is to relax trabecular smooth muscle. Other prostaglandins, such as PGI_2, may also play a role in preventing intracorporeal coagulation by their antiplatelet aggregation activity.

HEMODYNAMICS OF ERECTION

Penile erection is a hemodynamic response to a combination of humoral, neurogenic and local signals. Vasodilatory signaling coincides with reduced vasoconstrictor activity. The result is increased flow through the dilating cavernosal arteries. At the same time, the smooth muscle helicine arteries and lacunar spaces relax, thereby allowing blood to fill the intracorporeal space (Figures 23 and 24). Cavernosal filling compresses the obliquely running subtunical venules against the sturdy tunica albuginea, resulting in a hundred-fold increase in resistance to venous outflow (Figure 25). Intracavernosal blood pressure soon rises to approximate that of systolic blood pressure, thereby producing penile erection (Figure 26).

ORGASM AND EJACULATION

Orgasm and ejaculation are the result of a sudden increase in sympathetic efferent activity. This has a number of effects: the prostate, seminal vesicles and vasa deferentia contract, emptying their contents into the prostatic urethra. The bladder neck closes tightly to prevent retrograde ejaculation, and the external urethral sphincter relaxes. Semen is ejaculated in a pulsatile fashion as a result of rhythmic contractions of the bulbocavernosus muscles (Figure 27).

Pathophysiology of erectile dysfunction

Given the complexity of the system, it is not surprising that a wide variety of diverse disorders may result in erectile dysfunction (Table 1). Often, the cause is multifactorial, but vasculogenic causes are the most commonly implicated.

VASCULOGENIC CAUSES

Arterial insufficiency

Because the development and maintenance of a rigid erection depend on achieving a high intracavernosal pressure, it is not surprising that disorders affecting the peripheral arterial blood flow are strongly associated with erectile dysfunction (Table 2). The most common cause is atheroma involving either the common or internal iliac arteries or their more distal branches (Figure 28). The risk factors for this are similar to those for coronary artery disease (including smoking, hypertension, hyperlipidemia, diabetes mellitus and obesity). Narrowing or occlusion of the internal pudendal arteries reduces perfusion pressure to the corpora, resulting in a failure to achieve full rigidity. In the absence of such pressure, the normal veno-occlusive mechanisms cannot operate and, thus, the problem is compounded by secondary venous leakage. Obliterative disease of the aorta may also result in erectile dysfunction.

Venous leakage

In the presence of a normal arterial inflow, normal veno-occlusive mechanisms should slow egress of blood from the corpora to a virtual trickle during full erection. Failure to do so results in a flaccid erection and leakage of blood, either into the deep dorsal vein

Table 1 Risk factors for erectile dysfunction

Age
Vascular factors
myocardial infarction
coronary artery bypass surgery
cerebral vascular accident
peripheral vascular disease
hypertension
hyperlipidemia
smoking
Metabolic diseases
diabetes mellitus
renal failure
thyrotoxicosis
hypothyroidism
depression
alcoholism
chronic liver disease
adrenal disorders
hypogonadism

Age
hyperprolactinemia
Neurological diseases
multiple sclerosis
multiple system atrophy
Parkinson's disease
spinal cord injury
Other
acquired immunodeficiency syndrome (AIDS)

Table 2 Vascular pathophysiology of organic erectile dysfunction

Vascular etiology of erectile dysfunction present in 60% of patients. Small vessel vascular disease (e.g. diabetes) and large vessel arteriosclerosis (e.g. hypertension) cause arterial insufficiency/erectile dysfunction; erectile dysfunction occurs in 25% of men treated for hypertension and 60% of diabetics
Tobacco alters penile arterial hemodynamics, causing erectile dysfunction in a high proportion of elderly smokers; pelvic radiation leads to fibrosis/stenosis of pelvic arteries and accelerates existing arteriosclerosis; venous occlusive dysfunction may be due to decreased distensibility of corpora cavernosa or inherent abnormalities in tunica albuginea
Vascular endothelial growth factor may play a role in modulation of normal vascularity of penile architecture

or the cavernosal venous system (Figure 29). The etiology of this is obscure, but is more likely to be a primary disorder of intracavernosal smooth muscle than a problem primarily related to the penile veins themselves.

Intracavernosal smooth muscle fibrosis

Full erection depends on achieving complete intracorporeal vasodilatation. This, in turn, depends on normally functioning corporeal smooth muscle. Aging and/or ischemia may result in degeneration of smooth muscle cells, thereby impairing the ability to respond to vasodilator signals. During flaccidity, the oxygen saturation of the blood within the lacunar spaces is low (40 mmHg). During erection, however, the inflow of arterial blood raises the oxygen saturation of lacunar blood to >90 mmHg.

The current evidence suggests that the development of intermittent erections may be an important mechanism for maintaining full oxygenation and, thus, function of cavernosal smooth muscle. Conditions of low oxygenation promote the production and release of transforming growth factor-β_1. This molecule, in turn, results in the formation of collagen, with the resultant development of intracorporeal fibrosis (Figure 30). This may help to explain the physiological importance of the phenomenon of intermittent nocturnal penile tumescence. This is an important concept because it suggests that loss of erection due to any cause may be compounded by loss of cavernosal smooth muscle function and fibrosis. Clearly, such considerations may have an impact on the timing of treatment decisions in circumstances such as erectile dysfunction following radical prostatectomy.

Failure of intracavernosal neurotransmission

The molecular mechanisms of vasodilatation and vasoconstriction that underlie erection and detumescence have only recently been elucidated. Bearing in mind their complexity, it would be surprising if specific abnormalities of neurotransmission did not translate into clinical erectile dysfunction. As yet, however, none have been specifically described, but failure of NO production due to lack of NO synthase or abnormalities of receptor or second-messenger function may well underlie some cases. More research is needed in this rapidly evolving area.

NEUROGENIC CAUSES

The dependence of normal erectile and ejaculatory function on intact neural pathways to and from the brain has already been mentioned. Not surprisingly a considerable number of neurological disorders may result in erectile dysfunction (Table 3). Those involving the central nervous system include cerebrovascular accidents, Parkinson's disease and multiple sclerosis. Damage or degeneration of peripheral nerves supplying the corpora also results in erectile dysfunction. Examples include diabetic neuropathy, cauda equina lesions due to a prolapsed intervertebral disk, and iatrogenic neural injury during

abdominoperineal resection of the rectum. The unusual, but interesting, disorder known as multiple system atrophy is characterized by degeneration of both the sympathetic and parasympathetic central and peripheral autonomic neurons, as well as of Onuf's nucleus in the sacral spinal cord (Figure 31). The result is progressive and disabling ortho static hypotension, urinary incontinence and erectile dysfunction, together with ejaculatory failure.

ENDOCRINOLOGICAL CAUSES

Testosterone secreted from the Leydig cells of the testes under the influence of luteinizing hormone (LH) is necessary for normal male sexuality and sexual function (Table 4). Medications such as luteinizing hormone-releasing hormone (LHRH) agonists or stilbestrol, which lower circulating testosterone, result in loss of libido and in erectile dysfunction. Patients who are hypogonadal as a result of pituitary or testicular dysfunction frequently suffer from erectile dysfunction, which responds to treatment with exogenous androgens. More contentious is the suggestion that waning testosterone levels in men of middle age and beyond (Figure 32), the socalled 'male menopause', are a frequent cause of erectile dysfunction and, therefore, boosting serum testosterone levels has therapeutic benefits (Table 5). However, there is some evidence from experimental animal models that androgens are necessary for the support of intracavernosal smooth muscle function and maintenance of NO synthase levels. Exogenous androgens are certainly capable of enhancing the libido, which is an important component of sexuality.

Dihydrotestosterone (DHT), the potent androgenic metabolite of testosterone produced by the enzyme 5α-reductase, is crucial for the normal development of the male external genitalia, seminal vesicles and prostate, but is not essential for either the libido or erectile function. Compounds such as finasteride, which inhibit the activity of 5α-reductase type II, result in shrinkage of the prostate by 20–30%, but have been reported to cause erectile dysfunction in only around 3–5% of patients. However, in the 4-year placebo-controlled study of finasteride recently reported by McConnell and colleagues, nearly 14% of patients taking the active drug experienced some form of sexual dysfunction.

Prolactin, which is released from the pituitary gland, acts as an inhibitory factor in male sexual function. Hyperprolactinemia, either idiopathic or, less commonly, the result of a tumor such as a pituitary prolactinoma (Figure 33), is associated with erectile dysfunction, as is the more common entity of idiopathic hyperprolactinemia. Correction of the raised prolactin levels using bromocriptine may sometimes restore potency in such patients.

Table 3 Neurogenic pathophysiology of organic erectile dysfunction

Diabetes, alcoholism/vitamin deficiencies contribute to somatic/autonomic neuropathy
Demyelinating diseases (e.g. multiple sclerosis) decrease penile sensation
Aging elevates sensory thresholds to vibratory/electrical stimulation
Pelvic/retroperitoneal surgery (e.g. radical prostatectomy) may damage the autonomic nervous system controlling the physiology of penile erection/ejaculation

Table 4 Endocrinological pathophysiology of organic erectile dysfunction

Low testosterone levels associated with decreased libido
Decline in nitric oxide synthase activity in castrated animals reversed by androgen supplementation
Nitric oxide synthase mRNA increases with androgen supplementation
Hypogonadism may be due to primary testicular failure, decreased secretion of gonadotropin releasing hormone (e.g. hyperprolactinemia), or alterations in steroid hormone protein binding (e.g. alcoholism, liver failure)

Table 5 Age-related pathophysiology of organic erectile dysfunction

Cellular senescence alters collagen content in corpora cavernosa/tunica albuginea, leading to venous occlusive dysfunction/decreased neuronal transmission to cavernosal smooth muscle
Aging alters endothelial function, leading to decreased basal nitric oxide release and up-regulation of basal endothelin-1
Reproductive aging in animals impairs neurogenic erectile response: increase in latency period to attain an erection/decrease in maximal intracavernosal pressure; loss of function integrity of endoluminal structures; imbalance in expression of vasoconstricting/vasorelaxing modulators of penile erection/decrease in nitric oxide synthase/increase in endothelin-1 levels

PRIAPISM AND POSTPRIAPISM ERECTILE DYSFUNCTION

Priapism may be defined as an involuntary erection that lasts for more than 4–6 h. The condition may be spontaneous or secondary to intracavernous pharmacotherapy. Spontaneous priapism may be idiopathic or associated with blood disorders such as sickle cell anemia, leukemia or other malignancies (Figure 34).

After 4–6 h, a persistent erection usually becomes painful, but late presentation is not uncommon because of embarrassment. Initial therapy involves corporeal aspiration and injection of adrenergic vasoconstrictor substances such as phenylephrine or metaraminol (Aramine®). Because these potent vasoactive agents frequently enter the circulation after intracorporeal injection, blood pressure should be carefully monitored during therapy.

Although pharmacotherapy with aspiration and injection of vasoactive agents is often successful within 6–12 h of onset of priapism, beyond that time period the efficacy of any therapy is rapidly diminished. Initial high-flow priapism is followed by lower flow and progressive deoxygenation of the corpora. In these later cases, aspiration of the corpora reveals dark deoxygenated blood. Progressive ischemia to the intracorporeal smooth muscle renders the helicine arteries and walls of the trabecular spaces progressively less capable of developing sufficient vasoconstriction necessary to restore and maintain flaccidity.

The consequence of untreated priapism or priapism unresponsive to therapy is the development of corporeal fibrosis. This results in erectile dysfunction which is difficult, and sometimes impossible, to treat. Even insertion of a penile prosthesis may be technically difficult in such cases because the fibrosis renders dilatation of the corporeal space problematical.

PSYCHOGENIC CAUSES

Psychological causes were once widely assumed to be the predominant cause of erectile dysfunction. However, if the correct definition of erectile dysfunction is applied, namely, the persistent loss of penile rigidity in all circumstances, then psychogenic erectile dysfunction proves to be less common than its organic counterpart, especially in older men. Psychogenic erectile dysfunction typically occurs in younger men, and is variable and often associated with performance anxiety. Increased sympathetic vasoconstrictor tone and raised circulating norepinephrine levels are most probably involved. Psychogenic factors also come into play in other forms of erectile dysfunction, as failure of erection itself induces anxiety, loss of confidence and sometimes relationship difficulties. The conviction that an erection will not develop when required, therefore, becomes a self-fulfilling prophesy.

Epidemiology of erectile dysfunction

Ever since the ground-breaking work of Kinsey, the prevalence of erectile dysfunction has been a subject of debate. Although it is certain that many millions of men are affected by the condition, there is a surprising dearth of high-quality epidemiological data with which to quantify accurately the extent of the problem. A figure of one man in ten has often been quoted as an estimate of the prevalence of erectile dysfunction, but the frequency and severity of the disorder vary markedly with age. Erectile dysfunction is uncommon in young men (with the exception of intermittent psychogenic problems), becomes more common in middle age, and is highly prevalent in men more than 60 years of age. Thus, to some extent, erectile dysfunction is a natural expression of aging, but one that men are increasingly less willing to accept without seeking treatment. As the world's population ages over the next few decades (Figure 35), the number of men who will suffer erectile dysfunction seems certain to rise.

One problem for epidemiologists trying to quantify the extent and impact of erectile dysfunction is the frequent unwillingness of men to discuss the problem frankly. The accuracy of almost all data in this disease area is therefore impaired by the reluctance of many, particularly older, men to respond to what they regard as overly personal questions. However, with the development of simple questionnaires which can be self-administered, and the gradual breakdown of social taboos surrounding the open discussion of sexual issues, it is possible to anticipate higher-quality information in the future.

At this time, however, the best data available concerning the prevalence of erectile dysfunction are derived from the Massachusetts Male Aging Study (Figure 36). The findings of this study may be summarized as follows. A total of 1290 men aged 40–70 years were included in the study; erectile dysfunction was very common, with 52% of men reporting some degree of erectile dysfunction—mild in 17.1%, moderate in 25.2% and complete in 9.6%. Complete erectile dysfunction was reported by 5% of men at 40 years of age, rising to 15% at age 70 years. Loss of firm erections is often extremely bothersome to men. Figure 37 demonstrates the degree of worry, the loss of confidence, the negative feelings and the depression that can result.

Risk factors for erectile dysfunction

Risk factors for organic erectile dysfunction (see Table 1, page 20) mainly stem from the fact that the erectile mechanism is a vasodilatory response dependent on smooth muscle function under neurogenic control. Aging, which has the strongest association with erectile dysfunction, probably exerts its effects mainly through impaired vasodilatory and venoocclusive mechanisms. Atheroma of the internal iliac arteries and their pudendal branches may be one factor, but age-related degeneration of intracorporeal smooth muscle mechanisms is probably more important. Venous leakage, another age-related phenomenon, may in itself be a manifestation of deterioration of intracorporeal smooth muscle function.

DIABETES MELLITUS

This disease is an important risk factor for erectile dysfunction. Damage to small blood vessels is the main etiology and, therefore, erectile dysfunction often occurs in association with diabetic retinopathy. Diabetic peripheral autonomic neuropathy is a further contributory factor. Erectile dysfunction may develop as a result of the progressive loss of small unmyelinated so-called C fibers secondary to diabetes. Several groups have reported that diabetes is associated with loss of NO synthase from NANC nerve endings and endothelial cells in the corpora. This may explain the pathophysiological basis of the erectile dysfunction that so commonly accompanies diabetes.

HYPERTENSION

This is frequently associated with erectile dysfunction. Approximately one-third of men beyond middle age have a diastolic blood pressure >90 mmHg. Hypertension causes damage to small blood vessels and this may adversely affect intracorporeal vasodilatory mechanisms. Moreover, many of the agents used to control hypertension, especially β-blockers and diuretics, are associated with the development of erectile dysfunction. It has been postulated that, because high intracorporeal pressures are required to produce penile rigidity, the reduction of blood pressure by any agent is likely to increase the incidence of erectile dysfunction. However, α-blockers, perhaps through the induction of intracorporeal vasodilatation, appear to enhance erection, while still lowering both systolic and diastolic blood pressures.

HYPERLIPIDEMIA

This disease often occurs in association with hypertension and is also a cause of damage to the peripheral vascular system. Hypercholesterolemia and elevated serum triglyceride levels are both also associated with erectile dysfunction.

SMOKING

Although there have been few epidemiological studies to confirm this, it appears likely that heavy smoking is associated with erectile dysfunction because of its deleterious effects on blood vessels and its action leading to an increase of platelet stickiness.

PEYRONIE'S DISEASE

Fibrosis developing in the corpora albuginea may result in permanent scarring and consequent deformity of erection. When the fibrosis is severe (Figure 38), penetrative intercourse may be impossible. As a result of the loss of tunica elasticity, Peyronie's disease may also be associated with venous leak-induced erectile dysfunction.

PREVIOUS SURGERY

Various forms of pelvic surgery, particularly radical prostatectomy, cystoprostatectomy and abdominoperineal resection, are all strongly associated with subsequent erectile dysfunction.

DEPRESSION

Reactive or endogenous depression is strongly associated with erectile dysfunction: nearly 90% of severely depressed men report complete impotence. Treatment with antidepressants may sometimes improve the situation, although both monoamine oxidase inhibitors and tricyclic antidepressants may in themselves cause erectile dysfunction. Selective serotonin reuptake inhibitors, such as fluoxetine (Prozac®) may not only cause erectile dysfunction, but may also retard ejaculation.

Diagnosis of erectile dysfunction

The proper goal-oriented evaluation of a man proactive and complaining of erectile dysfunction requires a sympathetically elicited history, a focused physical examination and various carefully selected special investigations.

HISTORY

To obtain a clear history, it is important that the patient himself understands the distinction between loss of libido, erectile dysfunction and ejaculatory disturbance. This often may require some preliminary explanation. The onset, consistency and severity of the complaint need to be established. Recently, the development of self-administered symptom scores by O'Leary and colleagues (Table I, see Appendix, page 41) and Rosen and colleagues (Table II, see Appendix, page 43) have facilitated quantitative history-taking for erectile dysfunction.

Because sexual function is intimately related to the appropriate response of the sexual partner, tactful enquiries need to be made concerning previous and on-going relationships, and the attitude of the partner towards the problem. Underlying relationship problems are a common cause of erectile dysfunction, and this possibility needs to be tactfully explored in all cases. Although, by tradition, the question concerning the presence or absence of early morning erections has been proposed as a means to distinguish between psychogenic and organic erectile dysfunction, the value of this enquiry has recently been questioned. Many normal individuals do not regularly wake up with early morning erections, although the presence of a positive history of a firm erection on waking would make organic erectile dysfunction less likely. Although these symptom scores are admirable in their own way, they in fact tend to focus on the functional component of erectile dysfunction rather than its impact on the quality of life of the sufferer. This issue has recently been addressed by Wagner and colleagues, who have attempted to quantify the impact of erectile dysfunction on the sufferer (Table III, see Appendix, page 46).

A careful drug history is particularly important as a considerable number of pharmacological agents are associated with the development of erectile dysfunction. Most potent in this respect are the agents used in the treatment of prostate cancer, such as LHRH analogues, which cause loss of libido and erectile dysfunction. Many other agents have less profound, but none the less significant, effects. Some of the more commonly encountered compounds implicated are listed in Table 6. Antihypertensive agents, such as β-blockers and thiazide diuretics, are the most commonly implicated agents. Antidepressants, especially monoamine oxidase inhibitors and tricyclic compounds, are also common causes of erectile dysfunction. Serotonin reuptake inhibitors may not only cause erectile dysfunction, but also retard ejaculation.

The question of smoking and alcohol intake needs to be addressed. William Shakespeare himself noted that alcohol increases the desire, but diminishes sexual performance. Smoking should be strongly discouraged and, in some cases, the use of skin patches containing nicotine suggested.

Specific enquiry should be made concerning concomitant conditions, particularly those affecting the vascular or neurological systems such as angina, hypertension, diabetes mellitus, thyroid disease, renal

Table 6 Drugs associated with erectile dysfunction

Major tranquilizers	*Antikypertensives*
phenothiazines, e.g. fluphenazine	diuretics, e.g. thiazides, spironolactone
chlorpromazine, promazine, mesoridazine	vasodilators, e.g. hydralazine
butyrophenones, e.g. haloperidol	central sympatholytics, e.g. methyldopa,
thioxanthenes, e.g. thiothixene	clonidine, reserpine
Antidepressants	ganglion blockers, e.g. guanethidine, bethanidine
tricyclics, e.g. nortriptyline, amitriptyline,	β-blockers, e.g. propranolol, metoprolol, atenolol
calcium antagonists	
desipramine, doxepin	ACE inhibitors

Major tranquilizers	*Antikypertensives*
monoamine oxidase (MAO) inhibitors, e.g.	
isocarboxazide, phenelzine, tranylcypromine,	*Recreational drugs*
pargylene, procarbazine	alcohol
lithium	marijuana
Anxiolytics	amphetamines
benzodiazepines, e.g. chlordiazepoxide,	barbiturates
diazepam, chlorazepate	nicotine
Anticholinergics	opiates
atropine	*Antiandrogenics*
propantheline	cyproterone acetate
benztropine	flutamide
dimenhydrinate	bicalutamide
diphenhydramine	LHRH analogues
estrogens	
Cardiac	5α-reductase inhibitors
digoxin	
lipid-lowering agents	*Miscellaneous*
	cimetidine
	clofibrate
	metoclopramide
	baclofen
	indomethacin
	and many others

failure or peripheral vascular disease. The presence of previous pelvic surgery should be ascertained and accurately documented.

PHYSICAL EXAMINATION

Physical examination in erectile dysfunction should involve careful assessment of the external genitalia to detect the presence of cutaneous penile lesions, a Peyronie's plaque or testicular abnormalities (Figures 39–44). Rectal examination should be performed to exclude benign prostatic hyperplasia or induration/nodularity suggestive of prostatic cancer. A focused neurological evaluation, including assessment of anal sphincter tone, should be performed and peripheral pulses palpated to detect signs of vascular disease. The distribution of body hair may provide a clue to androgen status. Blood pressure should be recorded with the patient both standing and lying down, and the presence or absence of obesity and/or gynecomastia noted. The abdomen should be palpated to exclude aortic aneurysm.

SPECIAL INVESTIGATIONS

Blood and urine testing

A key condition to exclude is undiagnosed diabetes mellitus. This is best accomplished by random measurement of blood sugar, as dipstick testing of urine to detect glycosuria does not reliably exclude the diagnosis. Because renal failure is also frequently associated with erectile dysfunction, electrolytes and creatinine should also be measured in addition to liver function tests, especially in those who admit to a high alcohol intake. Documentation of a full blood count and erythrocyte sedimentation rate is also a sensible precaution.

Evaluation of the androgen status of the patient is usually indicated, as some may respond to hormone replacement therapy. A serum testosterone (best measured as an early-morning sample) and sex hormone binding globulin (SHBG) should be requested. In addition, if the free testosterone level is low, a prolactin level should be measured, as hyperprolactinemia is associated with erectile dysfunction and may be corrected by treatment with bromocriptine. Some specialists also advocate testing of thyroid function, although this is a relatively unusual cause of erectile dysfunction, at least in younger men. If prostate cancer is a possibility, then a prostate-specific antigen (PSA) test should be requested, especially if treatment with androgen replacement therapy is being contemplated, as this may stimulate occult prostate cancer cells.

Nocturnal penile tumescence testing

Although still advocated by some, nocturnal penile tumescence testing is a rather cumbersome way to differentiate psychogenic from organic impotence (Figures 45 and 46). The same information (whether or not an erection develops during sleep) may be gleaned with the use of the snap gauge device or even with a strategically located ring of postage stamps (Figure 47). Only a few laboratories continue to employ nocturnal penile tumescence testing as a routine assessment of patients with erectile dysfunction.

Diagnostic intracorporeal injection

Injection of a vasodilator substance into one or other of the paired corpora cavernosa provides the clinician with two valuable pieces of information. First, it confirms that a normal vasodilatory response is capable of developing (although a failure to respond does not necessarily indicate organic erectile dysfunction, since the response may be inhibited by excessive nervousness). Second, this technique assesses the feasibility of self-injection pharmacotherapy as a treatment option.

Originally, papaverine, with or without the α-blocker phentolamine, was used in this context. Nowadays, PGE_1 (5–20 mg in 1 ml) is preferred (Figure 48), sometimes in combination with other agents such as papaverine, because of a lower incidence of prolonged erectile responses and priapism.

Color duplex Doppler ultrasound assessment of intracorporeal blood flow

More precise quantitative information concerning the erectile response to intracorporeal vasoactive agents such as PGE_1 may be obtained by imaging the cavernosal arteries with color duplex Doppler ultrasonography as the erectile response develops. Normally, the velocity of blood flow through these vessels increases rapidly in response to PGE_1 to more than 30 cm/s. As the erection develops during systole, there is forward flow whereas, during diastole, the flow is reversed because of high intracorporeal pressures. Thus, this test may help to distinguish between venous leakage and arterial insufficiency (Figures 49–51).

Dynamic infusion cavernosometty and cavernosography

If veno-occlusive dysfunction is suggested by color Doppler ultrasonography investigation, then its presence and location may be confirmed by dynamic infusion cavernosometry and cavernosography (DICC). This investigation involves pre-dosing with intracavernous PGE_1, followed by infusion of saline with simultaneous measurement of intracorporeal pressure and flow required to maintain erection. Venous leak is characterized by an infusion of $\geq$120ml/min being necessary to maintain erection. The source of the venous leakage may be visualized by performing cavernosography using a 50:50 solution of radiographic contrast and saline. Leakage is usually visualized from the deep dorsal vein and/or the deep crural veins as well as into the corpus spongiosum of the glans. Although deep dorsal venous leakage is one of the most common appearances (Figure 52), multiple rather than single leakage sites are the rule rather than the exception.

Functional selective pharmacopudendal angiography

Pharmacopudendal angiograms may be indicated in the relatively small number of patients whose penile Doppler ultrasound studies suggest arterial insufficiency and who are candidates for arterial reconstruction. The selective pudendal angiogram may be performed under local anesthesia and some sedation through a single femoral percutaneous puncture. The test should also include a non-selective pelvic angiogram with the catheter above the aortic bifurcation—the pelvic flush—and a selective pudendal angiogram on each side. The non-selective pelvic angiogram is used to identify lesions of the common and internal iliac arteries as well as to visualize the inferior epigastric arteries, which are the potential future donor vessels for penile bypass surgery. Occasionally, an arteriovenous fistula is detected and its embolization may restore erectile function (Figure 53).

Treatment options for erectile dysfunction

Treatment options are best considered in steps, starting with the least invasive and moving incrementally to the more invasive treatment possibilities. As a first step, modification of reversible causes of erectile dysfunction should be considered. Most patients with erectile dysfunction who are smokers should be advised to stop. Coexistent hypertension or diabetes should be treated. It is also reasonable to consider treatment with a statin if the patient's serum low density lipoprotein cholesterol is consistently >3.3 mmol/1. Increased physical exercise is also good general advice as well as weight reduction for those who are obese. At all stages, patient preferences should be taken into account.

PSYCHOSEXUAL COUNSELING

Although organically induced erectile dysfunction is more common than psychogenic erectile dysfunction, almost all patients have a psychological component to their problem. Psychosexual counseling may therefore be helpful in many cases, especially where there are relationship difficulties which compound the problem. Psychosexual counseling generally involves obtaining a detailed history not only from the patient but also, if possible, from the partner.

Psychosexual counseling is most effective when the problem is due to technique or there are unrealistic expectations on one or both sides of the relationship. As already mentioned; severe relationship problems are a potent source of erectile dysfunction, and these may sometimes be resolved through counseling. The most commonly employed approach is that pioneered in 1970 by Masters and Johnson. Briefly this involves a program that aims to:

(1) Understand the problem;
(2) Establish relearning of sexual behavior;
(3) Remove anxiety;
(4) Teach communication skills;
(5) Redefine success; and
(6) Teach permission giving.

Psychosexual counseling may often be helpful. Unfortunately, there have been very few randomized controlled trials to evaluate outcome, so the evidence to support this treatment remains scanty. Psychosexual counseling may also be used in tandem with medical therapy for erectile dysfunction.

MEDICAL THERAPIES

Oral agents

Almost universally patients prefer medical therapies to either counseling or the more invasive treatment options. Until recently, however, there have been no agents combining efficacy with safety to the extent of being approved by the regulatory authorities. However, agents which have been used historically as well as the newer agents which have been, or are about to be, approved are reviewed here. Now medical therapy with oral agents is generally the first-line treatment option in men presenting with erectile dysfunction.

α-Adrenoceptor antagonists

Yohimbine hydrochloride is an α_2-adrenoceptor antagonist which acts both peripherally and centrally. It has been suggested that the α_2-presynaptic receptor may be localized on the NANC nitrergic nerves innervating the cavernosal arteries. Blockade of these receptors may enhance corporeal vasodilatation and thereby enhance erections. Furthermore, as α_2-adrenoceptors are

also widely distributed in the central nervous system, it is conceivable that the drug, derived from the bark of the yohimbe tree, may also have an effect there. Clinical trials have only involved small numbers of patients, but the data that are available suggest that yohimbine has no benefit beyond that of placebo in established organic impotence. However; in patients with psychogenic or early arteriogenic erectile dysfunction, some efficacy has been reported in small studies.

Yohimbine is utilized in doses of up to 10mg three times daily. Its central action probably accounts for the side-effects of tremulousness, insomnolence, headache, palpitations and minor elevations of blood pressure.

Doubt as to the true efficacy of yohimbine has been increased by the recent withdrawal from development of delaguamine hydrochloride, a compound with a thousand-fold higher affinity for the α_2-adrenoceptor, due to lack of efficacy.

α_1-Adrenoceptor antagonists are potent vasodilators and, as such; would be expected to enhance erectile response. Recent data from its use in men with symptomatic hypertension (approximately one-third of whom complain of some erectile dysfunction) suggest a mild beneficial effect with several of these compounds on sexual function as well as high blood pressure-related symptoms. In contrast, other antihypertensive agents; especially β-blockers and diuretics, were associated with a significant incidence of erectile dysfunction (Figure 54). Phentolamine, widely used for intracavernosal treatment; has recently been tried orally as Vasomax®. Clinical trials have confirmed it to be an effective treatment of erectile dysfunction. A buccal preparation with a shorter onset of action has also been used, with a success rate of 30–40%. Safety worries, however; have prevented its approval by the regulatory authorities.

Dopamine agonists

There are five specific dopamine membrane receptors that have been isolated and categorized into two sub-families, D_1-like and D_2-like. Apomorphine has been shown to be a dopamine agonist with somewhat more potent D_2-like effects than D_1-like effects. The presence of dopaminergic pathways in the paraventricular nucleus, which is known to be important in engendering the erectile response; provides the rationale for the use of dopamine agonists in erectile dysfunction (Figures 55 and 56). A 60% response rate was seen after its subcutaneous injection in men with psychogenic erectile dysfunction. Transbuccal apomorphine has also shown efficacy. Overall; a 70% response was reported in terms of erectile function. Some patients also experienced an improvement in sexual drive. Figure 57 reveals the response compared with placebo.

The drawback with apomorphine, however, is its side-effects, which include persistent yawning, nausea, vomiting and orthostatic hypotension. Recent formulations (a sublingual sustained-release tablet) appear to minimize these adverse effects.

Serotonin agonists

Trazodone is both a centrally acting serotonin agonist and a peripheral sympatholytic agent. Studies in small numbers of patients have suggested some efficacy in erectile dysfunction. It has been used with success in patients with erectile dysfunction according to anecdotal reports, but other results are less favorable; properly conducted longer-term studies are required to verify these data.

The side-effects include drowsiness, hypotension, nausea and vomiting. Trazodone combined with yohimbine has been recommended, although there is little scientific evidence of a synergistic effect.

Type 5 phosphodiesterase inhibitors

As mentioned earlier, phosphodiesterases (PDE) break down the cyclic nucleotide signal molecules cAMP and cGMP. Intracorporeal smooth muscle contains predominantly PDE5 as well as types 2 and 3. Inhibition of PDE5 increases levels of available cGMP and thereby enhances erectile dysfunction.

Sildenafil (Viagra®) is a selective inhibitor of PDE5 with a half-life of 3.8 h (Figure 58). It thus increases the duration of action of intracorporeal cGMP, thereby enhancing the normal erectile response without inducing priapism. Patients with erectile dysfunction who have participated in randomized controlled trials of sildenafil and who have continued medication in open-label extension trials for up to 3 years have reported high rates of satisfaction with treatment (96%) and improved ability to engage in sexual activity (99%) (Figure 59). Efficacy with the agent generally increases with increasing doses and duration of therapy (Figures 60 and 61).

At dosages of 25, 50 and 100mg, sildenafil is generally well tolerated, although vasodilatory effects, such as facial flushing and headaches, have been reported. The drug is most effective when taken approximately 1 h before intercourse but efficacy has been reported in as early as 14 min. When sildenafil is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 min and a mean reduction in C_{max} of 29%. However, this decrease in the rate of absorption is not expected to have any clinical consequences. A transient effect on color vision has been observed in a small subset of patients, which is apparently due to inhibition of PDE6 activity in the cells of the retina. Gastrointestinal disturbances may also occur (Figure 62). Because sildenafil increases the effect of NO, the use of Viagra® and organic nitrates in any form, at any time, is

contraindicated. Interactions between sildenafil and nitrates such as glyceryl trinitrate, isosorbide dinitrate, sodium nitroprusside and amyl nitrate may occur with profound hypotension and risk of cardiac arrest. Recently, two other PDE5 inhibitors, tadalafil (Cialis™) and vardenafil (Levitra™), have been tested in phase III studies (Figure 63). Cialis™ and Levitra™ have recently received approval.

Tadalafil (Cialis™) has a mean half-life of 17.5 h and has been reported; at a dose of 20 mg, to enable 73–80% of sexual intercourse attempts to be completed successfully (with appropriate sexual stimulation) between 30 min and 36 h after dosing (Figure 64). Tadalafil was administered without restrictions to alcohol or food intake, although substantial alcohol consumption is not recommended. Therapy was well tolerated; with an overall incidence of side-effects such as headache and dyspepsia of 2.1% compared with 1.3% for placebotreated patients. Tadalafil is contraindicated with organic nitrates—and at least 48 h must elapse after taking tadalafil before their administration. With the exception of once-daily tamsulosin (Flomax®) 0.4 mg, it is also contraindicated with α-blocker therapy.

Vardenafil HCl (Levitra™) has a half-life of 4.7 h, a value not dissimilar from that of sildenafil (Viagra®). At a dose of 20 mg, up to 85% of men reported significant improvement in erections at 26 weeks compared with 28% of men who received placebo. Similar to sildenafil, vardenafil seems effective even in challenging patient groups such as those with diabetes mellitus (Figure 65) or post-prostatectomy erectile dysfunction (Figure 66). Side-effects include headache and facial flushing, and, like sildenafil (Viagra®) and tadalafil (Cialis™), vardenafil (Levitra™) should not be used in conjunction with any form of nitrate therapy. Because of its mild hypotensive effect, vardenafil (Levitra™) should not be taken in conjunction with α-blockers, such as terazosin. In addition, vardenafil (Levitra™) has been shown to produce minor prolongation of the QT interval and, as a consequence, should be avoided in patients with congenital QT prolongation and those taking Class 1A (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications.

Transdermal drug delivery system

Although the attempts that have been made to achieve transdermal drug delivery have received some publicity, the efficacy of these methods is, in fact, low. Nitroglycerin paste was evaluated by Heaton and colleagues, and Kim and McVary assessed PGE_1 and papaverine. Whereas some enhancement of intracorporeal blood flow is detectable on color duplex Doppler ultrasonography, rigid erections have only been obtained in the occasional patient with neurogenic erectile dysfunction (these patients already exhibit a supersensitive response to intracorporeal vasodilators and should therefore be ideal subjects).

Transurethral corporeal drug delivery

Contrary to the expectations of some, the epithelial lining of the distal urethra has proven to be an excellent route for the absorption and transfer of vasoactive substances to the corpora cavernosa. The urethra is lined by complex columnar cells, and there are submucosal vessels that connect the corpus spongiosum and corpora cavernosa. The transurethral route of drug delivery has proved to be capable of inducing hemodynamic changes in the corpora comparable with those obtained by direct intracavernosal injection.

The novel delivery system developed by Vivus, the so-called MUSE (medicated urethral system for erection), consists of a polypropylene applicator with a hollow stem measuring 3.5 cm in length and 3.2 mm in diameter (Figure 67). The tip contains a solid pellet of PGE_1 in doses up to 1000mg, but combinations of PGE_1 and the α_1-adrenoceptor blocker prazosin are also undergoing evaluation for delivery by this route.

Patients should be titrated up to the most effective dose (usually 500–1000 mg), usually starting with a smaller dose (125 or 250mg). Intraurethral insertion is advised immediately after voiding, when the urethra is moist, to obviate the need for a lubricant. Prior urination also helps the semi-solid pellet of PGE_1 to dissolve and become distributed along the length of the urethra. With the penis held vertically, the applicator is gently introduced into the urethra; the button on the end of the applicator is depressed to expel the medication (see Figure 67). The applicator is then rocked gently to ensure that the medication separates from the applicator, which is then withdrawn. The medication is dispersed along the urethra by gently rolling the penis between the palms of the hands. The smooth muscle relaxation and vasodilatory action are aided by standing or walking around for approximately 10 min. An erection develops within 5–10 min and lasts for 30–60 min.

A 64.9% rate of successful intercourse was reported from a randomized controlled trial involving 1511 men. Other studies, however, have reported lower rates of success, and men usually prefer to use oral agents.

The side-effects are minor and include urethral pain and occasional bleeding. Prolonged responses leading to priapism have been reported in only a handful of cases.

Direct intracorporeal injection

The discovery that direct injection of vasoactive substances into the corpora could produce a rigid erection suitable for intercourse was made simultaneously by Brindley (using phenoxybenzamine) and Virag (using papaverine). These observations produced the first truly effective non-surgical therapies for erectile dysfunction which are widely used. Papaverine (a non-specific PDE inhibitor) and phentolamine (an α_1-adrenoceptor blocker) were initially used either singly or in combination. Prolonged responses, however, which on occasions led to priapism and risk of ischemic injury to intracavernous smooth muscle, were not infrequently seen.

Approval by the US FDA of PGE_1 for intracavernous injection led to the widespread use of this substance as an alternative to papaverine. The efficacy of PGE_1 is similar to that of papaverine, but the incidence of prolonged responses is much lower. There may also be a lesser tendency towards intracavernous fibrosis with PGE_1. However, the disadvantage of PGE_1 is that many patients complain of penile pain after the injection due to the PG-induced activation of intracorporeal pain receptors. Intracavernous PGE_1 has been reported in one study to be more effective than the intracavernosal delivery system.

With this delivery system even more than with intraurethral PGE_1, dose titration is of major importance. The usual starting dose is 5 mg, increasing to 10–20 mg as maintenance therapy (Figure 68).

Other vasodilatory agents may also be employed. Vasoactive intestinal polypeptide (VIP) has been used. Padma-Nathan and colleagues have advocated a cocktail of agents, the so-called tri-mix (prostaglandin, papaverine, phentolamine), and have reported responses in patients who had failed with single-agent therapy. Complications of intracavernous pharmacotherapy include priapism, hematoma formation and fibrosis leading to erection deformities. Patients should be informed of these drawbacks before initiating therapy, and receive written instructions as to what they should do if an erection persists for more than 4 h.

VACUUM DEVICES

The basic principle underlying the use of vacuum devices for erectile dysfunction is simple. Arterial inflow and storage in the corpora may be insufficient, but this may be overcome by the suction effect of a vacuum; retention of rigidity is accomplished by the use of a constriction ring (Figure 69). The devices are non-invasive and relatively inexpensive, and many patients find them helpful. They may be used in conjunction with other therapies, such as intraurethral, intracavernosal PGE_1, or sildenafil.

Side-effects are uncommon, but petechial hemorrhage and bruising may occasionally occur. Some patients complain that the erection is unnatural and that the constriction ring is uncomfortable, especially at the moment of ejaculation. Others are discouraged by the lack of spontaneity and the rather cold erection produced by these somewhat cumbersome contraptions.

SURGICAL THERAPIES

Current surgical treatments for erectile dysfunction consist of correction of venous leak, arterial revascularization for inflow insufficiency and implantation of penile prostheses. Only the last of these, however, may truly be described as resulting in a reliably satisfactory outcome. In addition, patients with considerable deformity due to Peyronie's disease may be helped by surgery designed to correct the penile curvature.

Correction of venous leak

Wespes originally described venous leak as a cause of erectile dysfunction. It was hoped that simple excision/ligation of the deep dorsal vein would be curative (Figure 70). However, leakage points are usually multiple and, unfortunately, the improved function resulting from this procedure, even when combined with bilateral plication of the corpora or embolization of pelvic veins, is usually only temporary. This procedure should only occasionally be performed in fully informed consenting patients.

Arterial revascularization

In younger patients with localized blockage of the internal arteries, such as those who have suffered major pelvic trauma, revascularization of the corpora may be a possible option. The donor vessel is usually the inferior epigastric artery (Figure 71), which is mobilized and anastomosed either to the dorsal artery or to a combination of the dorsal artery and deep dorsal vein. Anastomosis to the flimsy cavernosal artery is not usually a realistic option. Unfortunately, because the run-off into the corpora is slow when the penis is flaccid, failure of revascularization often occurs in the longer term. Complications include glans hypervascularization, which may require reversal of the procedure.

Implantation of penile prostheses

For a number of years, it has been recognized that the insertion of silicone prostheses into the paired corpora cavernosa restores sufficient rigidity to the penis to permit intercourse. These prostheses are available in three basic forms: semi-rigid selfcontained single-piece devices that bestow limited rigidity and flaccidity, two-component inflatable devices, and three-component inflatable devices that provide the closest approximation to normality (Figures 72–78).

Implantation is accomplished under a general anesthetic with an antibiotic cover. A catheter is inserted to empty the bladder and reduce the risk of injury. Both corpora are incised and dilated to 14F in diameter and carefully measured. A prosthesis of the correct length is then implanted and the corpora closed (Figures 79–86). With the three-component prosthesis, the appropriate connections are then made to the pump located in the scrotum and to the reservoir (Figure 87), which is implanted extraperitoneally anterolateral to the bladder. Prior to surgery, the patient should be counselled about the small risk of infection, which will necessitate device removal, and the possibility of subsequent mechanical failure of the device.

Surgical correction of erectile deformity

Deformity of the corpora cavernosa resulting in bending on erection may be congenital but, more often, is a result of scarring due to the disease described by François de la Peyronie (Figures 88 and 89). In either case, correction may be achieved by excision of an elliptical portion of tissue (or a series of elliptical pieces) from the side opposite the curvature. This maneuver (see Figure 89), first described by Nesbit, usually leads to a good outcome, but is achieved at the cost of penile shortening (usually 2–3 cm). The plication technique (Figure 90) also results in loss of erectile length. To avoid this, other techniques have been described, including plaque incision (Figure 91) and excision (Figure 92), and grafting of the defect with a segment of vein or other material. These procedures carry some risk of damage to the dorsal neurovascular bundle. Long-term outcome data are awaited to confirm that the initial benefit is sustained.

Penile enlargement

A proportion of patients with erectile dysfunction attribute their problem to the small size of their penis. In fact, a penis of any proportion is generally able to function effectively in terms of achieving sufficient rigidity for penetrative sexual intercourse. Penile lengthening procedures have been described which involve division of the suspensory ligament and an advanced V-Y plasty of the intrapubic skin (Figure 93). Liposuction of abdominal wall fat and subcutaneous injection have been described, but the long-term outcome has often proved to be a disappointment to both the patient and the surgeon.

Conclusions

Erectile dysfunction is a highly prevalent disorder which is frequently associated with loss of selfesteem and a reduced quality of life. The condition affects not only the individual, but also their partner. As it is strongly age-related, the incidence of erectile dysfunction is likely to increase with the 'graying' of society.

Rapid advances have recently been made in our understanding of the mechanisms of penile erection and the pathophysiology of erectile dysfunction. These have now been translated into a number of safe and effective treatment possibilities that offer a practical solution to the large numbers of men and their partners who are suffering as a result of this disorder. These therapies need to be employed in a goal-oriented manner, with careful attention being paid to patient preferences.

Unfortunately, many health-care practitioners are still too embarrassed to discuss sexual problems frankly and, as a consequence, avoid raising these issues with their patients. The onus now falls on those who care for the many patients with erectile dysfunction to initiate the discussion and to inform and instruct them and their partners as to the cause of their problem, and the safest and most effective means by which natural erectile function may be restored and sexual activity resumed.

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Appendix

Table I A brief sexual function inventory

SEXUAL DRIVE—Let's define sexual drive as a feeling that may include wanting to have a sexual experience (masturbation or intercourse), thinking about having sex or feeling frustrated due to lack of sex.

1. During the past 30 days, on how many days have you felt sexual drive?	No days	Only a few days	Some days	Most days	Almost every day
0	1	2	3	4	
2. During the past 30 days, how would you rate your level of sexual drive?	None at all	Low	Medium	Medium high	High
0	1	2	3	4	
ERECTIONS					
3. Over the past 30 days, how often have you had partial when you were sexually or full sexual erections stimulated in any way?	Not at all	A few times	Fairly often	Usually	Always
0	1	2	3	4	
4. Over the past 30 days, how often have you had erections, how to have sexual intercourse? often were they firm enough	0	1	2	3	4
5. How much difficulty did you have getting an erection during the last 30 days?	Did not get erections at all	A lot of difficulty	Some difficulty	Little difficulty	No difficulty
0	1	2	3	4	
EJACULATION					
6. Over the past 30 days, how much difficulty have you had in ejaculating when you have been sexually stimulated?	No sexual stimulation in past month	A lot of difficulty	Some difficulty	Little difficulty	No difficulty
0	1	2	3	4	
7. In the past 30 days, how much did you consider the amount of semen you ejaculate?	Did not climax	Big problem	Medium problem	Small problem	No problem
0	1	2	3	4	
8. In the past 30 days, to what extent have you considered a lack of sex drive to be a problem?	Big problem	Medium problem	Small problem	Very small problem	No problem
0	1	2	3	4	
9. In the past 30 days, to what extent have you	0	1	2	3	4

EJACULATION					
considered your ability to get and keep an erection a problem?					
10. In the past 30 days, to what extent have you to be a problem? considered your ejaculation	0	1	2	3	4
11. Overall, during the past 30 days, how satisfied have you been with your sex life?	Very dissatisfied	Mostly dissatisfied	Neutral or mixed	Mostly satisfied	Very satisfied
0	1	2	3	4	

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Table II Individual items from the International Index of Erectile Function (IIEF) Questionnaire and response options (US version)

QUESTION	RESPONSE OPTIONS
(All questions are preceded by 'Over the past 4 weeks,')	
1. How often were you able to get an erection during sexual activity?	0=No sexual activity 1=Almost never/never 2=A few times (much less than half the time) 3=Sometimes (about half the time) 4=Most times (much more than half the time) 5=Almost always/always
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0=No sexual activity 1=Almost never/never 2=A few times (much less than half the time) 3=Sometimes (about half the time) 4=Most times (much more than half the time) 5=Almost always/always
3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	0=Did not attempt intercourse 1=Almost never/never 2=A few times (much less than half the time) 3=Sometimes (about half the time) 4=Most times (much more than half the time) 5=Almost always/always
4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0=Did not attempt intercourse 1=Almost never/never 2=A few times (much less than half the time) 3=Sometimes (about half the time) 4=Most times (much more than half the time) 5=Almost always/always
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0=Did not attempt intercourse 1=Extremely difficult 2=Very difficult 3=Difficult 4=Slightly difficult 5=Not difficult
6. How many times have you attempted sexual intercourser	0=No attempts 1=One to two attempts 2=Three to four attempts 3=Five to six attempts 4=Seven to ten attempts 5=Eleven+attempts
7. When you attempted sexual intercourse, how often was it satisfactory for you?	0=Did not attempt intercourse 1=Almost never/never

	2=A few times (much less than half the time) 3=Sometimes (about half the time) 4=Most times (much more than half the time) 5=Almost always/always
8. How much have you enjoyed sexual intercourse?	0=No intercourse 1=No enjoyment 2=Not very enjoyable 3=Fairly enjoyable 4=Highly enjoyable 5=Very highly enjoyable
9. When you had sexual stimulation or intercourse, how often did you ejaculate?	0=No sexual stimulation/intercourse 1=Almost never/never 2=A few times (much less than half the time) 3=Sometimes (about half the time) 4=Most times (much more than half the time) 5=Almost always/always
10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	1=Almost never/never 2=A few times (much less than half the time) 3=Sometimes (about half the time) 4=Most times (much more than half the time) 5=Almost always/always
11. How often have you felt sexual desire?	1=Very low/none at all 2=Low 3=Moderate 4=High 5=Very high
12. How would you rate your level of sexual desire?	1=Very dissatisfied 2=Moderately dissatisfied 3=About equally satisfied and dissatisfied 4=Moderately satisfied 5=Very satisfied
13. How satisfied have you been with your overall sex life?	1=Very low 2=Low 3=Moderate 4=High 5=Very high
14. How satisfied have you been with your sexual relationship with your partner?	1=Very low 2=Low 3=Moderate 4=High 5=Very high
15. How do you rate your confidence that you could get and keep an erection?	1=Very low 2=Low 3=Moderate 4=High 5=Very high

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Table III Quality of life and erectile dysfunction

Item list	
1.	I feel frustrated because of my erection problem
2.	My erection problem makes me feel depressed
3.	I feel like less of a man because of my erection problem
4.	I have lost confidence in my sexual ability
5.	I worry that I won't be able to get or keep an erection
6.	My erection problem is always on my mind
7.	I feel that I have lost control over my erections
8.	I blame myself for my erection problem

Item list	
9.	I feel angry because of my erection problem
10.	I worry about the future of my sex life
11.	I have lost pleasure in sex because of my erection problem
12.	I am embarrassed about my problem
13.	I worry about being humiliated because of my problem
14.	I try to avoid having sex
15.	I feel different from other men because of my erection problem
16.	I get less enjoyment out of life because of my erection problem
17.	I feel guilty about my erection problem
18.	I am afraid to 'make the first move' towards sex
19.	I worry that my partner blames herself for my erection problem
20.	I worry about letting her down because of my erection problem
21.	I worry that I'm not satisfying her because of my erection problem
22.	I worry that we are growing apart because of my erection problem
23.	I worry that she is looking for someone else because of my erection problem
24.	I feel that she blames me for my erection problem
25.	I worry that she thinks I don't want her because of my erection problem
26.	I have trouble talking to her about my erection problem
27.	My erection problem interferes with my daily activities

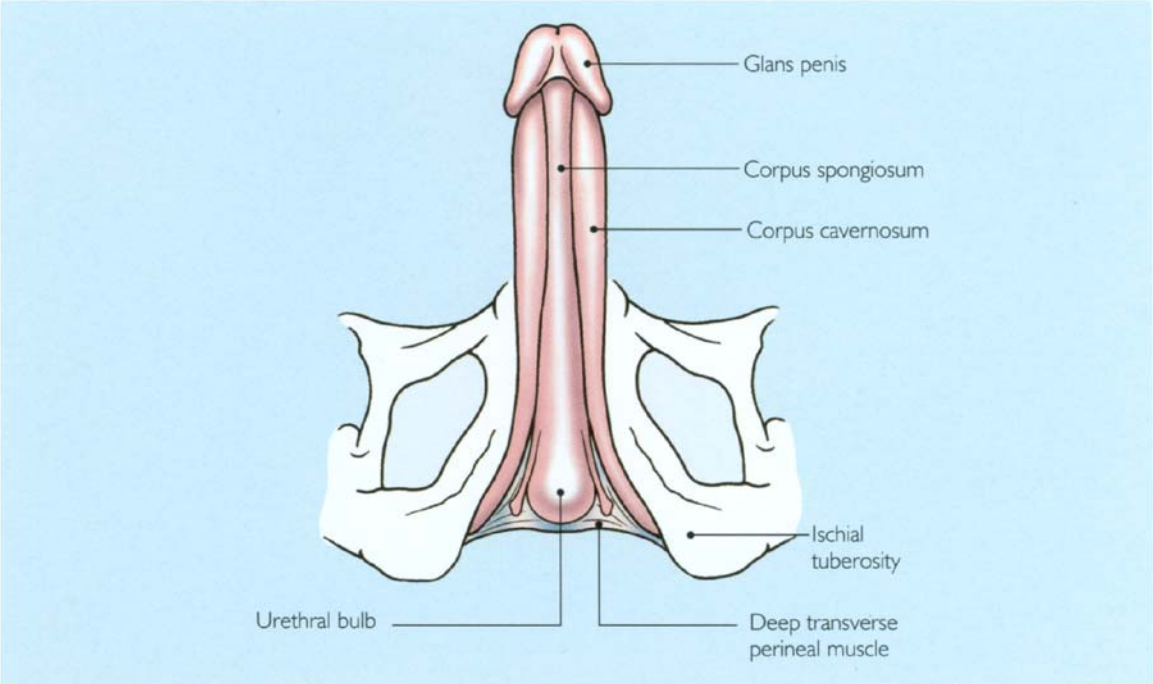


Figure 1 Key structures mediating erection are the corpora cavernosa or 'erectile bodies', which are fused distally for approximately three-quarters of their length. They separate proximally to fuse with each ischial tuberosity of the pelvis. On their ventral surface lies the corpus spongiosum, which surrounds the urethra

Section 2:

Erectile Dysfunction lllustrated

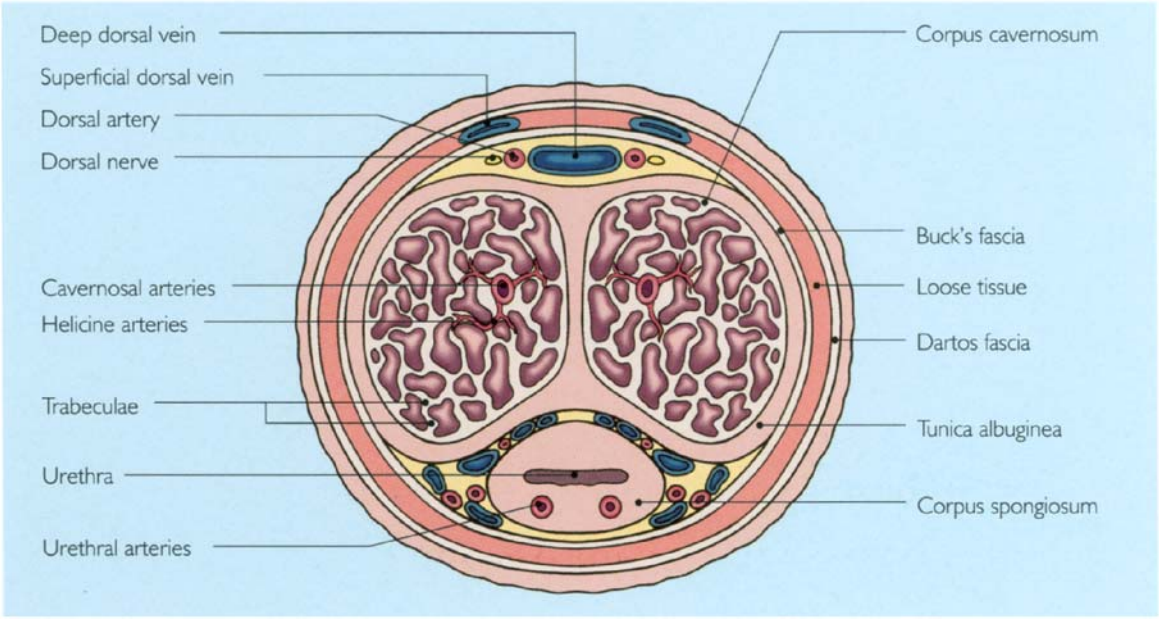


Figure 2 Each corpus cavernosum comprises a thick fibrous sheath, the tunica albuginea, which surrounds the erectile tissue. Each corpus has a centrally running cavernosal artery, which supplies blood to the multiple lacunar spaces, which are interconnected and lined by vascular endothelium

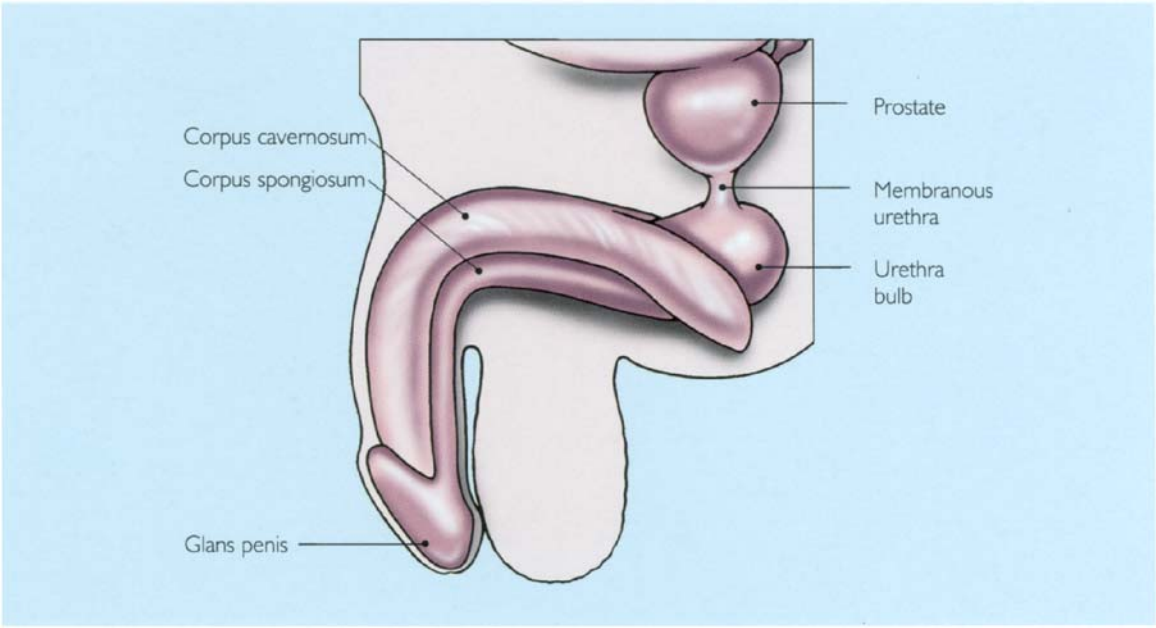


Figure 3 The corpus spongiosum is firmly attached to the undersurface (ventral aspect) of the corpora cavernosa and expands distally to form the glans penis. Proximally, it forms the urethral bulb, where the urethra curves cranially to form the sphincter-active membranous urethra

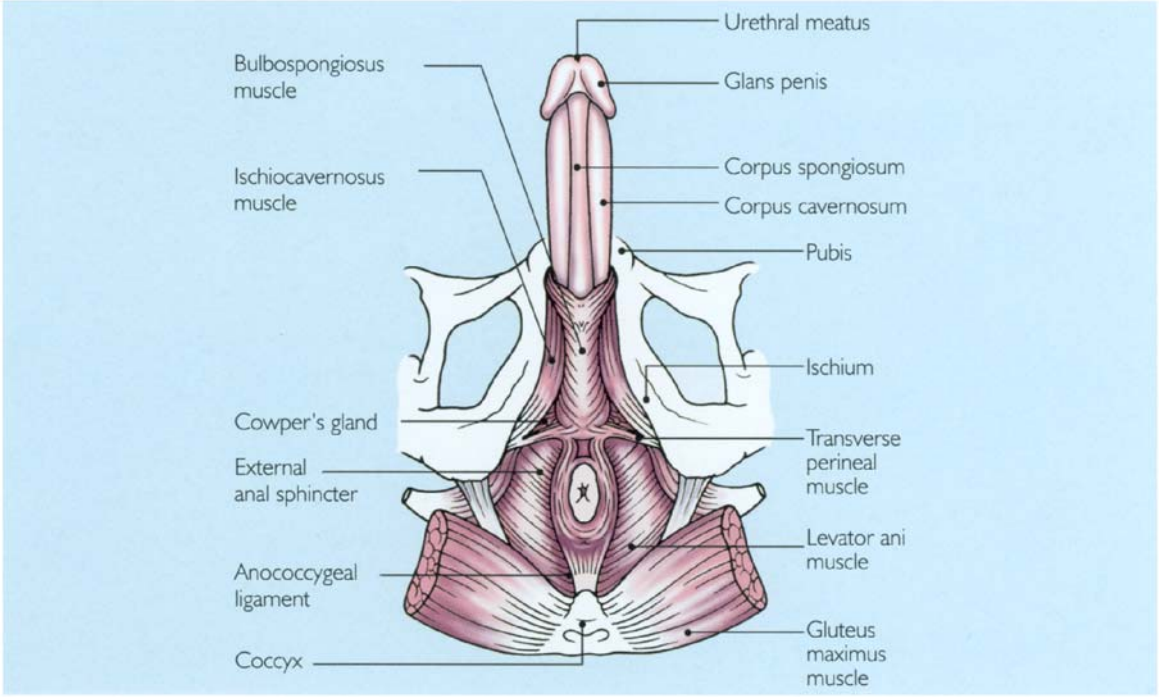


Figure 4 Muscles of the pelvic floor surround and support the erectile bodies and corpus spongiosum. In terms of sexual function, the most important muscles are the bulbospongiosus and the ischiocavernosus. These support the erect penis and also contract rhythmically at the time of orgasm to facilitate ejaculation

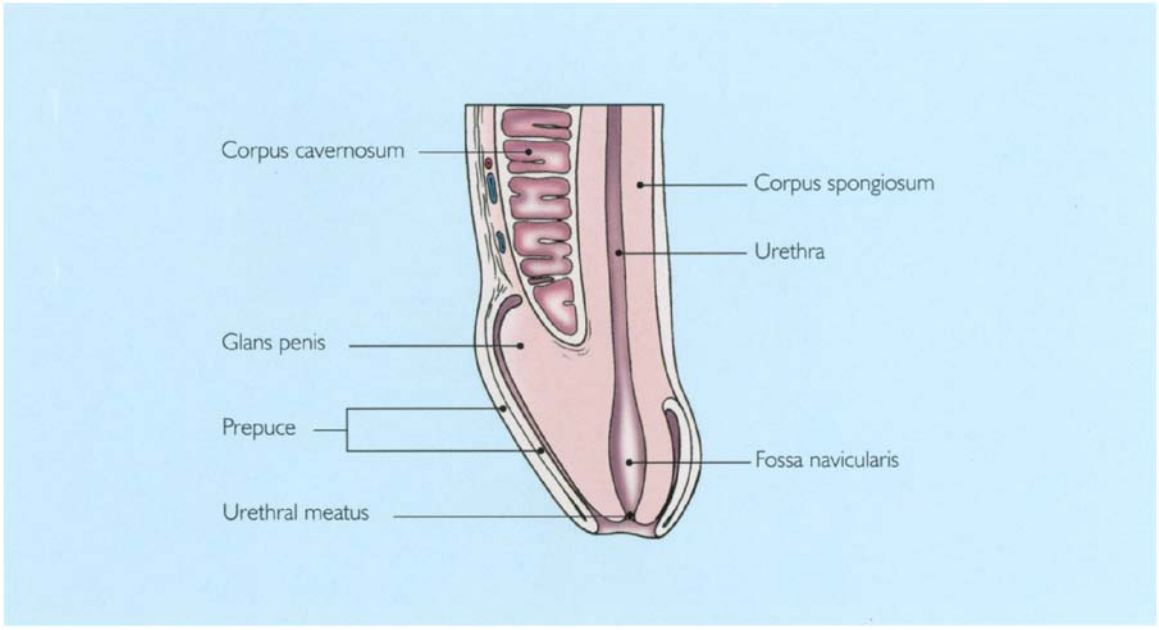


Figure 5 Skin overlying the penis is exceptionally mobile and expandable to accommodate the considerable increase in length and girth that occurs during erection. Distally the penile skin is reflected forwards over the glans penis to form the prepuce, before folding back on itself to attach to the corona of the glans penis

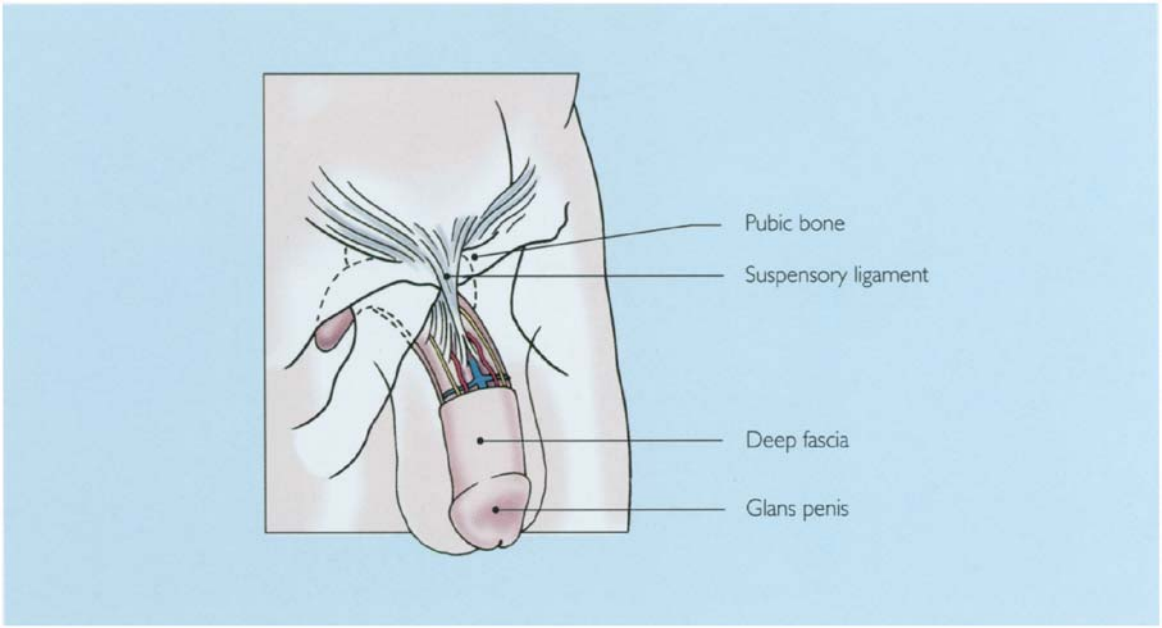


Figure 6 The pendulous portion of the penis is supported by the suspensory ligament, a fibrous condensation which supports and stabilizes the erect penis. Division of this structure makes the penis appear longer in its flaccid state, but does not enhance the proportions of the organ when erect

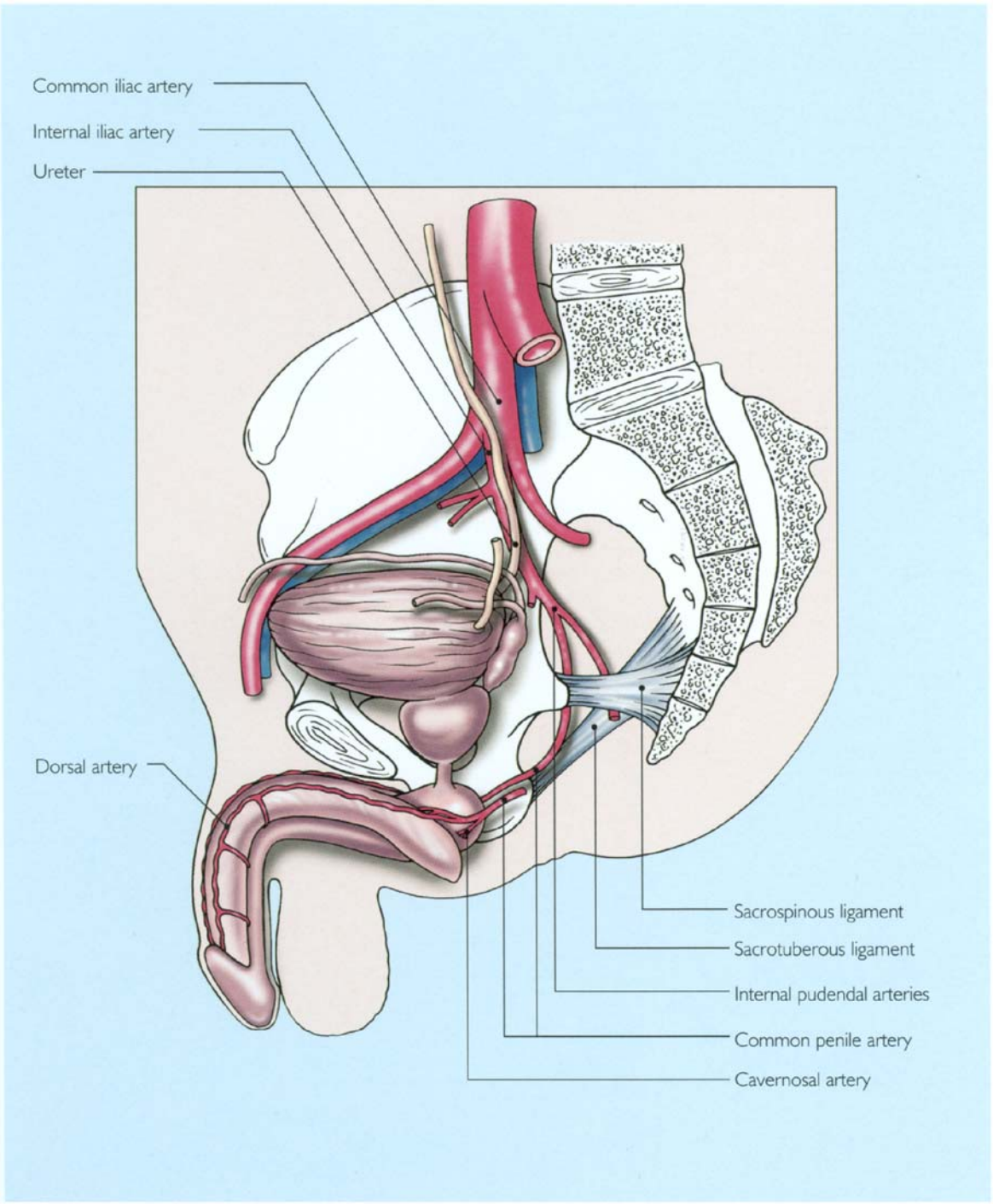


Figure 7 Blood supply to each corpus cavernosum is derived from the internal iliac artery, a branch of the common iliac artery; the internal pudendal artery is one of the terminal branches of the internal iliac. In the pelvis, the internal iliac passes beneath the sacrospinous ligament and over the sacrotuberous ligament into Alcock's canal, where it runs under the pubic symphysis. After giving off the perineal artery, it becomes the common penile artery, giving off the bulbourethral, dorsal and cavernosal arteries before reaching the corpus cavernosum to form one element of the paired dorsal arteries

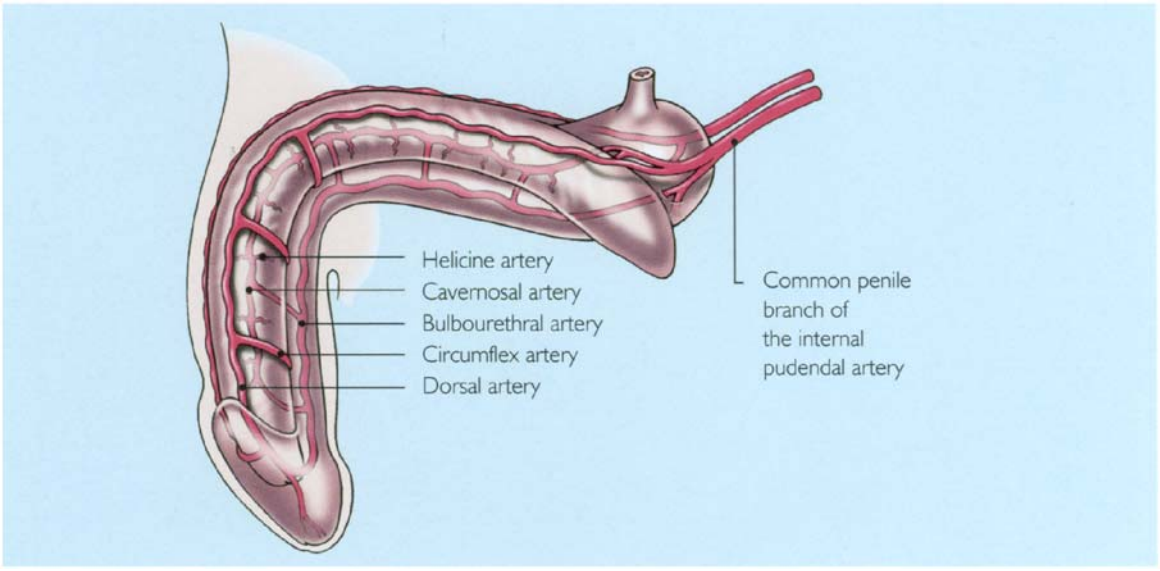


Figure 8 Paired dorsal arteries run along the dorsal aspect of the corpora beneath Buck's fascia, giving off multiple circumflex branches and, eventually, supplying blood to the glans penis. The cavernosal arteries run along the middle of each corpus cavernosum, giving off multiple helicine branches, which supply blood to the lacunar spaces

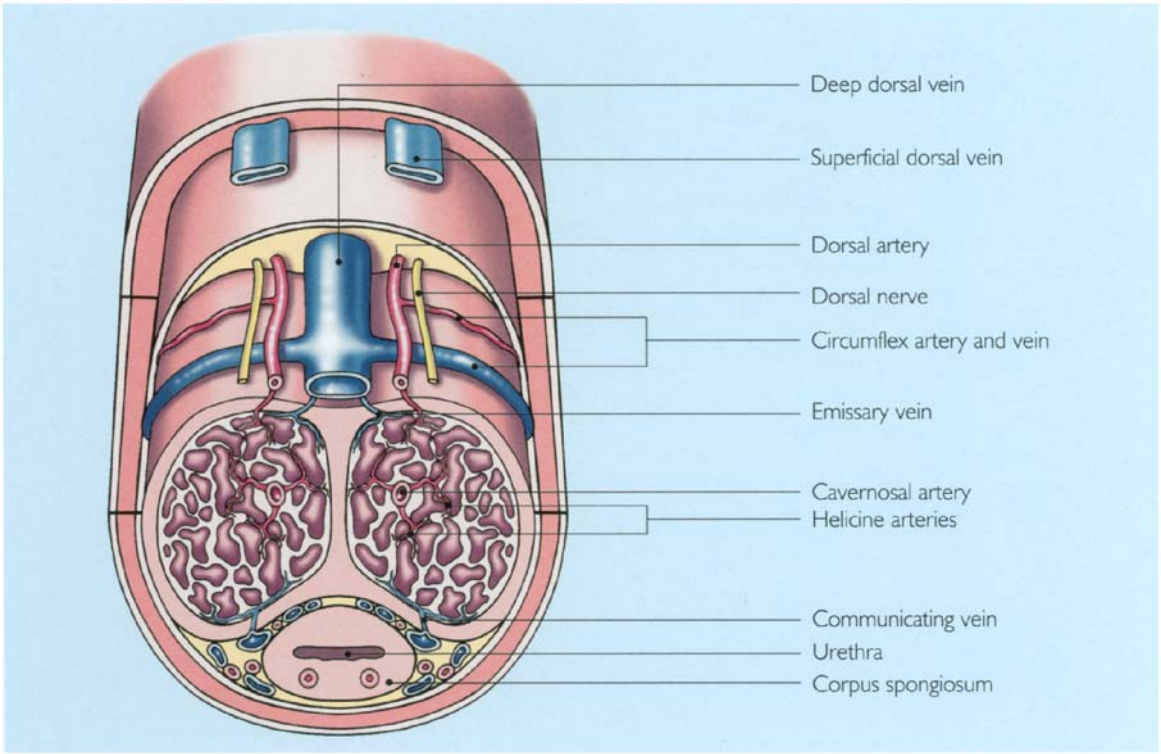


Figure 9 Cross-section of the penis showing the locations of the paired dorsal arteries and cavernosal arteries. Note the helicine arteries, which supply arterial blood to the lacunar spaces

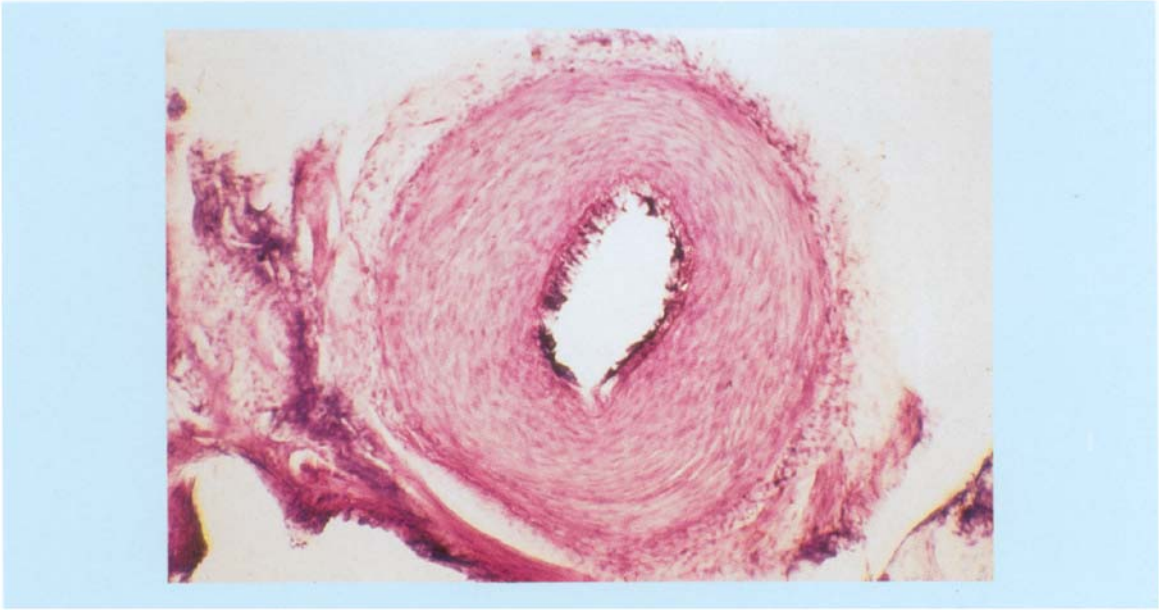


Figure 10 Cross-section of a helicine artery from a human penis. The thick smooth muscle walls allow the artery to function as a resistance vessel controlling blood flow within the lacunar spaces to maintain flaccidity. By courtesy of D. Prieto and U. Simonsen

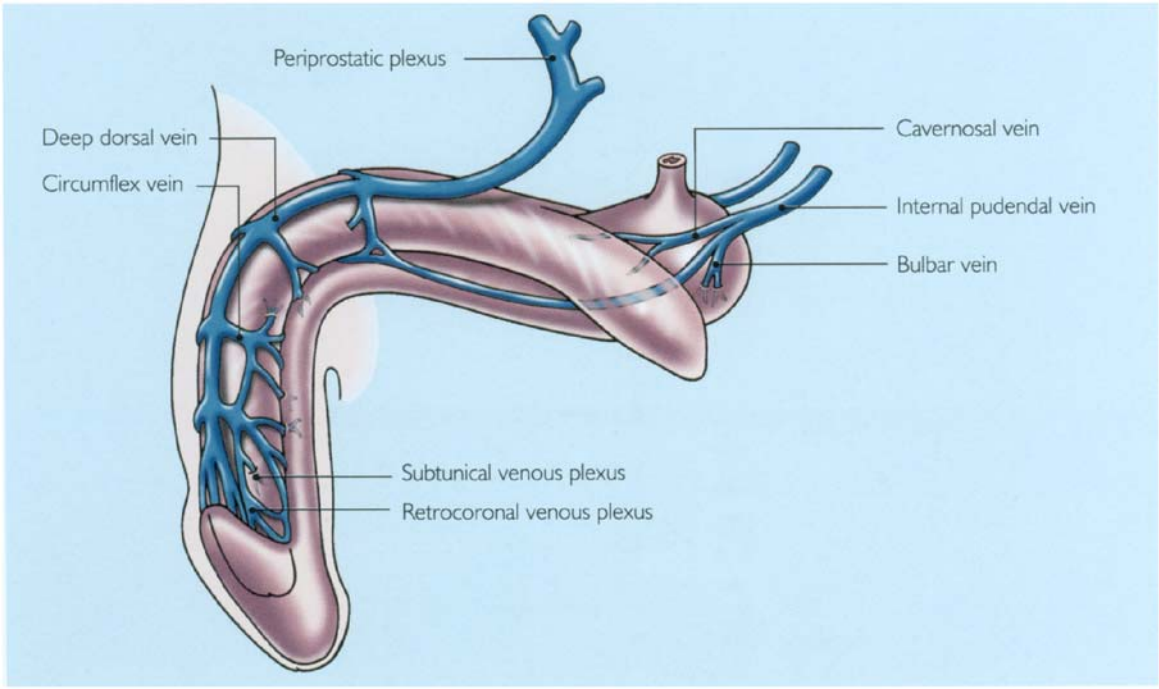


Figure 11 Venous drainage from the corpora cavernosa takes place mainly through the deep dorsal vein, which lies dorsally in the groove between the corpora and passes beneath the pubic arch to join the dorsal venous complex at the urethroprostatic junction. The less surgically accessible bulbar and cavernosal veins join to form the internal pudendal vein

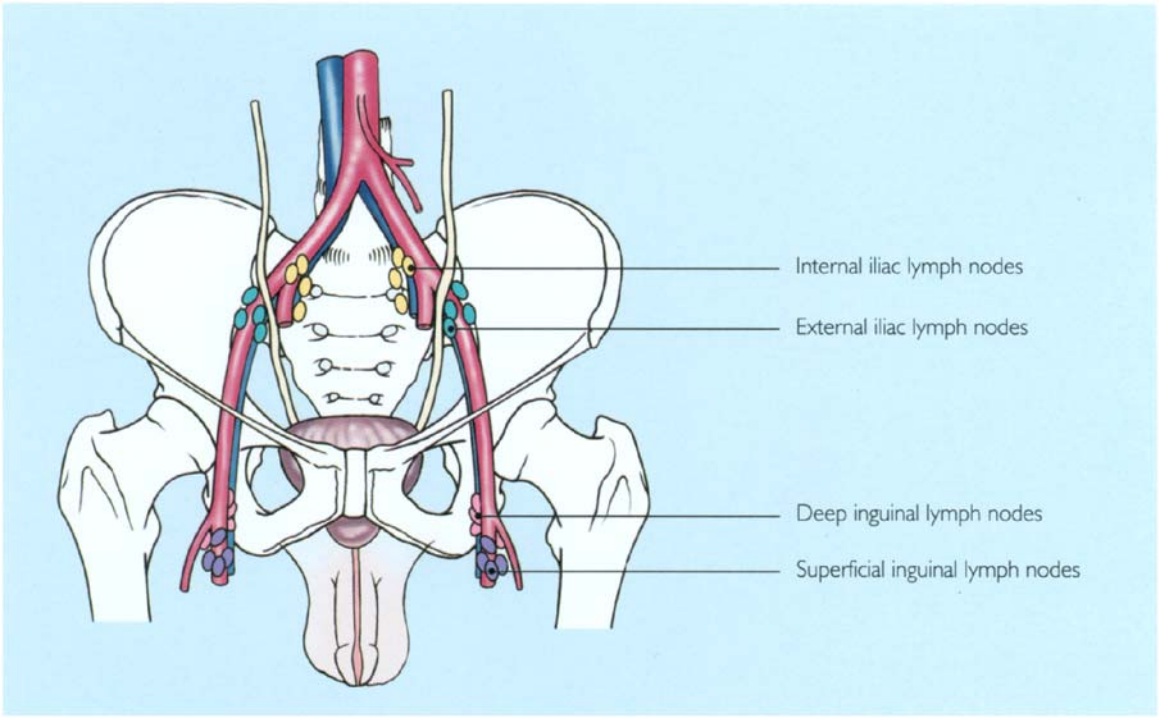


Figure 12 Lymphatic drainage of the penis is accomplished by the superficial and deep inguinal nodes which, in turn, drain to the iliac and para-aortic lymph nodes

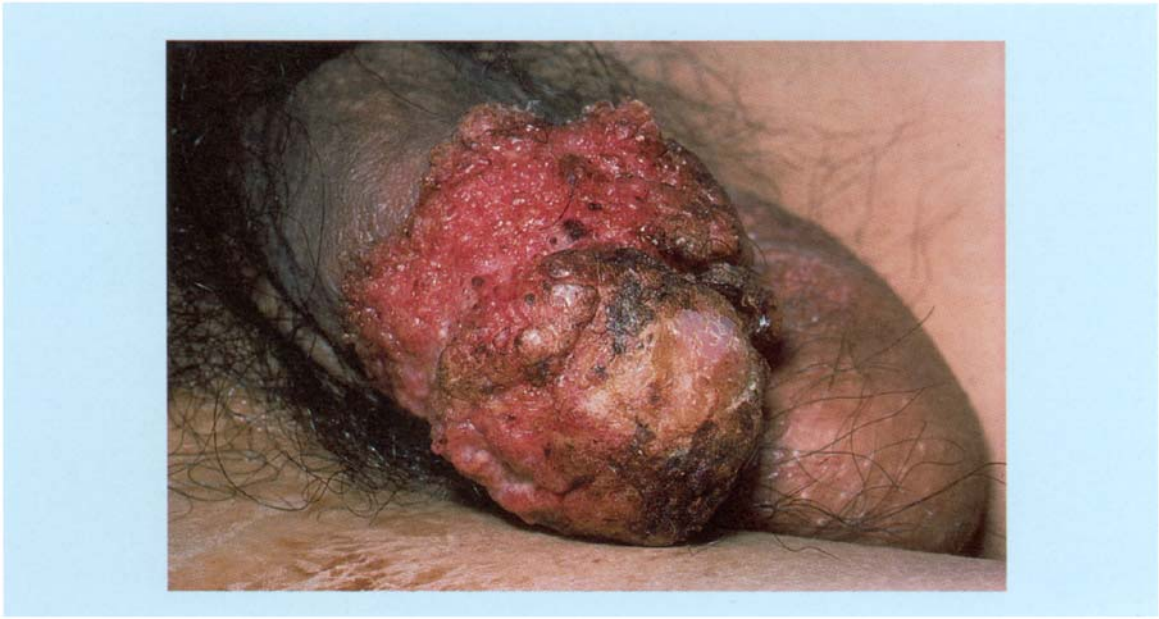


Figure 13 Locally advanced squamous cell carcinoma of the penis. In this case, the inguinal lymph nodes were involved bilaterally. Occasionally, these tumors are picked up in erectile dysfunction clinics

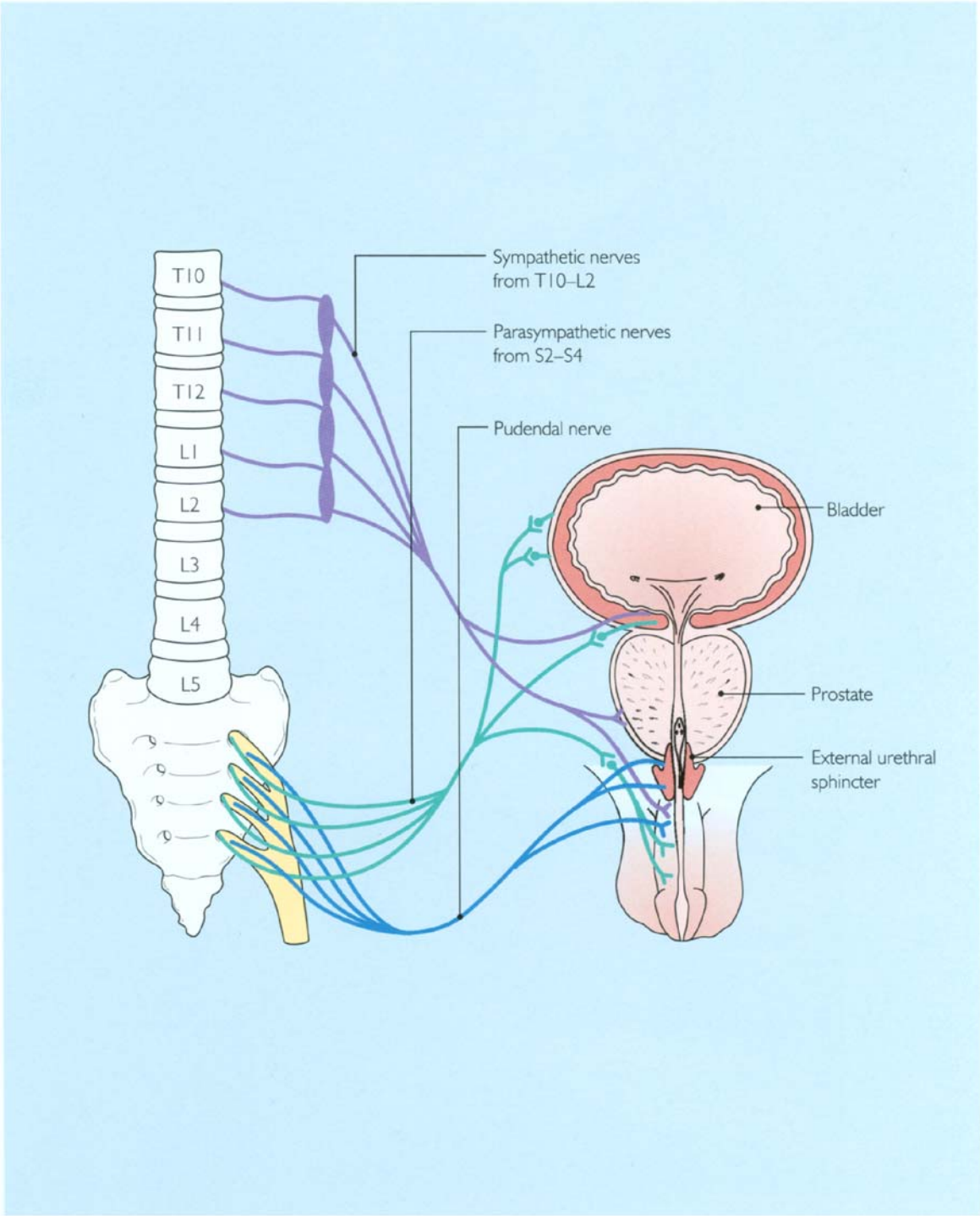


Figure 14 Three sets of peripheral nerves are involved in penile erection: two are autonomic and one is somatic. Parasympathetic nerves stem from the second to the fourth sacral segments (S2–S4), whereas sympathetic nerves have their preganglionic cell bodies in the intermediolateral cell columns of the thoracolumbar (T10–L2) segments. Somatic fibers travel in the pudendal nerves and their cell bodies are situated in the S2–S4 segments

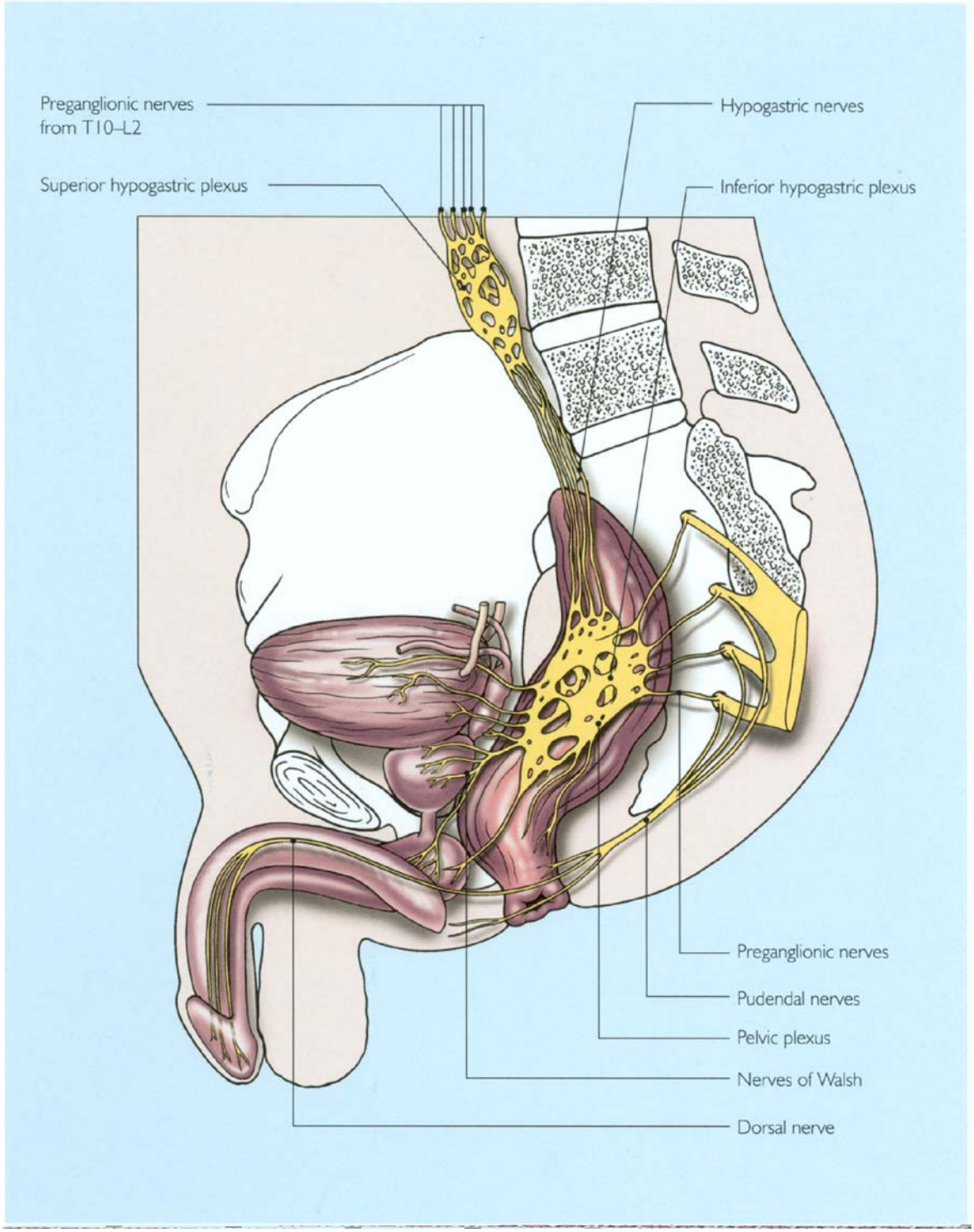


Figure 15 The hypogastric nerves are vulnerable during retroperitoneal lymph node dissection. Both sympathetic and parasympathetic nerves merge in the pelvic plexus and pass posterolateral to the prostate gland in the so-called neurovascular bundles of Walsh, where they may be damaged during radical prostatectomy and cystoprostatectomy

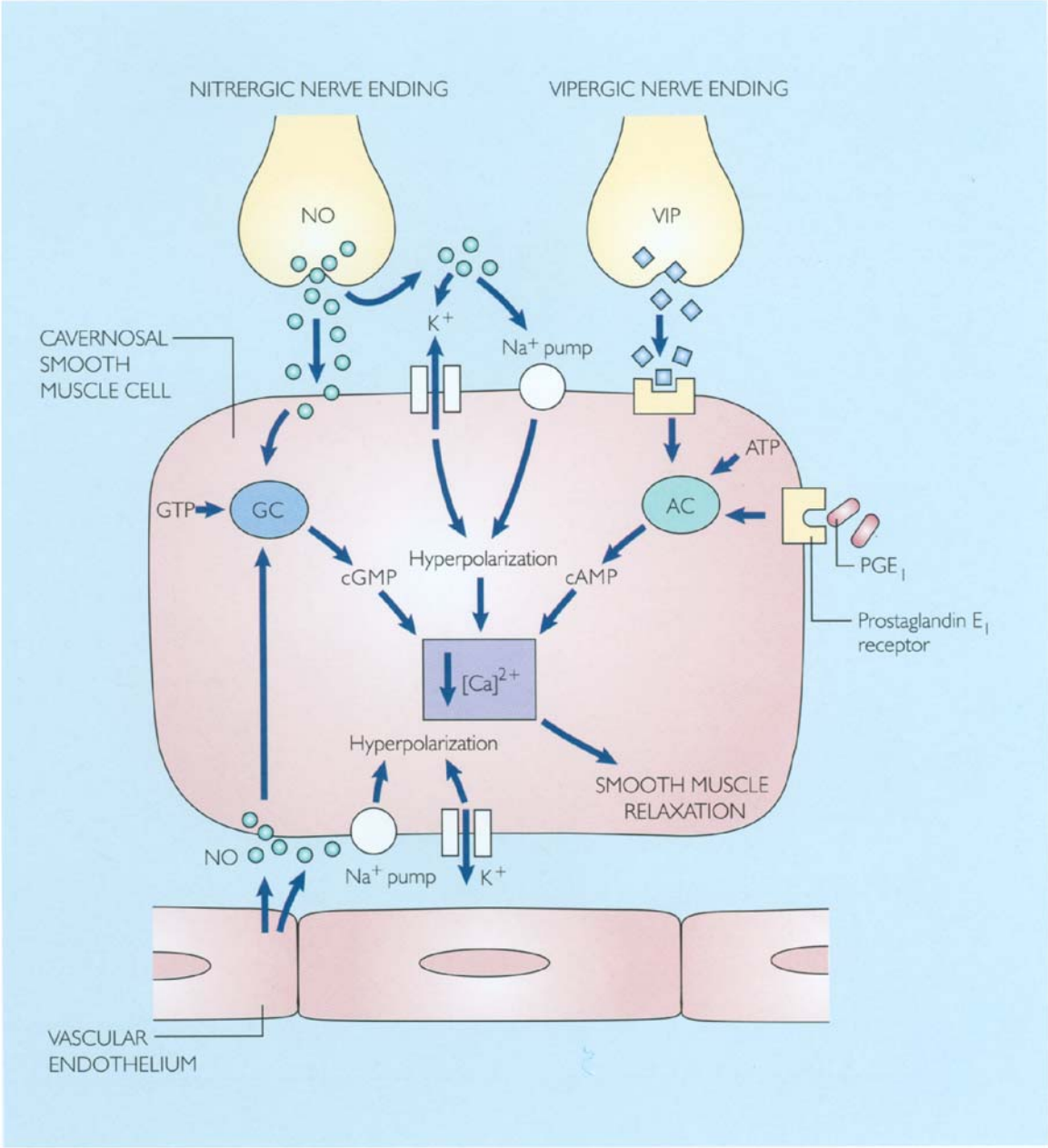


Figure 16 Cavernosal smooth muscle tone is the most important determinant of penile blood flow. This, in turn, is critically dependent on the level of intracellular calcium ($[Ca]^{2+}$), modulated by a number of mechanisms. The most important vasodilator transmitter is nitric oxide (NO), released from both nitrergic nerve endings and vascular endothelium. NO stimulates production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP) by the enzyme guanylate cyclase (GC). A second vasodilator mechanism involves the production of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP) by adenylate cyclase (AC). Both vasoactive intestinal polypeptide (VIP) and prostaglandin E1 (PGE_1) activate AC. Both cGMP and cAMP lower intracellular calcium, thereby triggering smooth muscle relaxation. NO also activates sodium (Na^+)/potassium (K^+)-channel ATPase, resulting in hyperpolarization of the smooth muscle cell membrane which, in turn, prevents the opening of voltage-dependent calcium channels, thereby reducing intracellular calcium

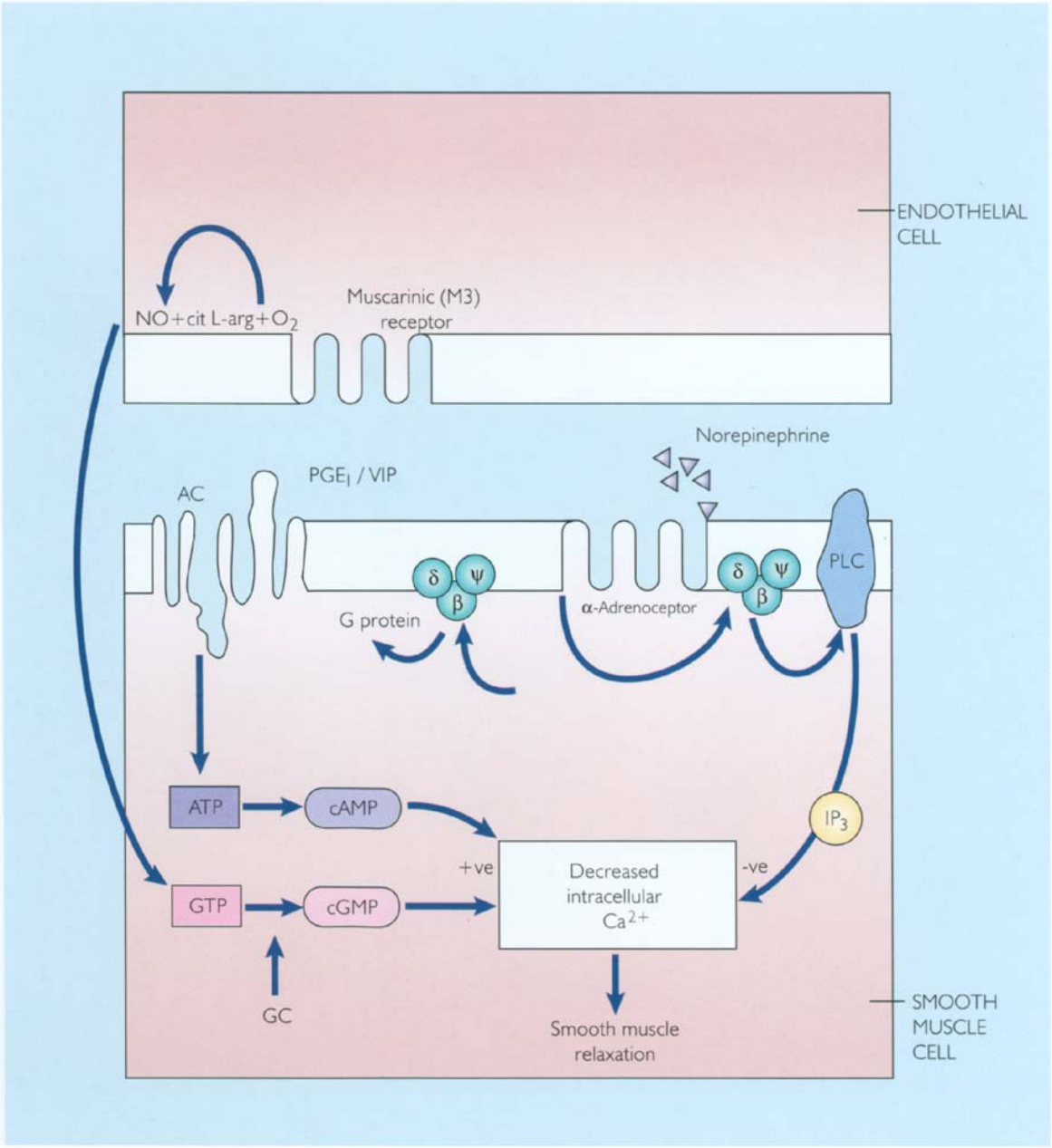


Figure 17 Vasodilatory actions of nitric oxide (NO), prostaglandin E_1 and vasoactive intestinal polypeptide (VIP) and the opposing vasoconstrictory effect of norepinephrine on intracorporeal smooth muscle cells. NO together with citrulline (cit) is produced by the enzyme nitric oxide synthase (NOS) from L-arginine (arg) and oxygen (O_2). NO acts as a neurotransmitter to stimulate the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). Membrane-bound adenylate cyclase (AC) produces cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). AC activity is dependent on guanidine nucleotide binding protein (G protein). Both cAMP and cGMP lower intracellular calcium (Ca^{2+}). In contrast, norepinephrine acts via the α-adrenoceptor. Activation of this G-protein-linked receptor stimulates production of inositol phosphate (IP_3) by a phospholipase C (PLC)-dependent mechanism. IP_3 acts to increase intracellular Ca^{2+}, thereby inducing contraction of intracavernosal smooth muscle cells

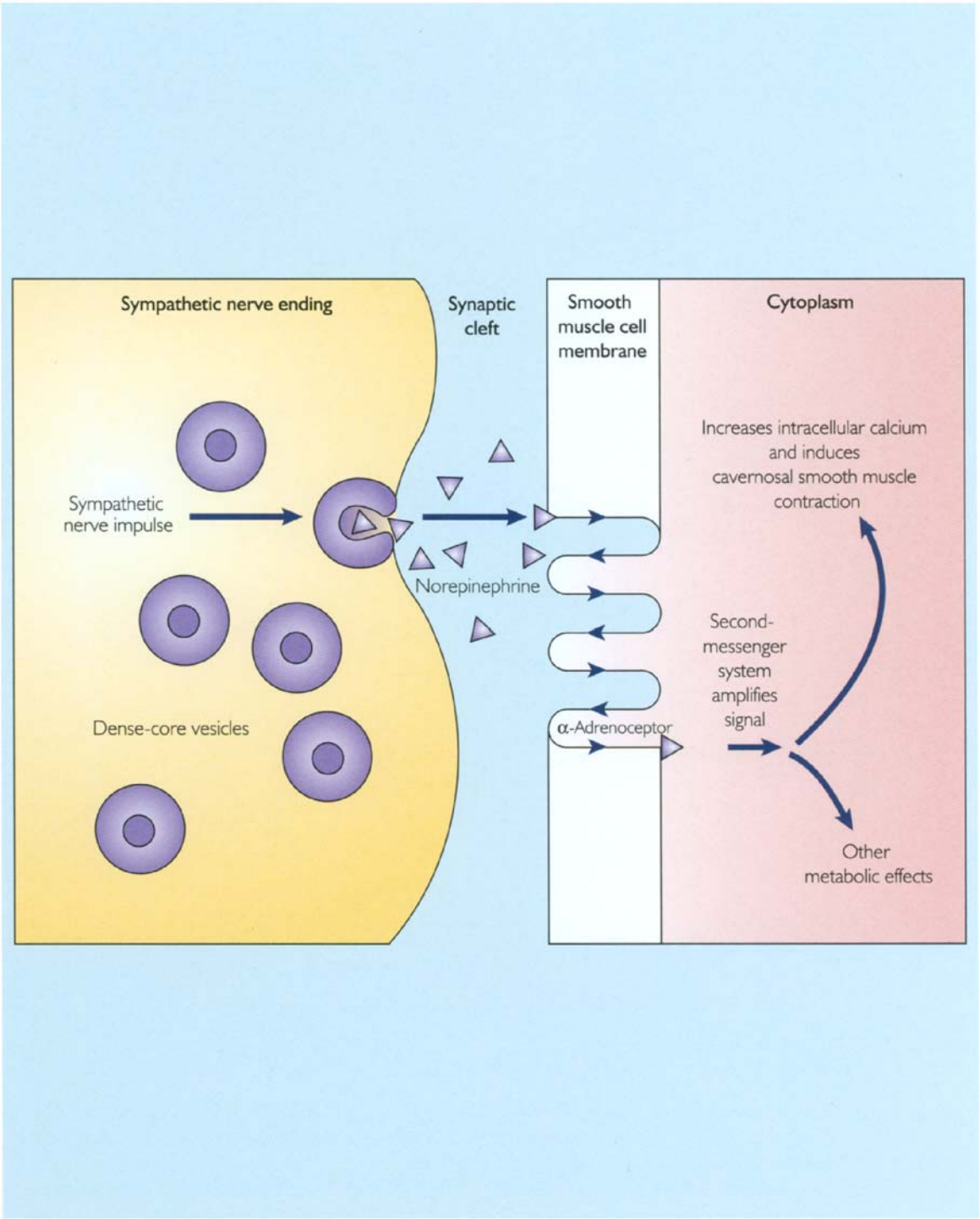


Figure 18 Norepinephrine is released from dense-core vesicles in sympathetic nerve terminals within the corpora. Norepinephrine then diffuses across the synaptic gap to activate α-adrenoceptors located on the cavernosal smooth muscle cell membrane. Second-messenger systems amplify the signal and induce smooth muscle contraction by increasing levels of intracellular calcium. By contrast, α-blockers such as phentolamine (Vasomax®) interrupt this pathway thereby enhancing penile erection

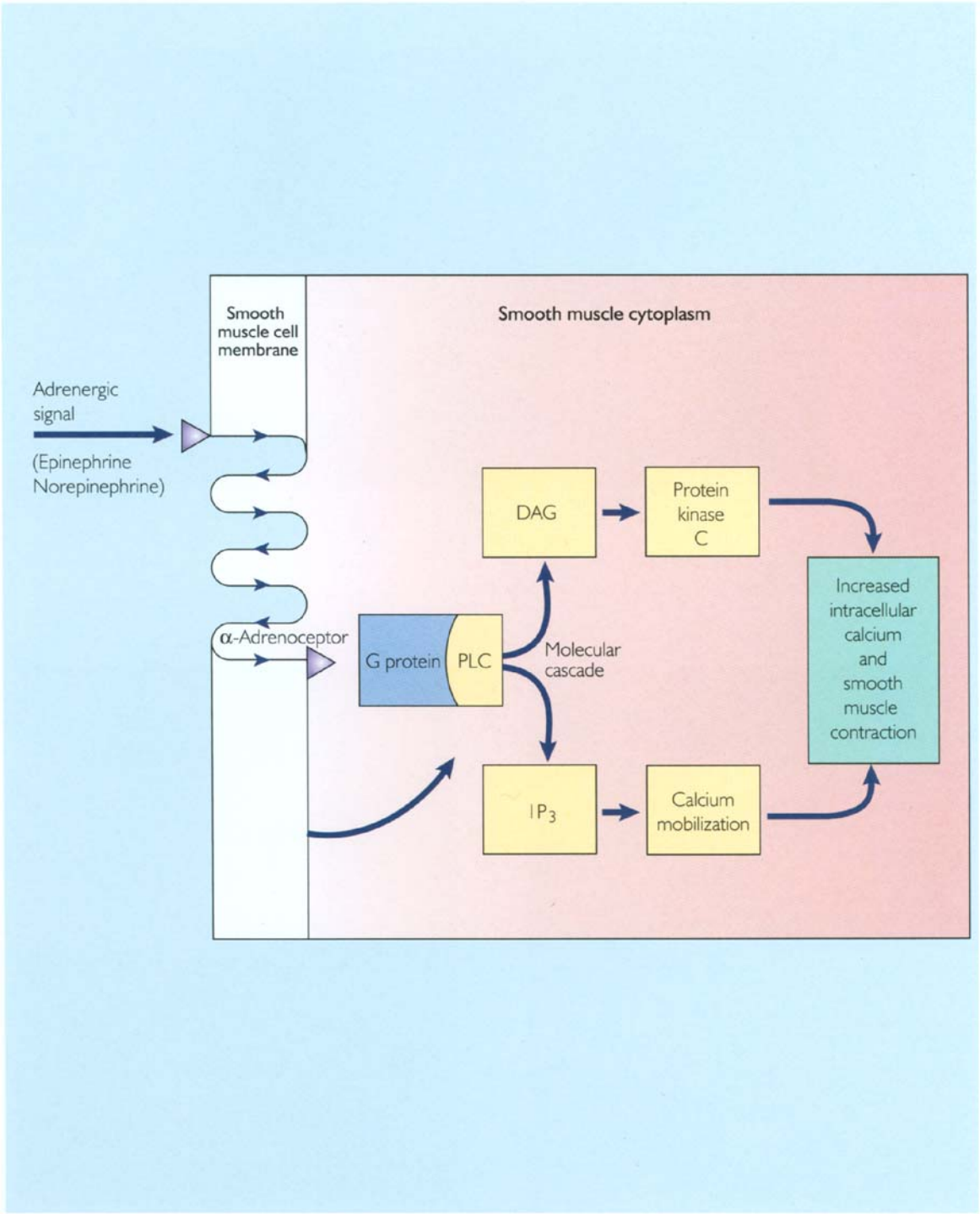


Figure 19 Second-messenger systems following stimulation of α-adrenoceptors on the membranes of smooth muscle cells within the corpora involve guanidine nucleotide binding protein (G protein) and phospholipase C (PLC). The signal is amplified by two pathways involving inositol phosphate (IP_3) and diacylglycerol (DAG), respectively. The result is an increase in the level of intracellular calcium and consequent smooth muscle contraction

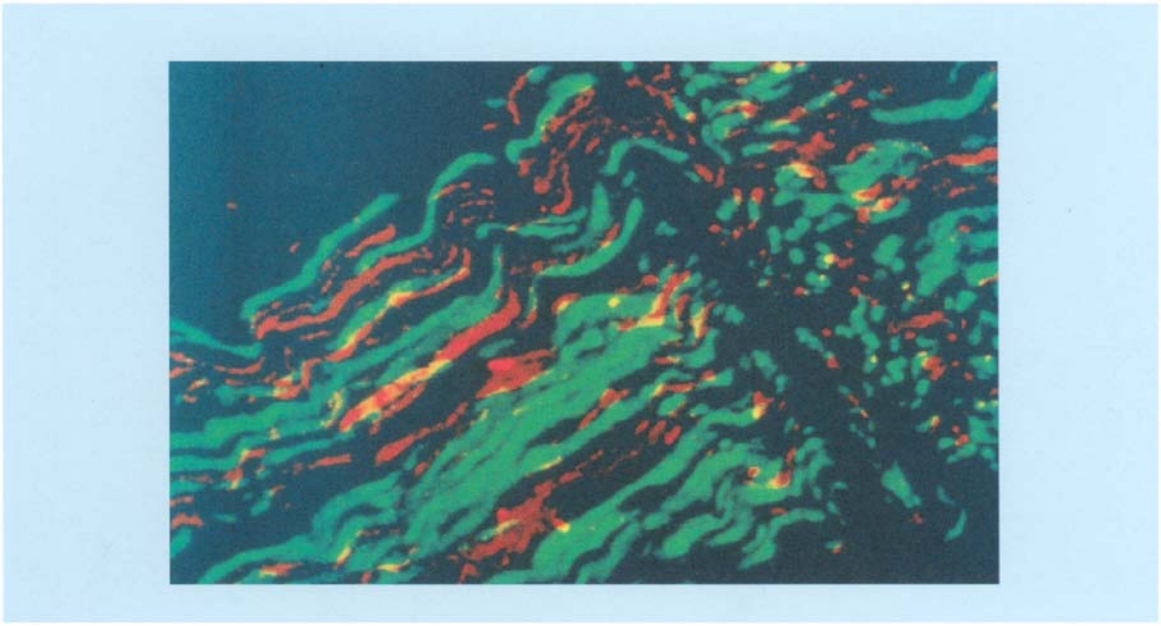


Figure 20 Neurohistochemical preparation of a microscopy section through a human pelvic nerve demonstrates the presence of nitric oxide synthase (staining green)

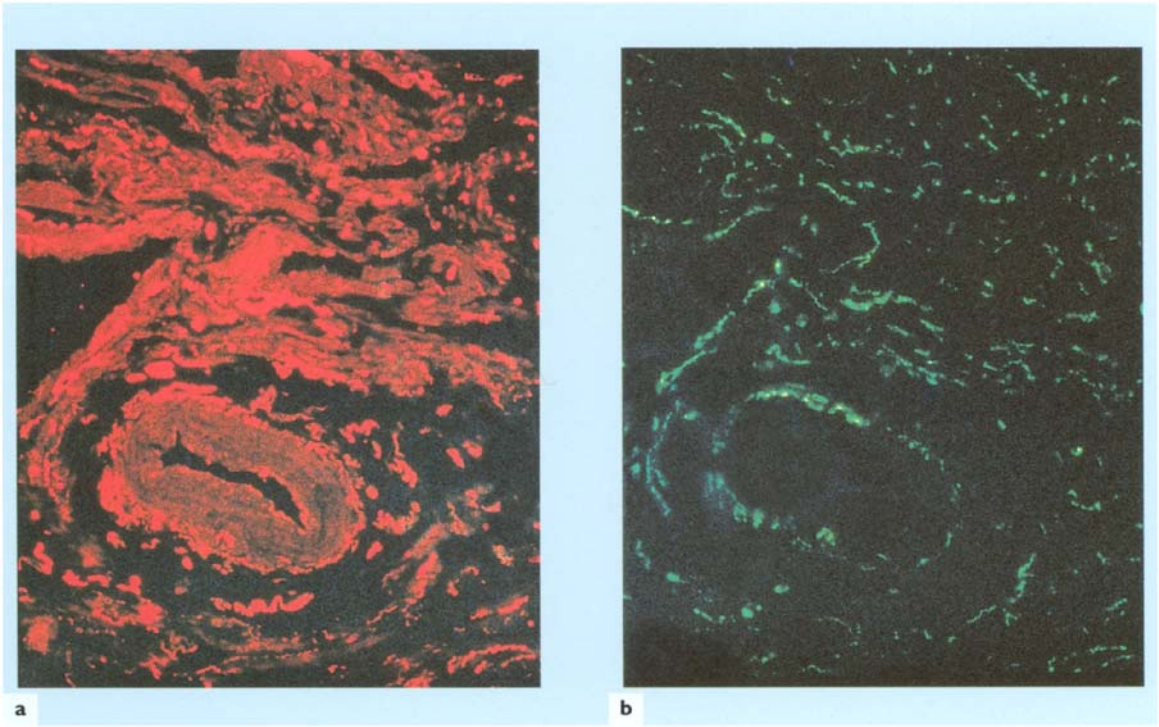


Figure 21 Neurohistochemical preparation of a microscopy section of dog corpus cavernosum demonstrates the presence of nitric oxide synthase (a; staining red) and vasoactive intestinal polypeptide (b; staining green). The two mediators of penile erection are co-localized to a non-adrenergic non-cholinergic nerve ending

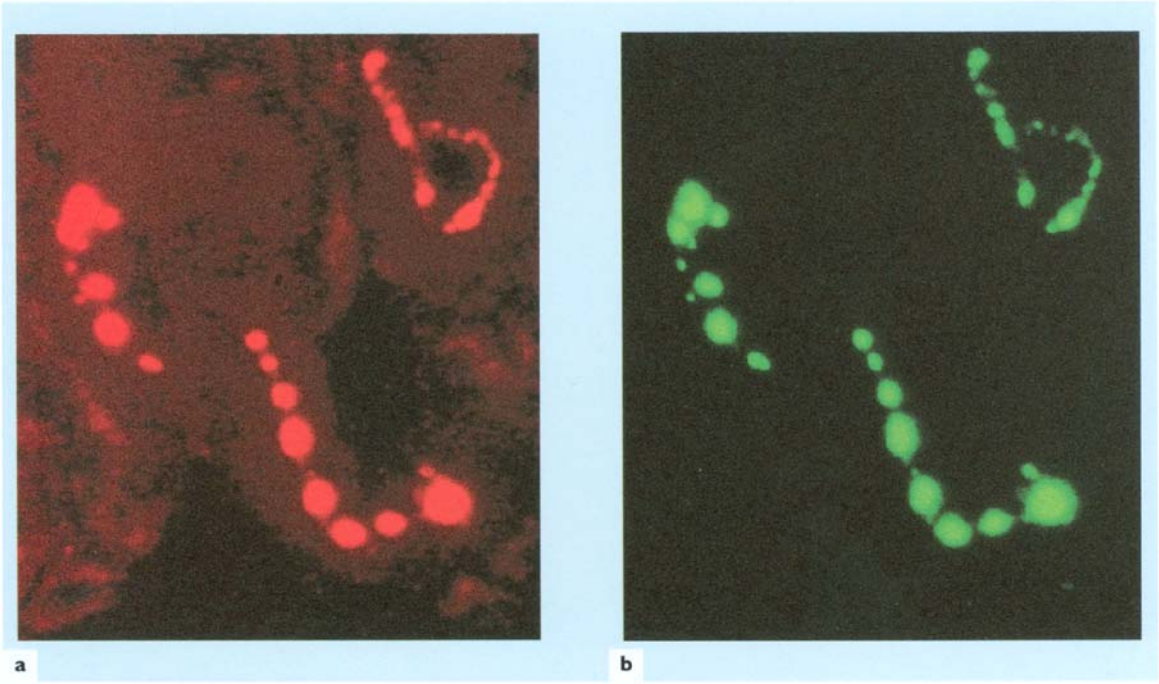


Figure 22 Neurohistochemical preparation of a microscopy section of human corpus cavernosum confirms the colocalization of nitric oxide synthase (a; staining red) and vasoactive intestinal polypeptide (b; staining green)

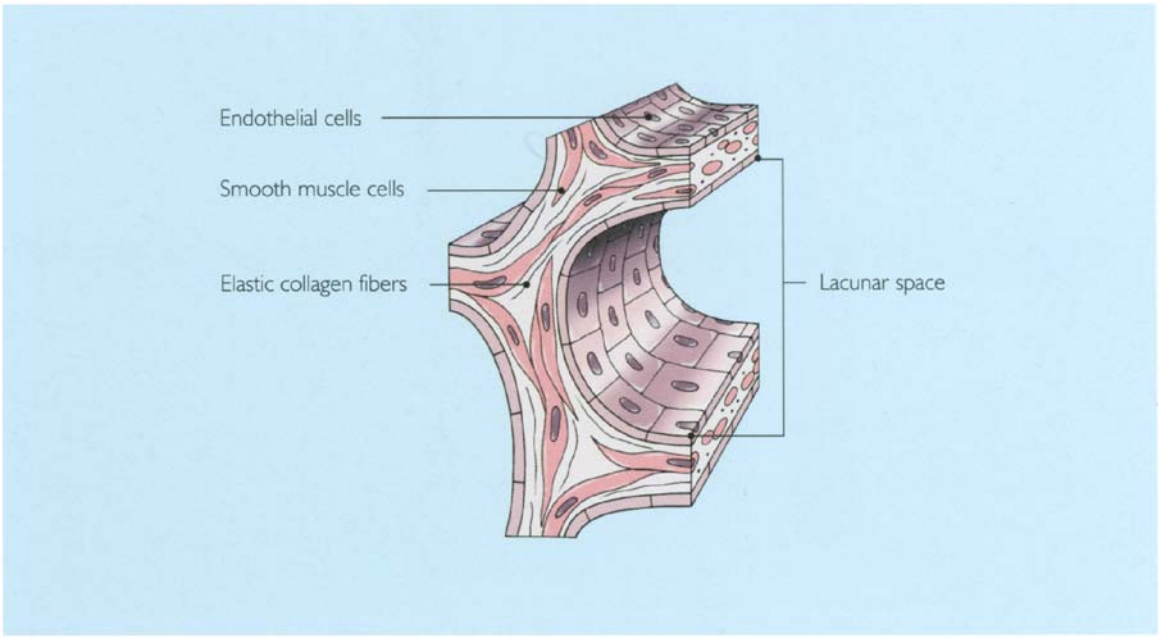


Figure 23 Smooth muscle architecture and vascular endothelium of the walls of the lacunar spaces within the corpora. Relaxation of these smooth muscle cells is an important component of the erectile mechanism

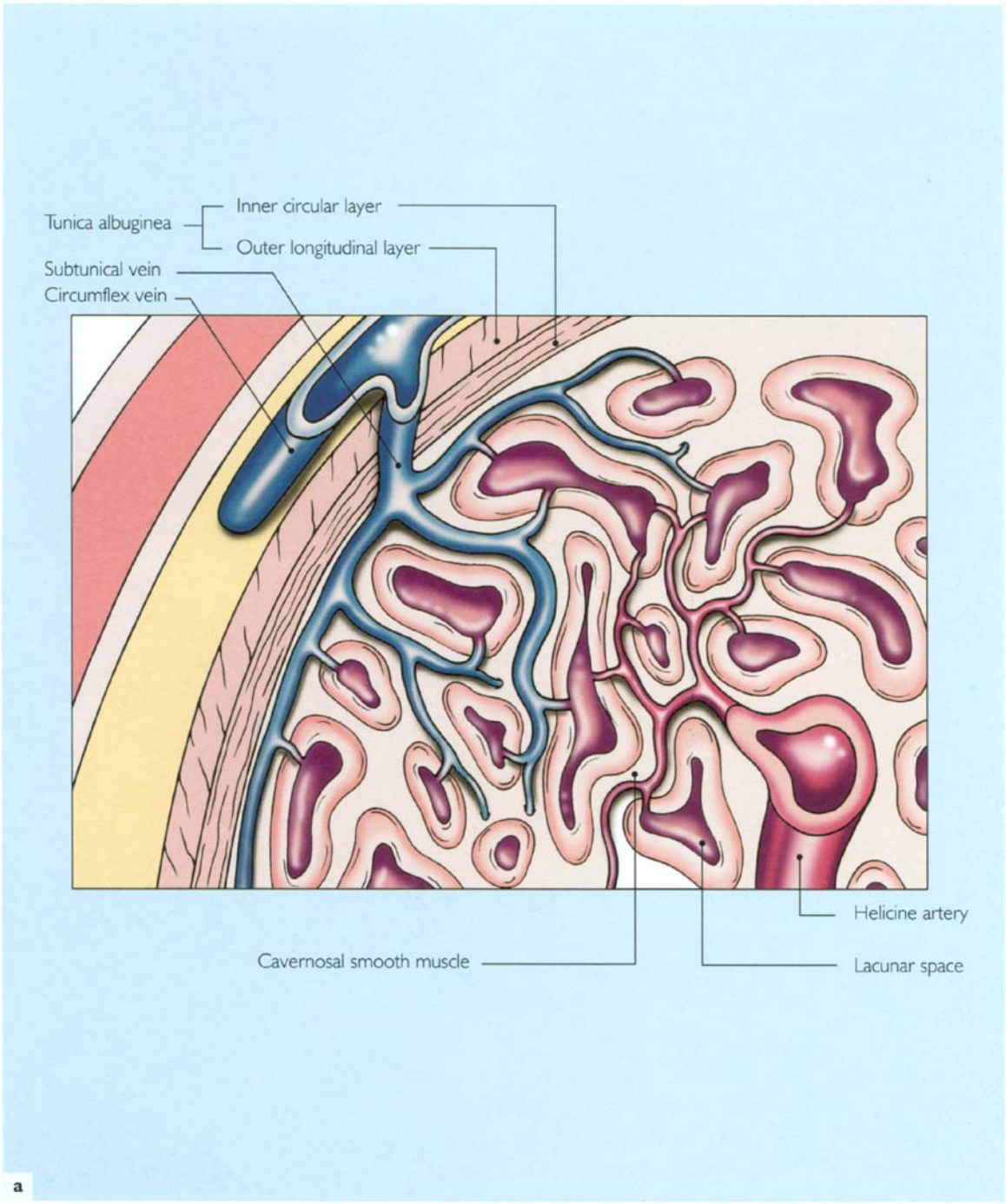
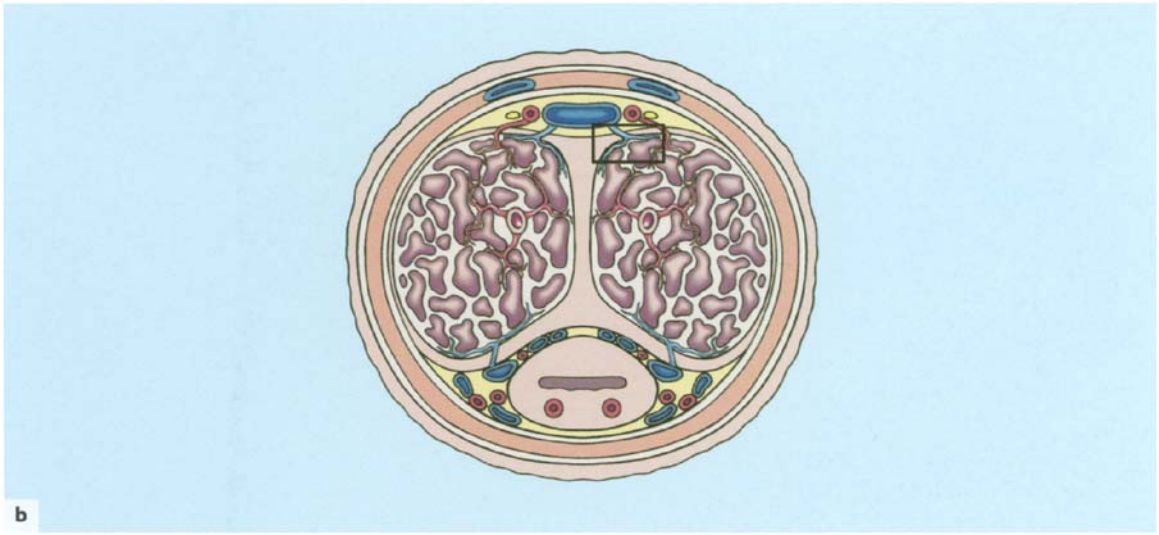


Figure 24 Hemodynamics of flaccidity. (a) Tonic contraction of the walls of the helicine arteries and trabeculae allows only relatively small amounts of blood into the lacunar spaces. Whatever blood is entering is drained through the walls of the tunica albuginea by subtunical vessels. (b) Cross-section of penis: the box indicates the area shown enlarged in (a) and (c). (c) Hemodynamics of erection: dilatation of the helicine arteries and relaxation of the trabeculae allow the lacunar spaces to fill. Their engorgement compresses the obliquely oriented subtunical veins against the tunica albuginea. This veno-occlusive mechanism prevents venous leakage and facilitates the development of a full and rigid erection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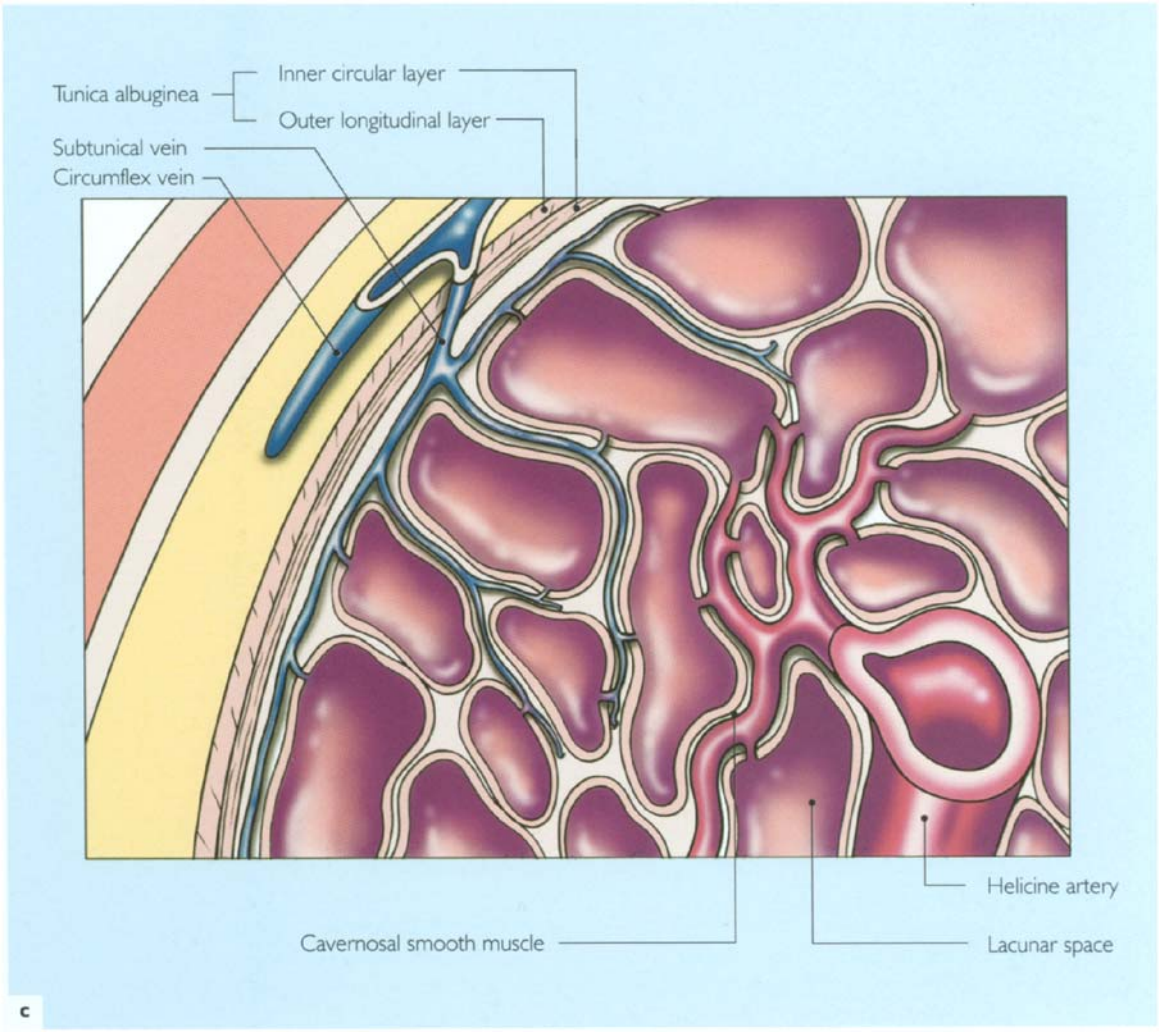

Tunica albuginea
Inner circular layer
Outer longitudinal layer
Subtunical vein
Circumflex vein
Helicine artery
Cavernosal smooth muscle
Lacunar space
c

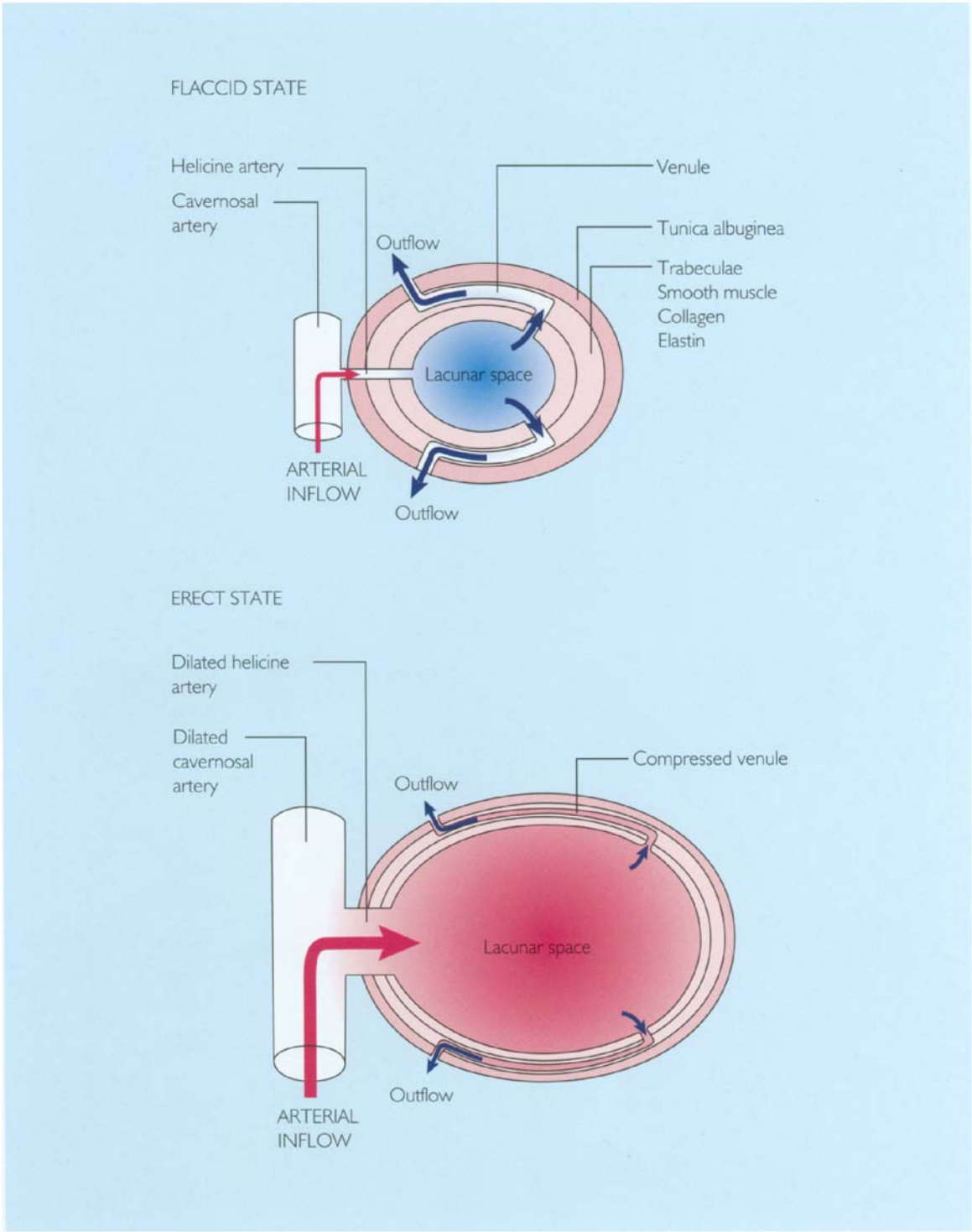


Figure 25 Schematic representation of the hemodynamics of flaccidity and erection. The key event in the induction of erection is vasodilatation of the helicine arteries, which is induced by nitric oxide and other neurotransmitters. The veno-occlusive mechanism is a secondary event brought about by compression of the subtunical veins against the sturdy tunica albuginea

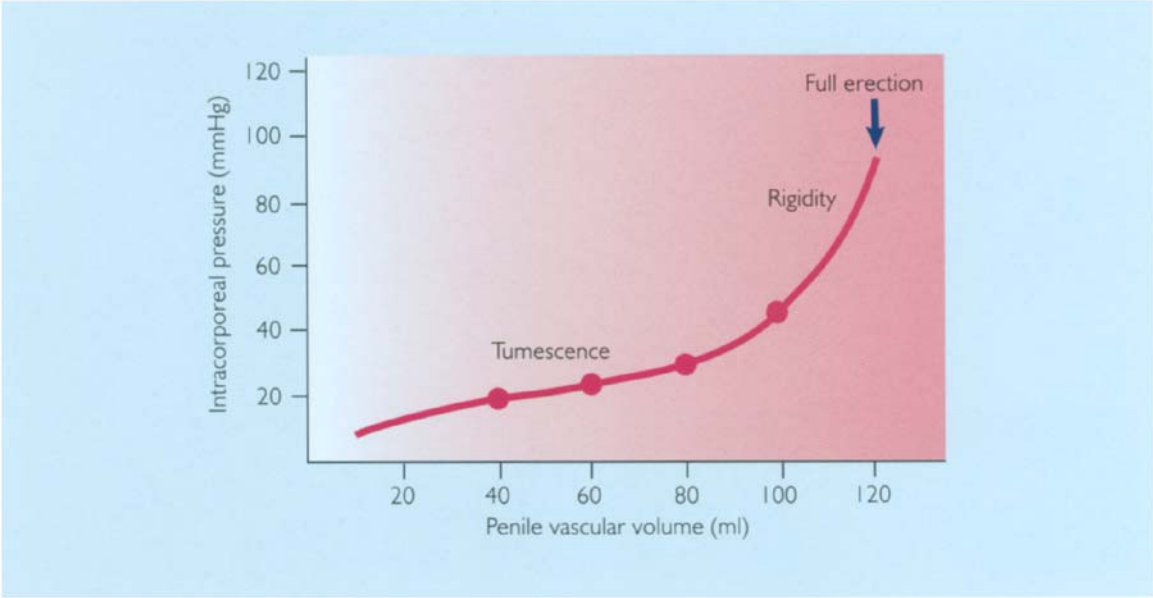


Figure 26 During erection, the penile vascular volume increases rapidly. Full erection is achieved when intracorporeal pressure approximates systolic blood pressure

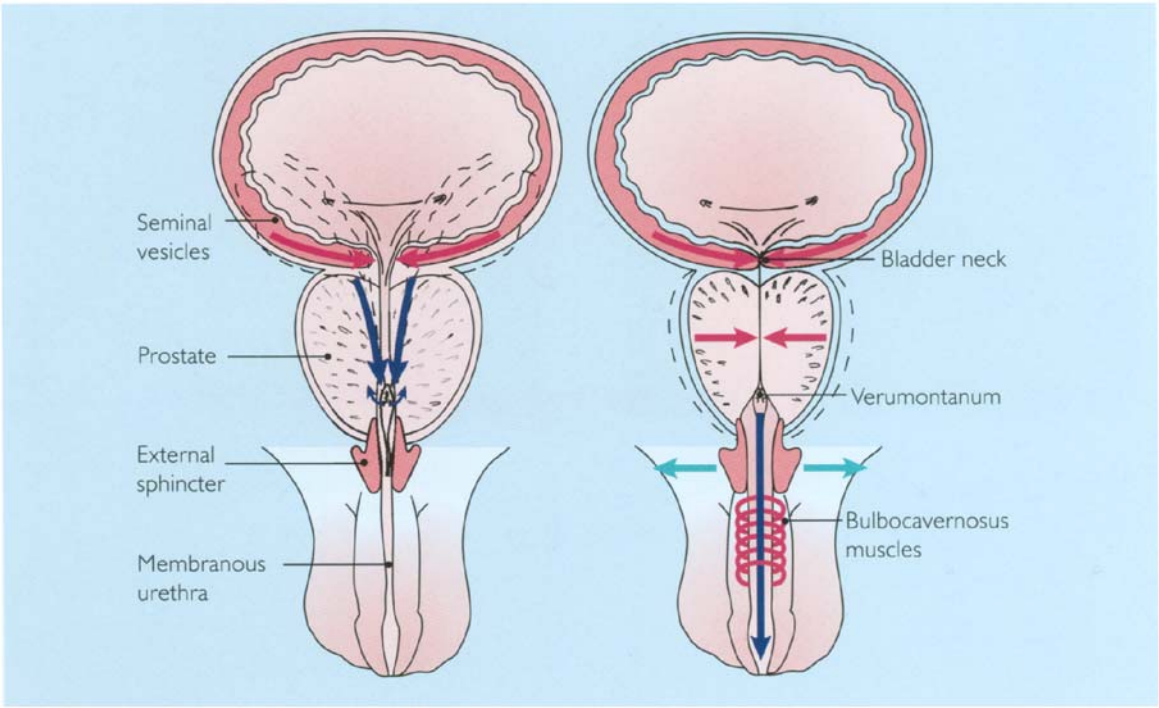


Figure 27 Mechanism of ejaculation: ejaculation is a reflex response involving both sympathetic and pudendal nerve activity. Sympathetic nerve discharge results in contraction of the bladder neck, seminal vesicles and prostate gland. Seminal fluid and prostatic secretions are emptied via the verumontanum into the prostatic urethra. Reflex relaxation of the membranous urethra and rhythmic contraction of the bulbocavernosus muscles result in the pulsatile emission of semen from the urethral meatus

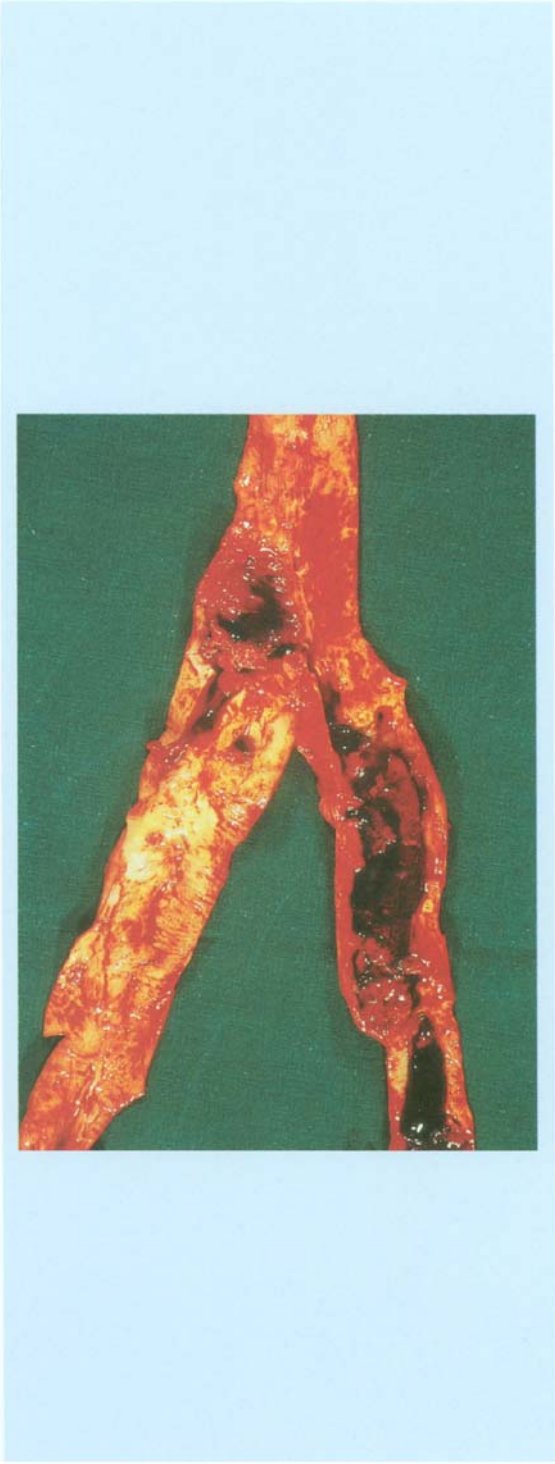


Figure 28 An atheroma affecting both common iliac arteries results in vascular insufficiency, a major cause of erectile dysfunction

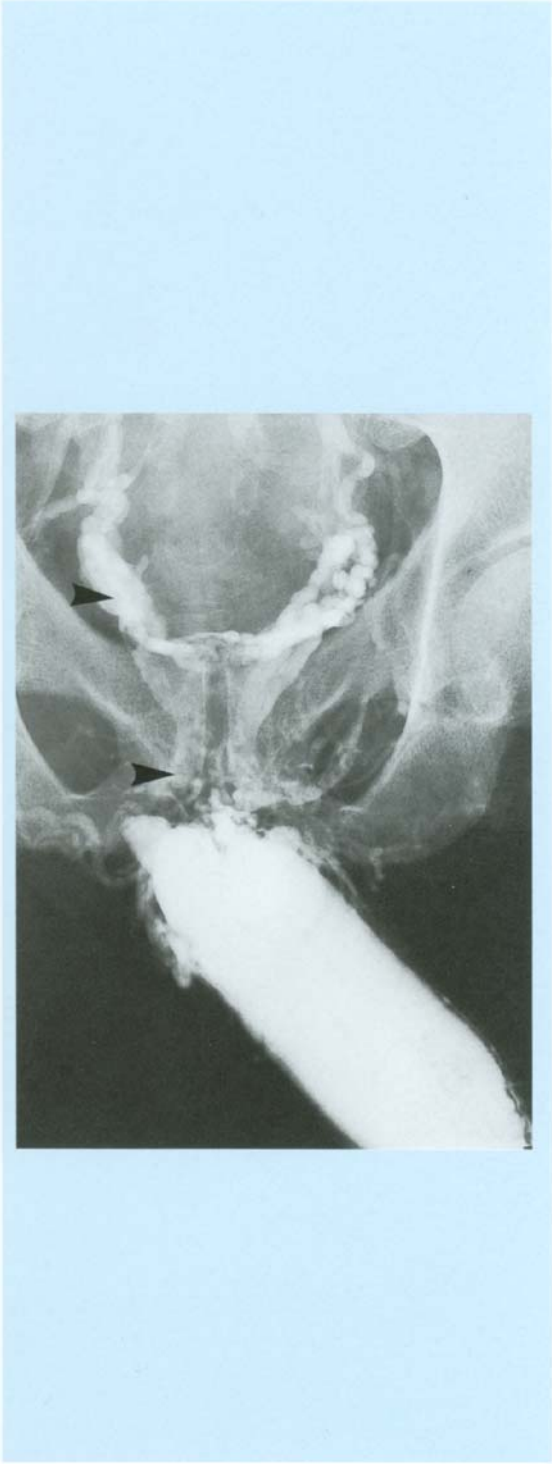


Figure 29 Dynamic infusion cavernosometry and cavernosography show a venous leak (arrowed) into the pelvic veins

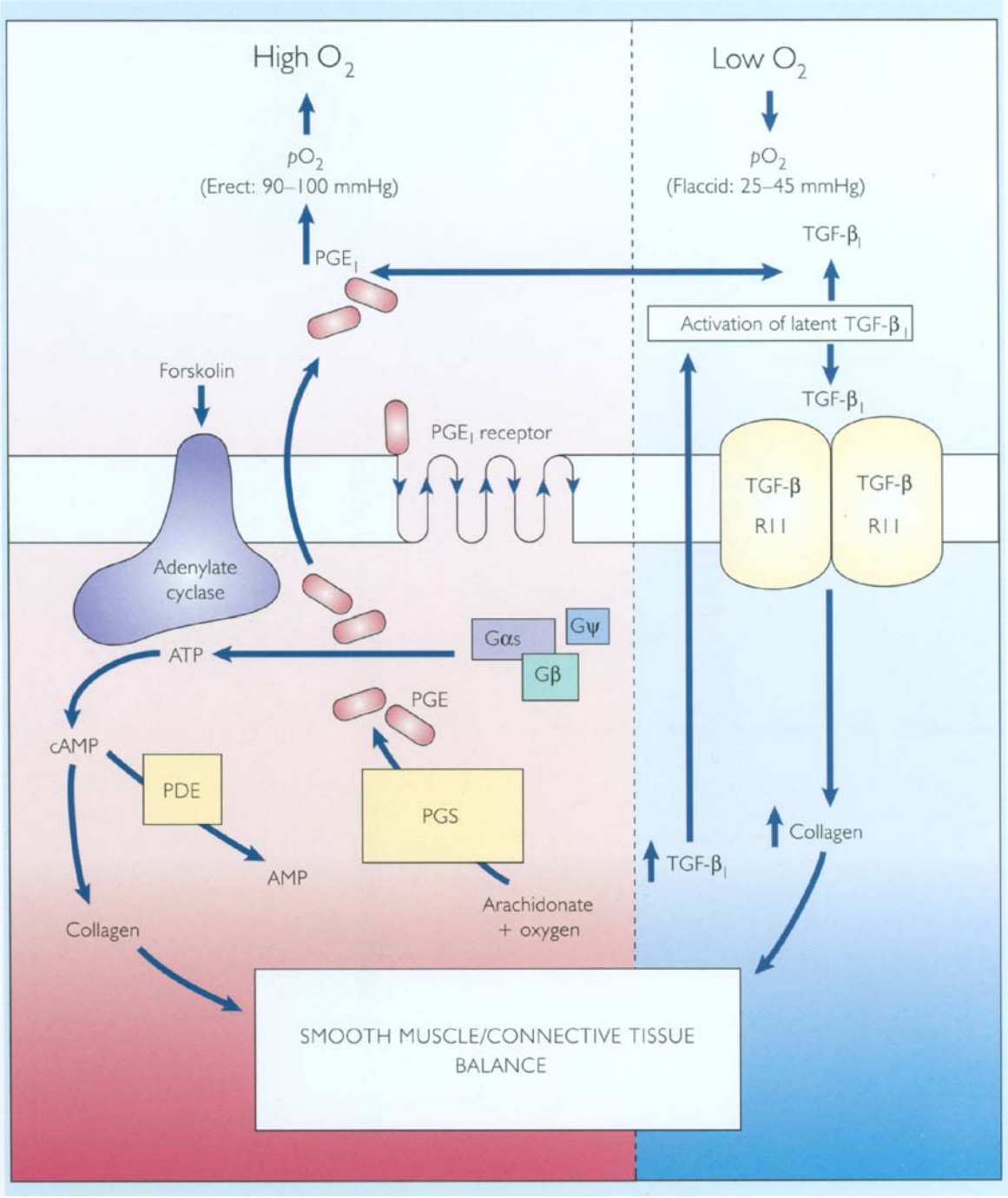


Figure 30 Deleterious effects of low oxygen (O_2) levels on intracorporeal smooth muscle. Low O_2 tension promotes the release of transforming growth factor β_1 ($TGF-\beta_1$), which acts on $TGF-\beta_1$ receptors to stimulate the production of collagen-inducing fibrosis. In contrast, high O_2 tension, as occurs during nocturnal erections, stimulates the production of prostaglandin E_1 (PGE_1) which, in turn with forskolin, stimulates adenylate cyclase to produce cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP induces and maintains healthy smooth muscle activity. PDE, phosphodiesterase; PGS, prostaglandin synthase

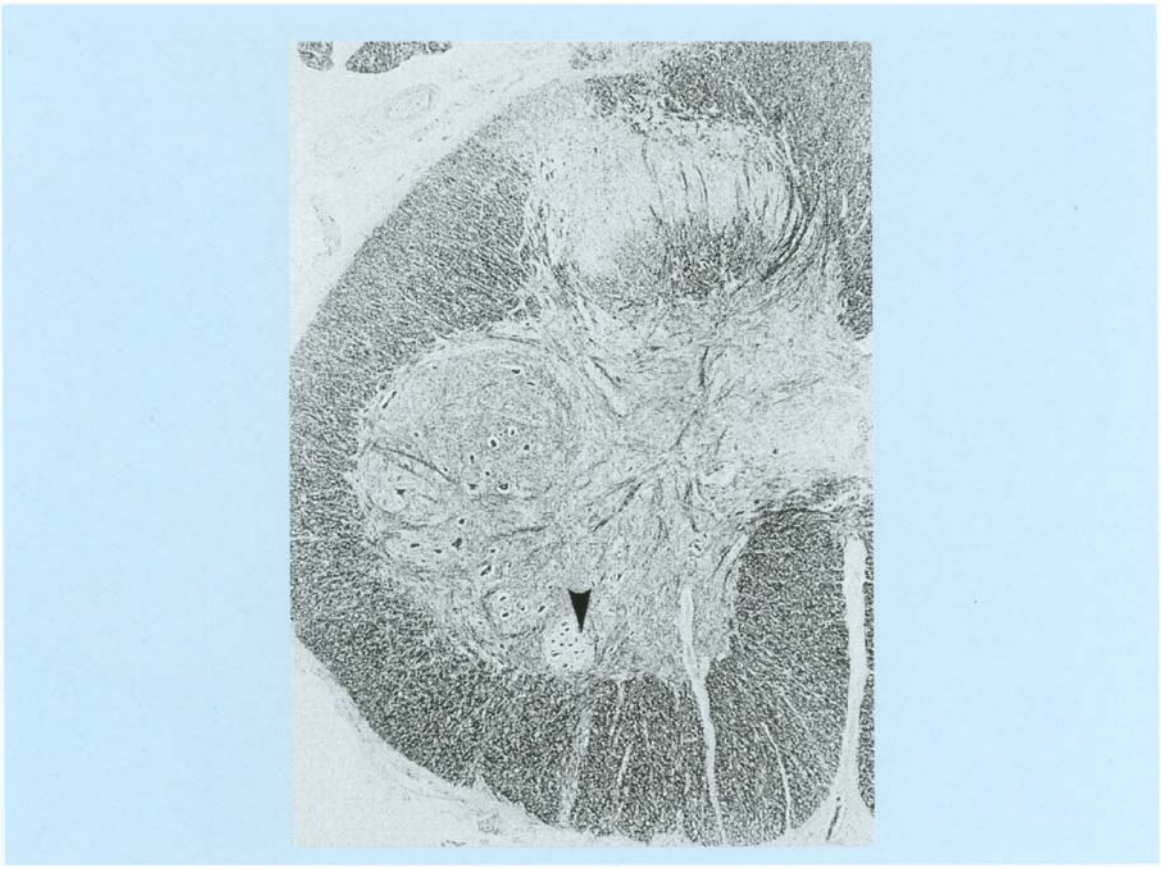


Figure 31 Histological section of the spinal cord at the level of the S2 segment shows selective degeneration of Onuf' s nucleus (arrowed), which contains the cell bodies of the pudendal nerve, responsible for innervating the pelvic floor, a feature of multiple system atrophy (formerly known as Shy-Drager syndrome). Men who have this disorder often present with erectile dysfunction and incontinence

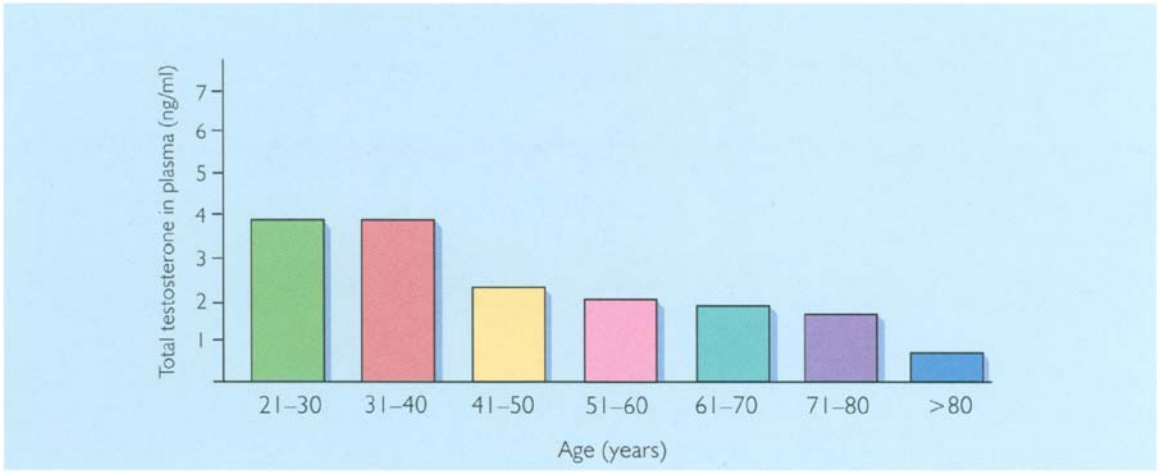


Figure 32 Progressive decrease in free testosterone levels with age. In some men, the lack of testosterone may be associated with a loss of libido and erectile dysfunction. This has been termed the 'male menopause'

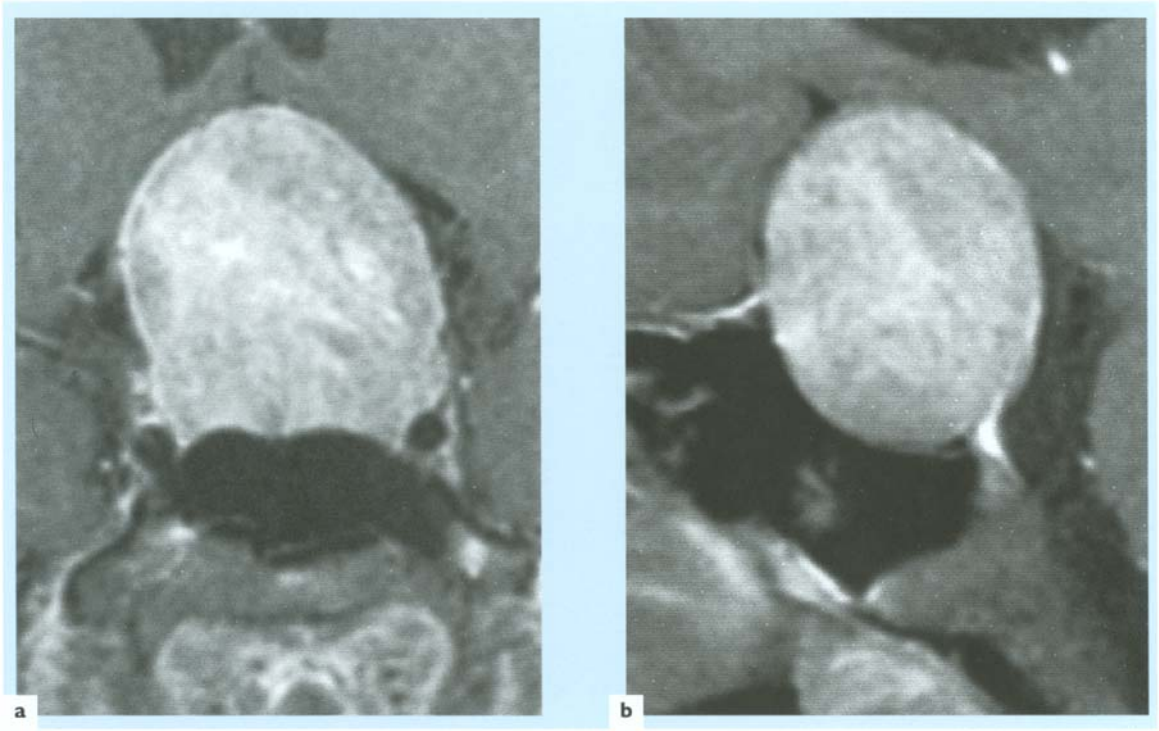


Figure 33 Magnetic resonance imaging with gadolinium enhancement ((a) anteroposterior view; (b) lateral view) of a pituitary tumor (chromophobe adenoma). This is a rare cause of erectile dysfunction, and is usually associated with elevated levels of prolactin and diminished levels of testosterone

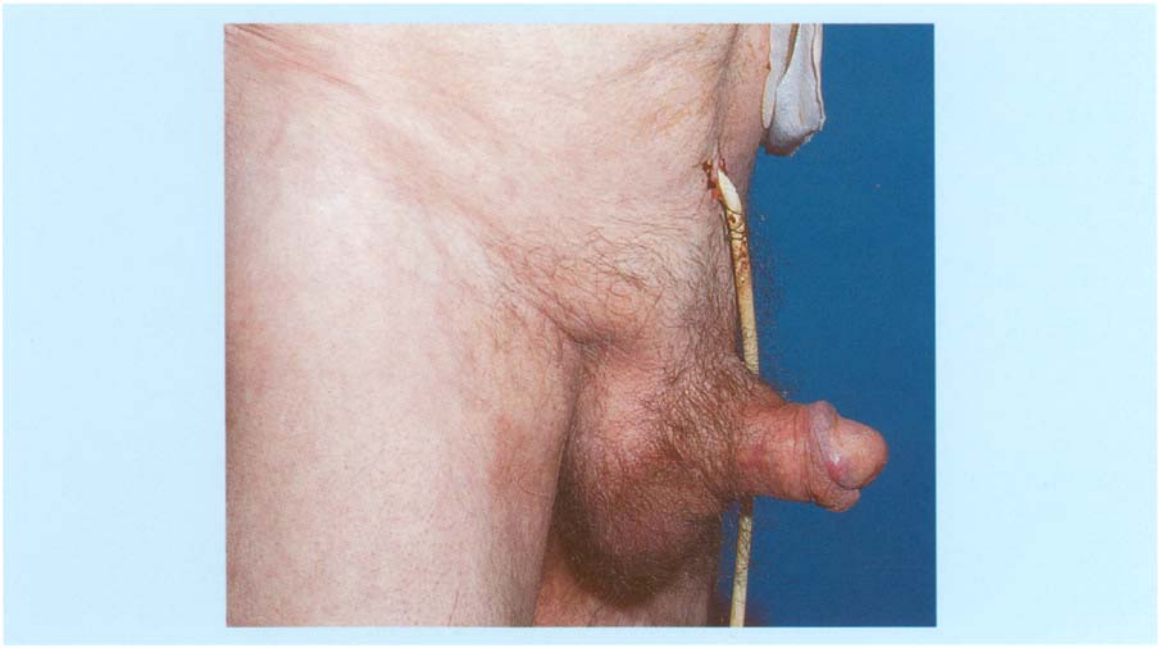


Figure 34 Priapism in a patient who also had a carcinoma of the prostate gland, and hence the need for a suprapubic catheter

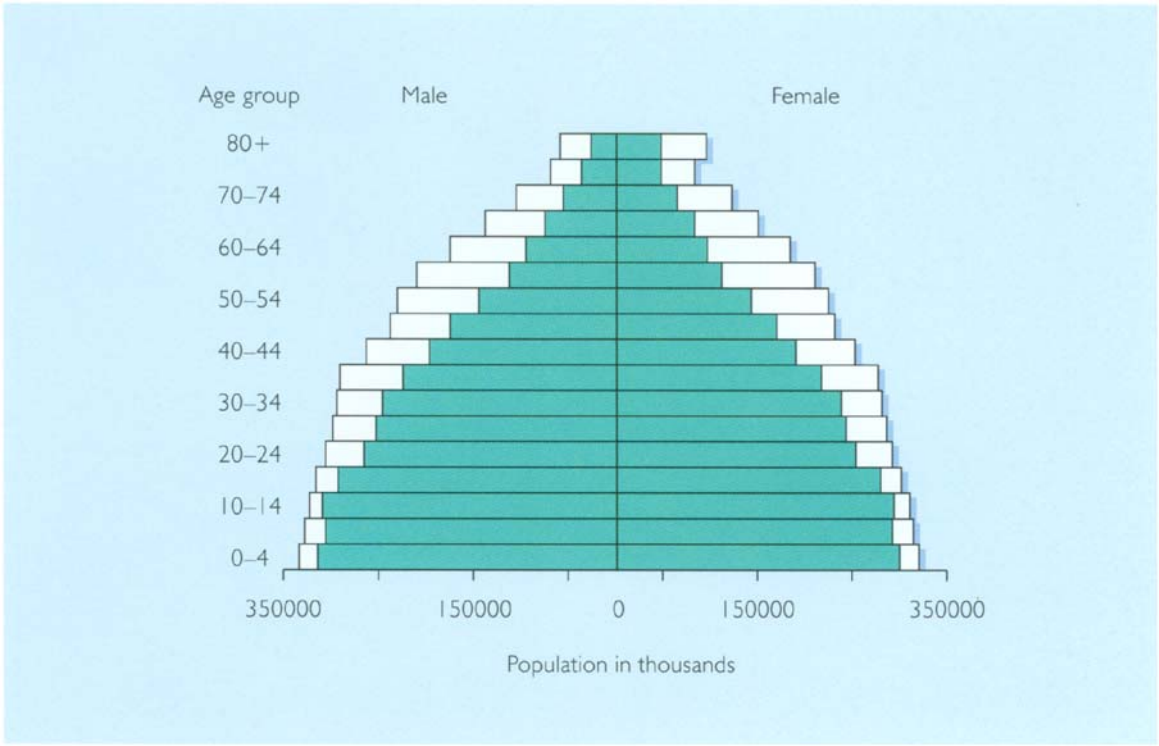


Figure 35 The projected world population pyramid for 2002 (green) and 2025 (white) demonstrating how many more older people will be around to be affected by erectile dysfunction

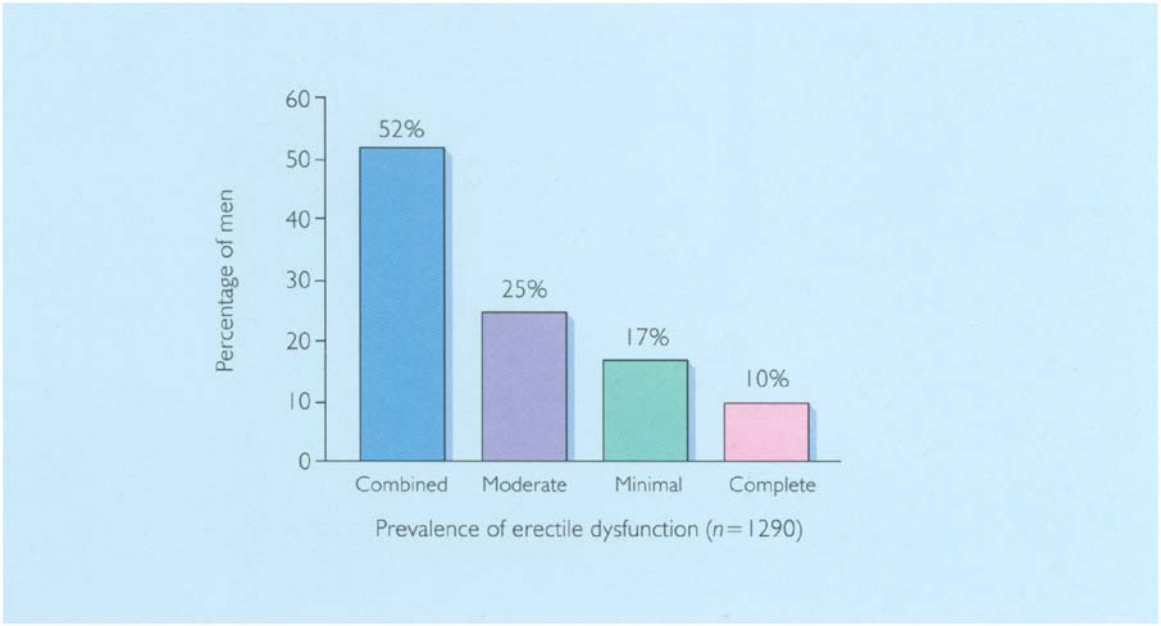


Figure 36 The proportion of men with either complete, moderate or minimal erectile dysfunction in the Massachusetts Male Aging Study

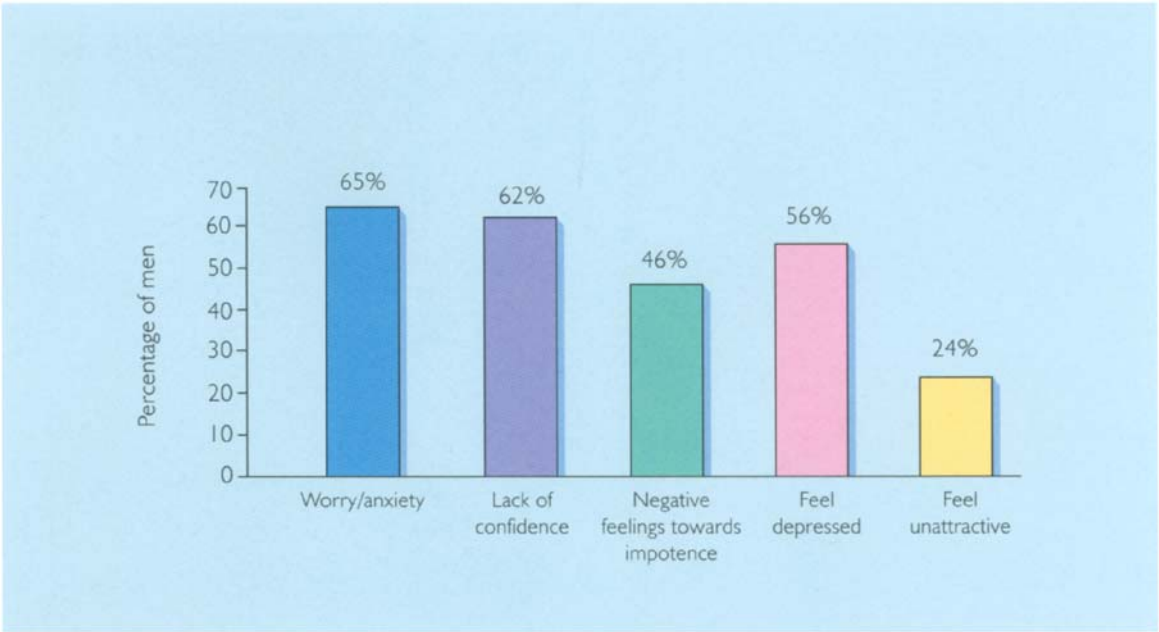


Figure 37 Negative effects of erectile dysfunction on men's quality of life

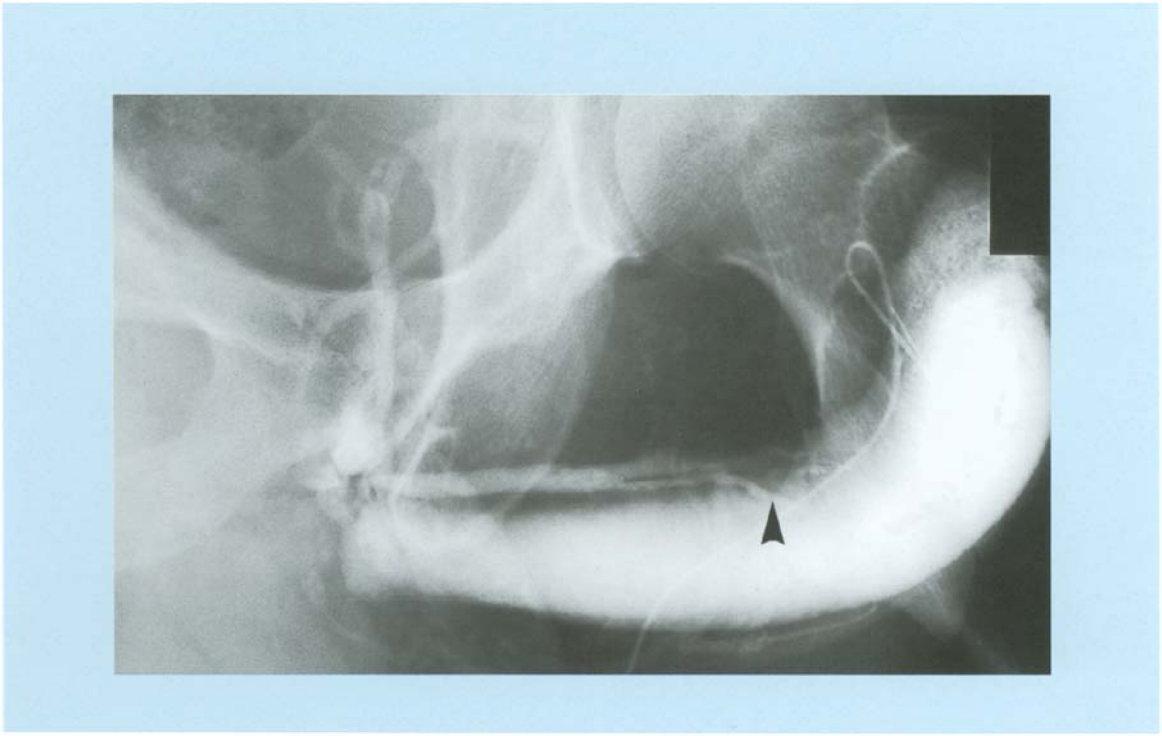


Figure 38 Cavernosogram showing the typical dorsal deformity seen in Peyronie's disease as well as a venous leak (arrowed) into the deep dorsal vein at the site of the fibrotic Peyronie's plaque

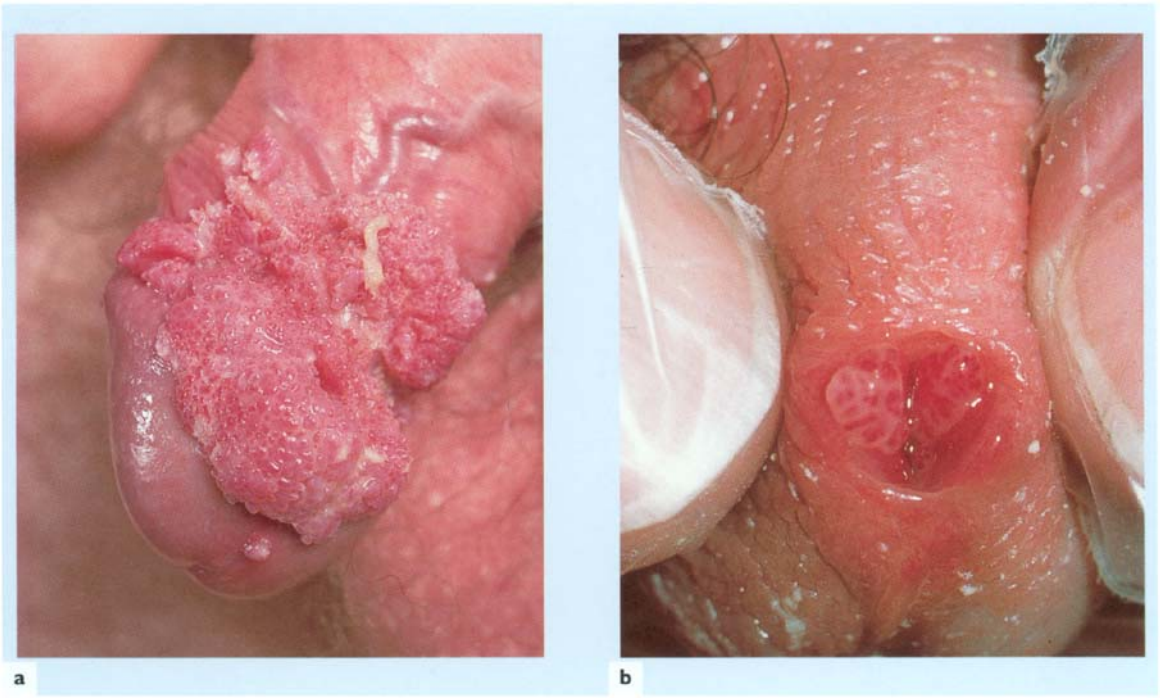


Figure 39 Multiple condylomata acuminata on the glans penis and penile shaft (a); and urethral condylomata acuminata (b). This papillomatous condition is due to an infection with human wart virus

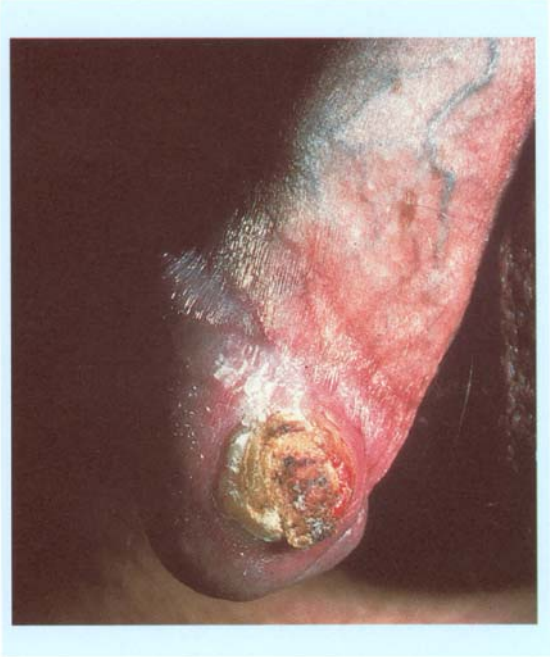


Figure 40 Erythroplasia of Queyrat involving the glans penis

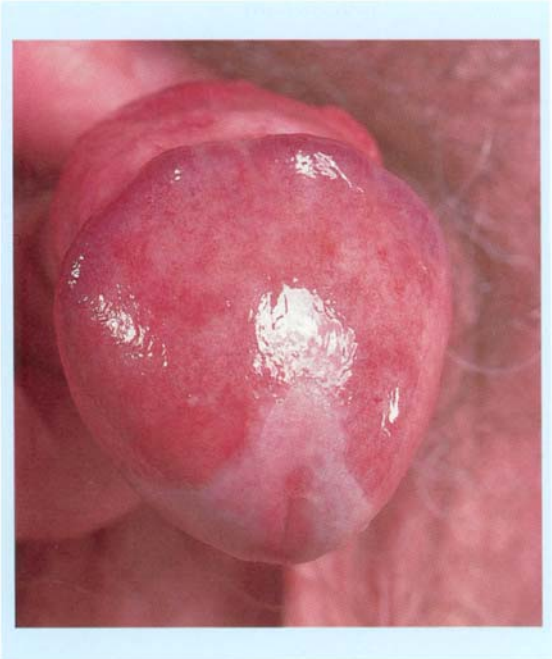


Figure 41 Early squamous cell carcinoma of the penis typically presents as an ulcerative lesion

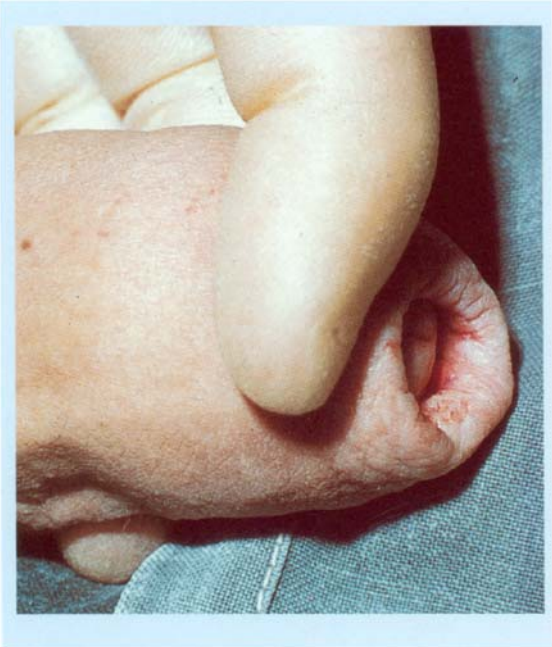


Figure 42 Balanitis xerotica obliterans is a dermatological condition that affects the prepuce, causing phimosis. It may spread to the glans and, if the meatus is involved, result in meatal stenosis

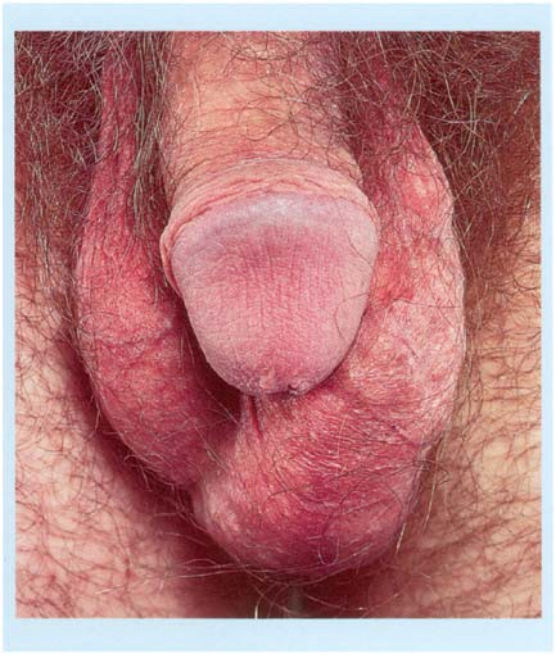


Figure 43 Left-sided scrotal varicocele. These are most prominent on standing and are described as feeling like a bag of worms. It may be associated with a feeling of dragging discomfort and with infertility

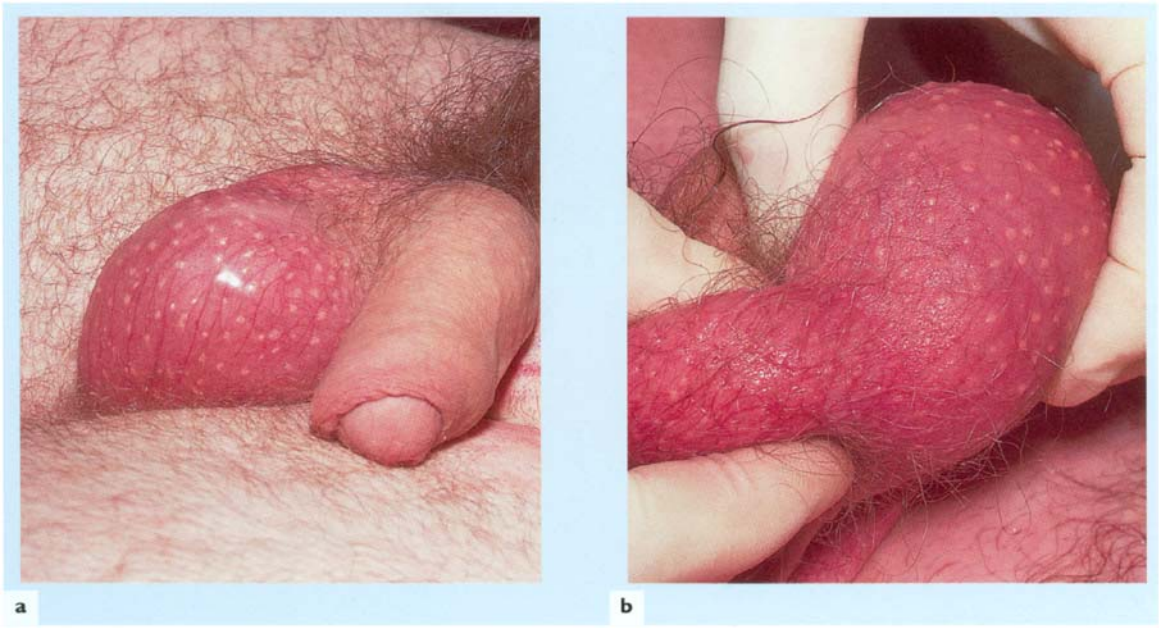


Figure 44 Testicular tumor. (a) The testis is expanded. These are most commonly seen in men 20–40 years of age; (b) on palpation, the tumor feels harder than its normal fellow on the opposite side

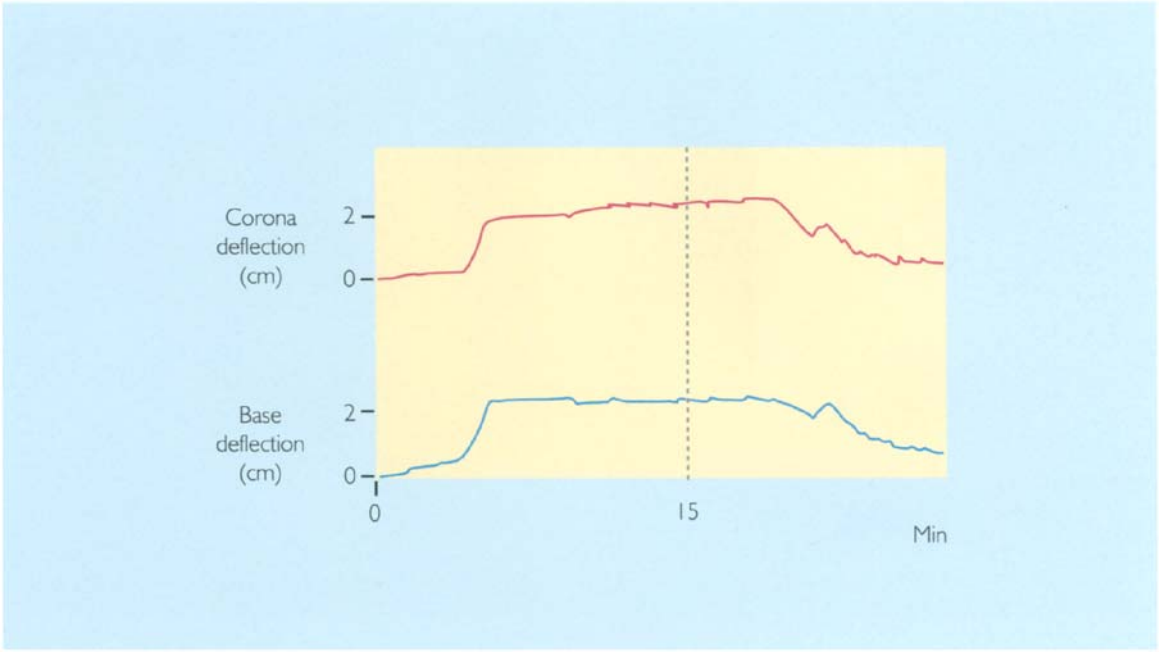


Figure 45 Trace of a normal nocturnal erection recorded during measurement of nocturnal penile tumescence. Normally, erections occur every 20 min or so during sleep, and are now believed to be a mechanism for bringing oxygenated blood to the lacunar spaces, thereby helping to maintain the functional integrity of the trabecular smooth muscle cells

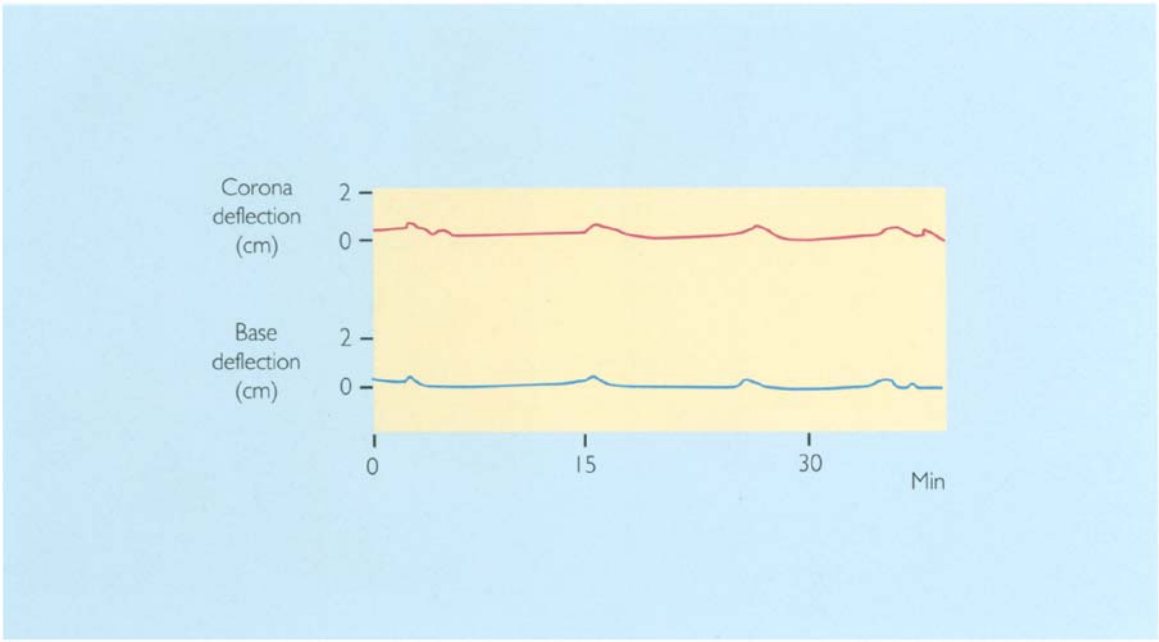


Figure 46 Nocturnal penile tumescence trace from a man with erectile dysfunction showing a lack of tumescence during sleep, suggesting an organic basis for his symptoms

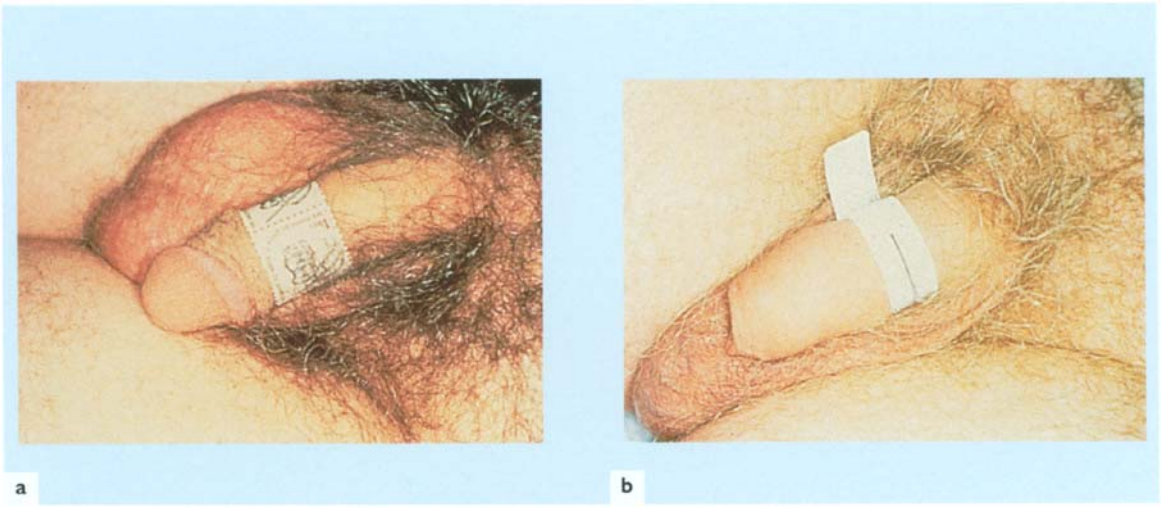


Figure 47 There are other methods for assessing the presence or absence of nocturnal penile tumescence that do not require a sleep laboratory; these include the stamp test (a) and the snap gauge (b)

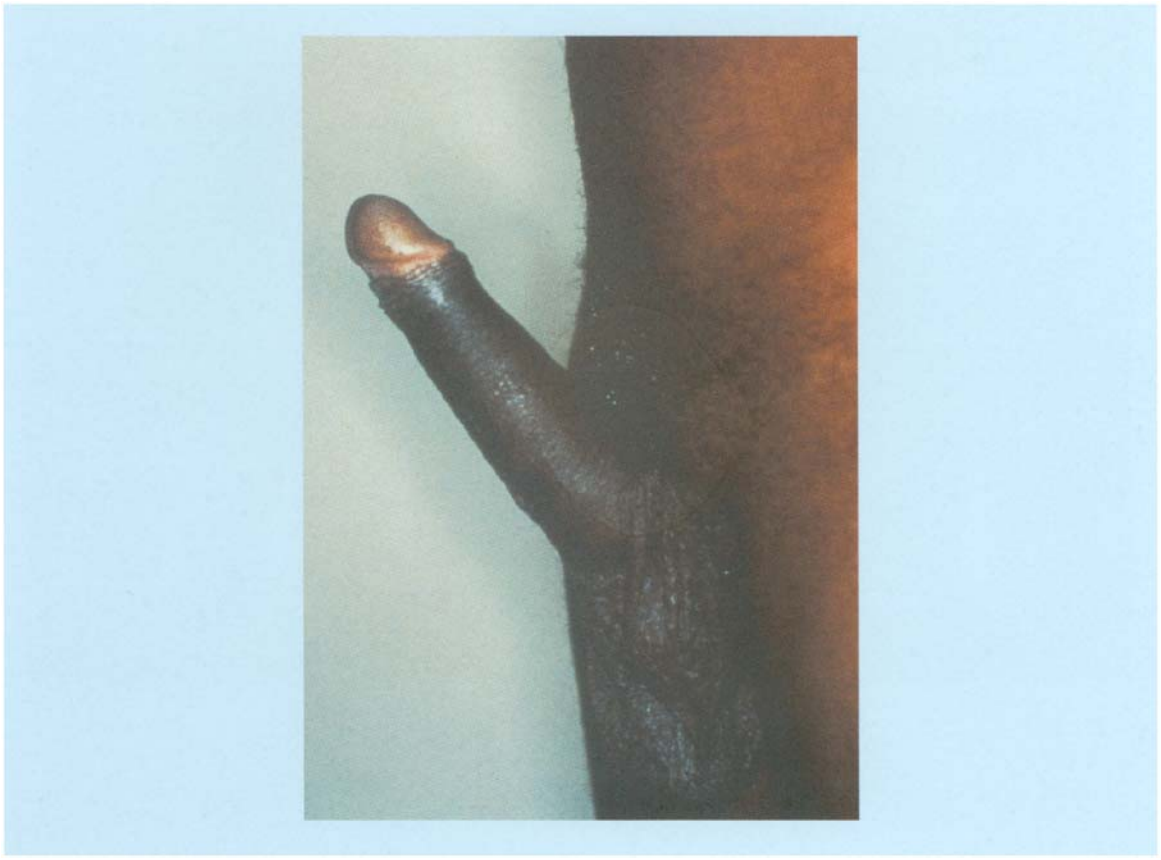


Figure 48 An erection induced by intracavernous injection of 20 mg of alprostadil (prostaglandin E_1). Such an erection may last from 30 min to 4 h. Patients should receive written information concerning what they need to do should the erection fail to subside after 4 h or more

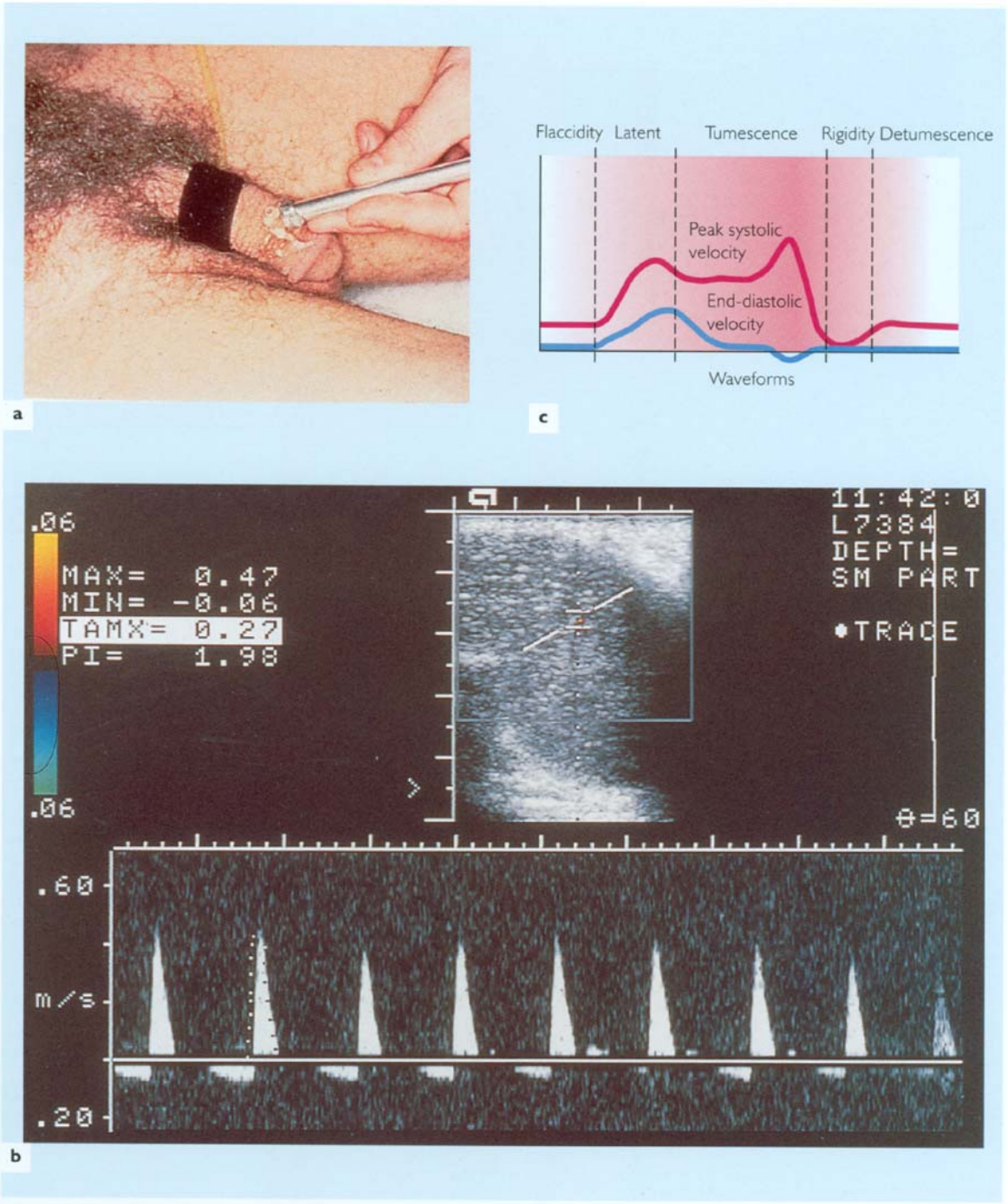


Figure 49 Color duplex Doppler ultrasonography (CDDU). (a) The probe is placed on the penis, which has been lubricated with ultrasound jelly. Both dorsal arteries and the paired cavernous arteries can usually be visualized; (b) normal CDDU trace after injection of 20 mg of prostaglandin E_1 when full erection has been achieved. Systolic velocity is normal and the flow is reversed during diastole; (c) schematic representation of the time course of changes in peak systolic and end-diastolic velocities during development of a pharmacologically induced erection. Once full rigidity is achieved, end-diastolic velocity is very low and the flow may be reversed at this point

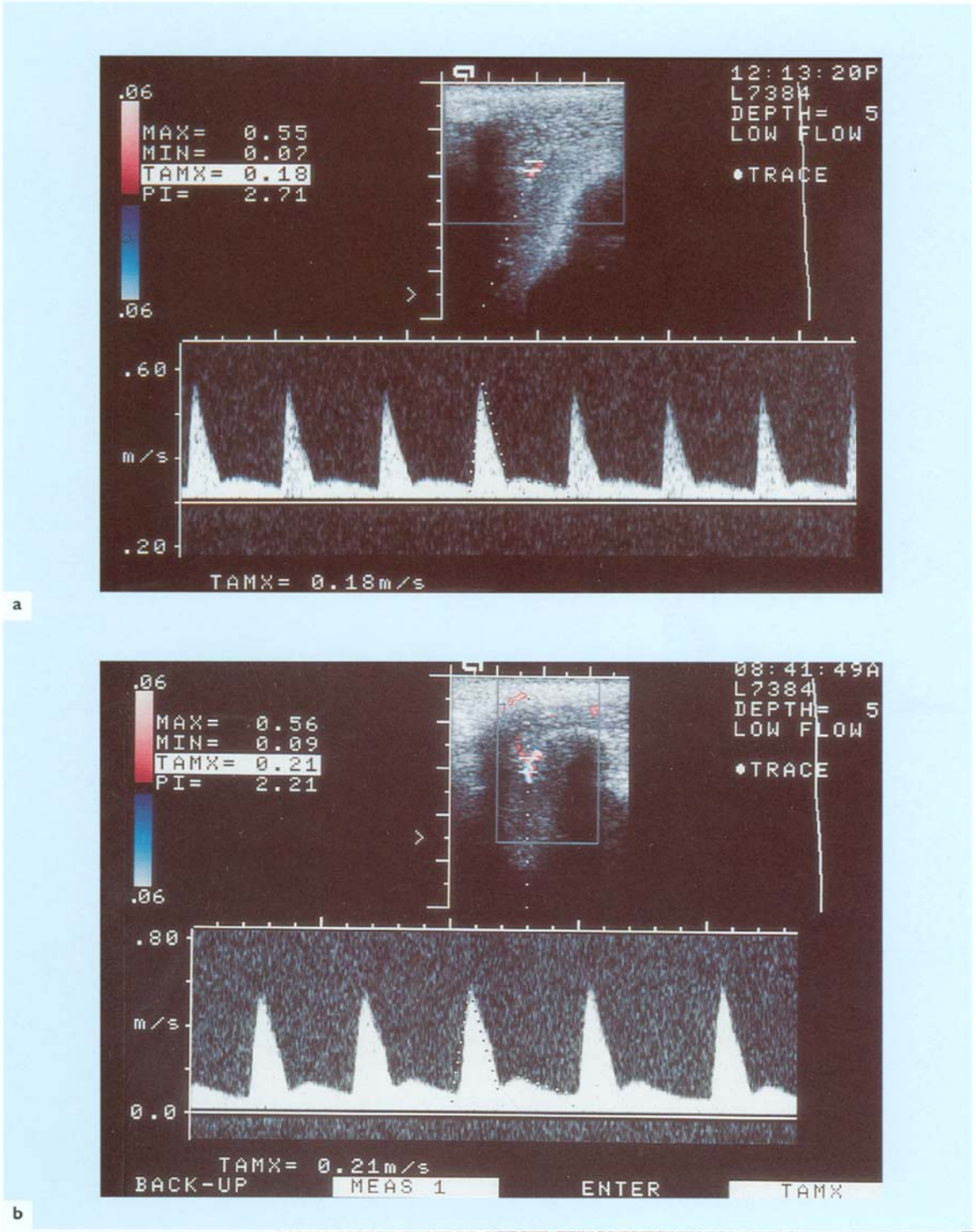


Figure 50 Color duplex Doppler ultrasonography (CDDU) of a patient with (a) arteriogenic erectile dysfunction shows poor tumescence, a normal peak systolic velocity and continuing flow during diastole; CDDU of a patient with venous leak-induced erectile dysfunction (b) shows failure of normal veno-occlusive mechanisms resulting in continuous flow during diastole despite adequate peak systolic velocities

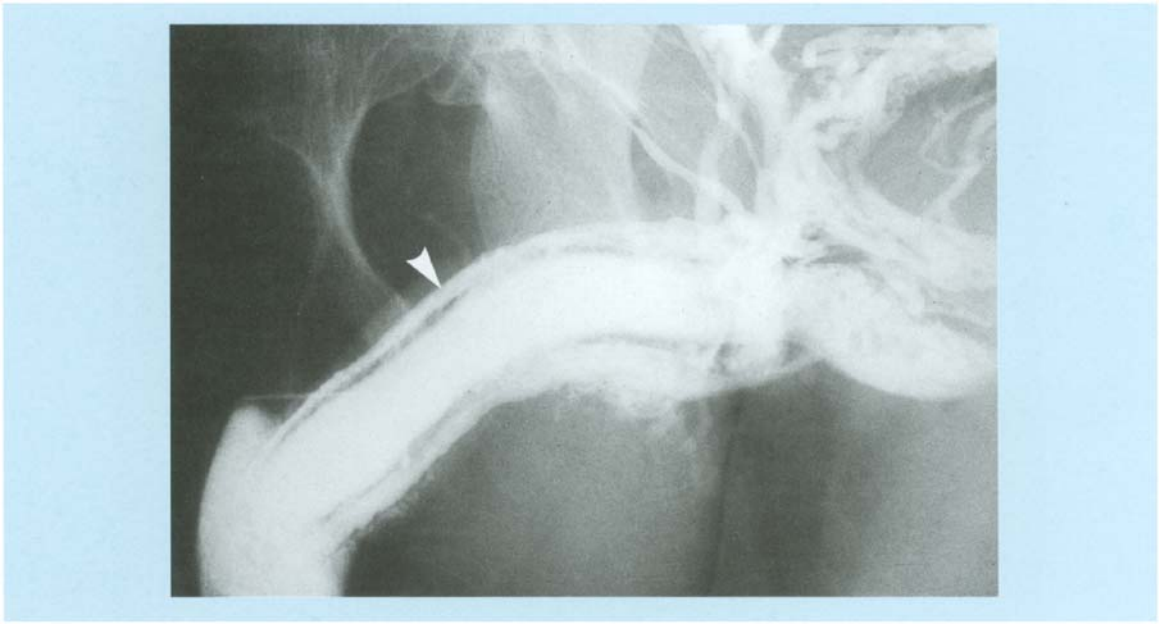


Figure 51 Dynamic infusion cavernosography and cavernosometry show venous leakage into the deep dorsal vein (arrowed) and corpus spongiosum of the penis

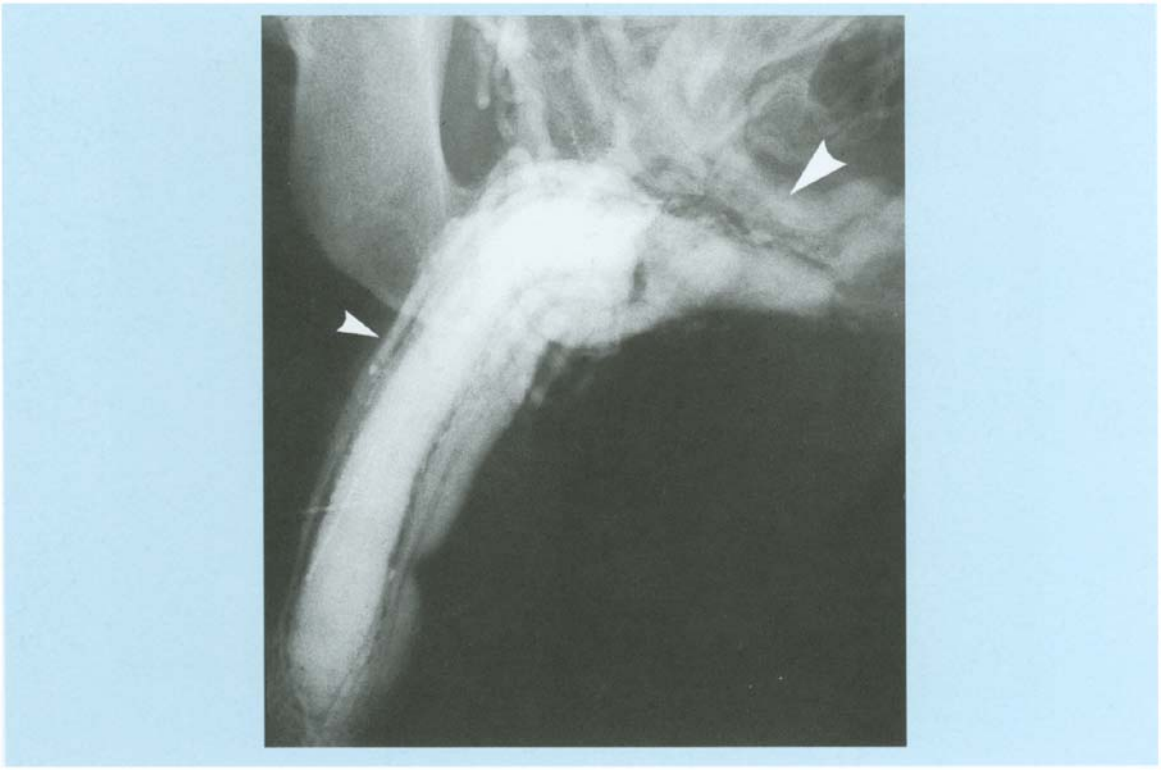


Figure 52 Dynamic infusion cavernosography and cavernosometry show venous leakage into the deep dorsal vein (small arrow) and deep cavernous veins (large arrow) of the penis. Most venous leaks occur at multiple sites

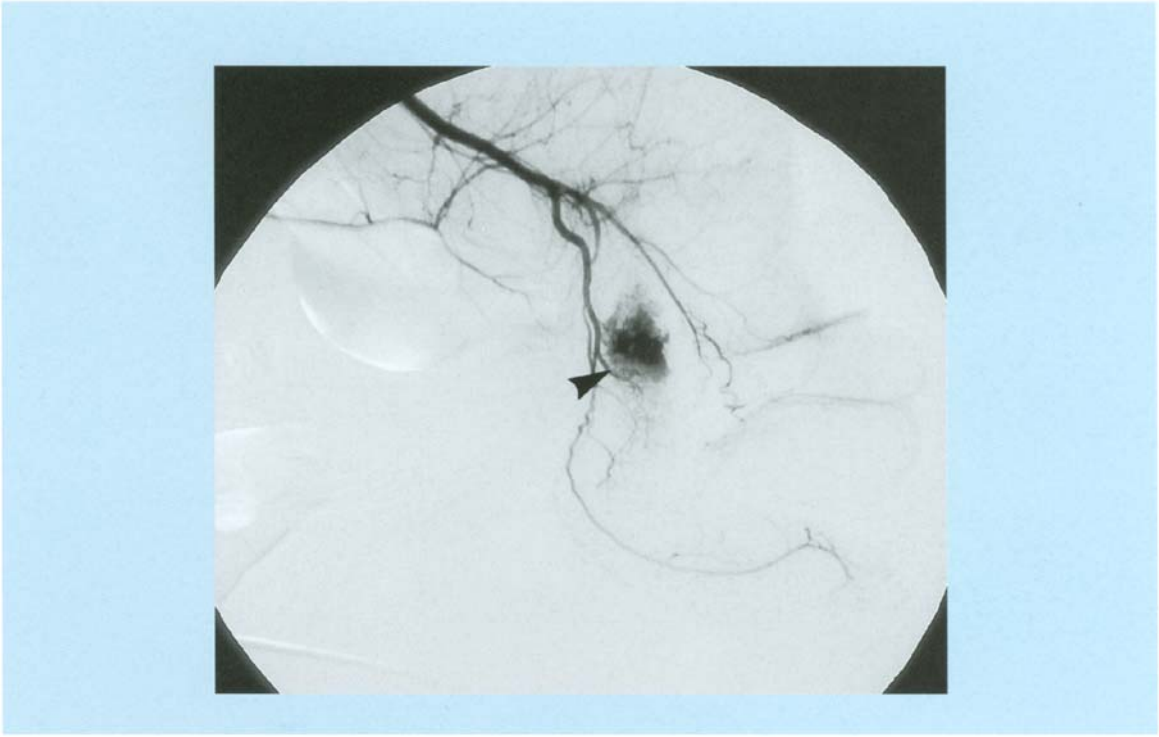


Figure 53 Highly selective pudendal arteriogram shows an arteriovenous fistula (arrowed) between the pudendal artery and pudendal vein. Subsequent embolization of this lesion restored erectile function in this case

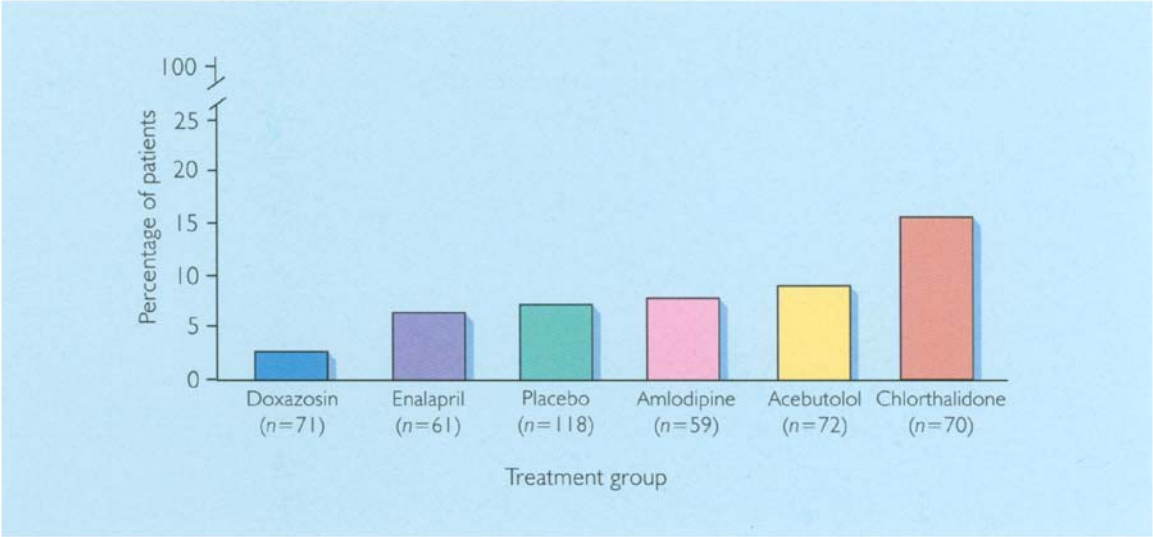


Figure 54 Incidence of patients reporting difficulty in either obtaining or maintaining an erection in a 4-year comparative study of representatives from five classes of antihypertensive agents. Patients treated with either a β-blocker or a diuretic experienced the highest incidence of erectile dysfunction whereas those receiving the α-blocker doxazosin reported less erectile dysfunction than those receiving placebo, suggesting a mild beneficial effect with this agent (Neaton *et al.,* 1993; TOMHS Research Group, 1996)

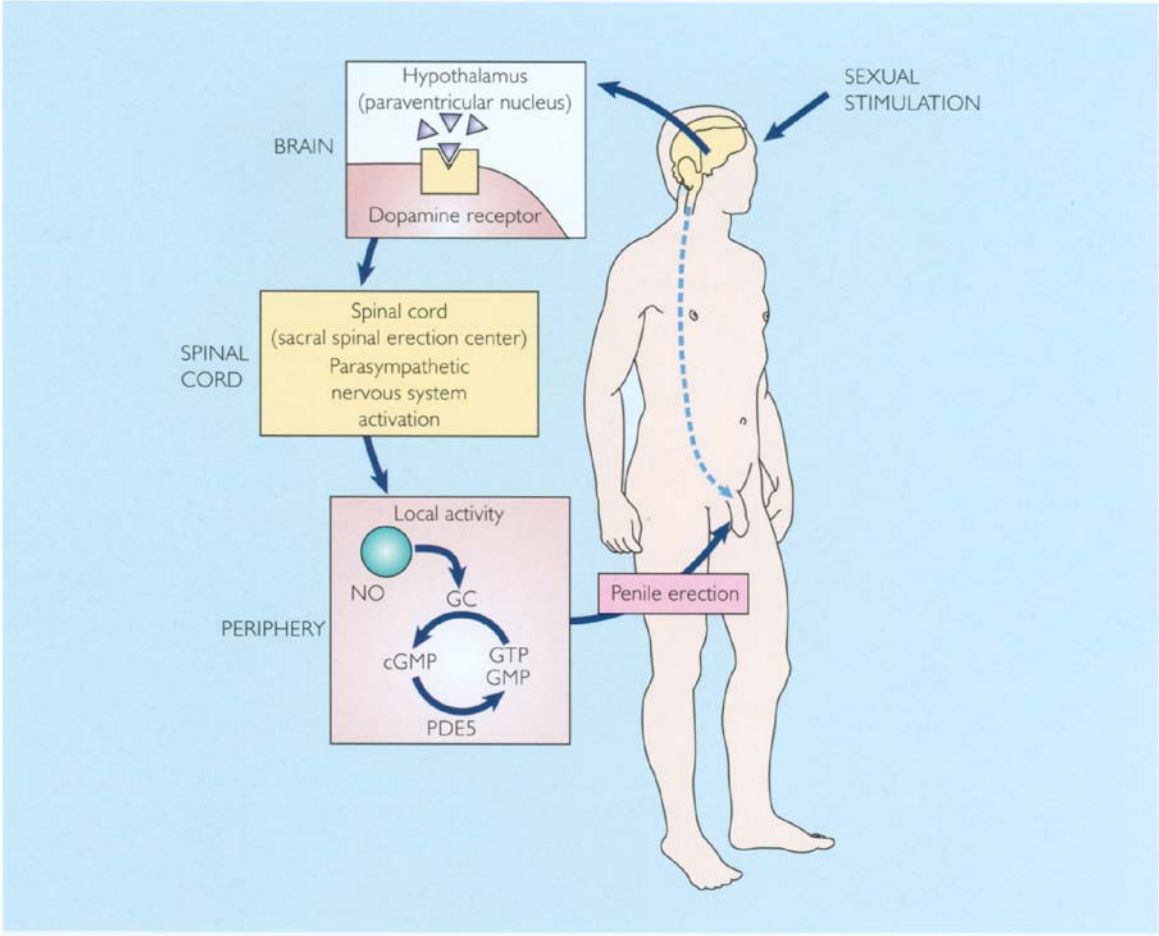


Figure 55 The mechanism of action of dopamine agonists in men with erectile dysfunction

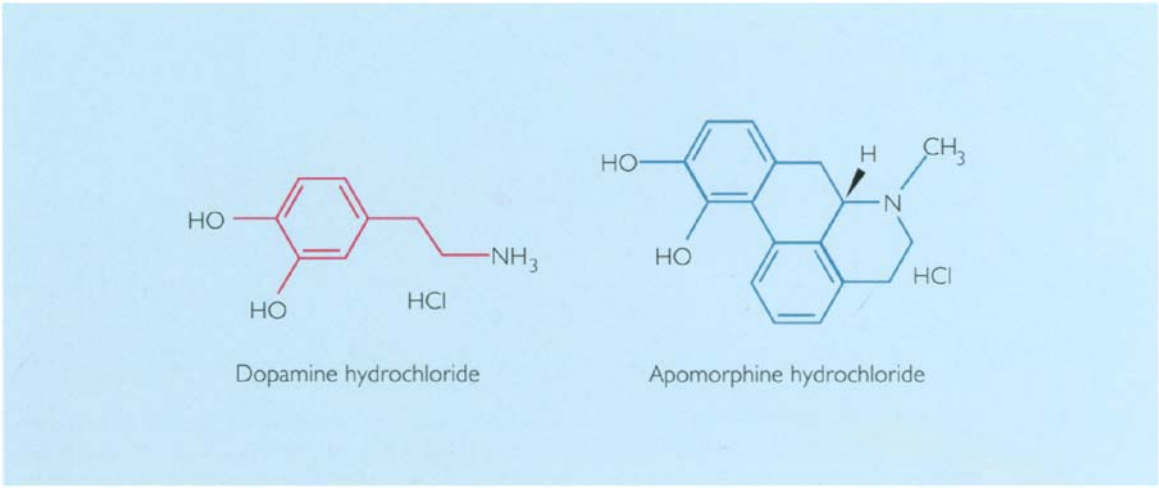


Figure 56 The chemical structures of dopamine and apomorphine

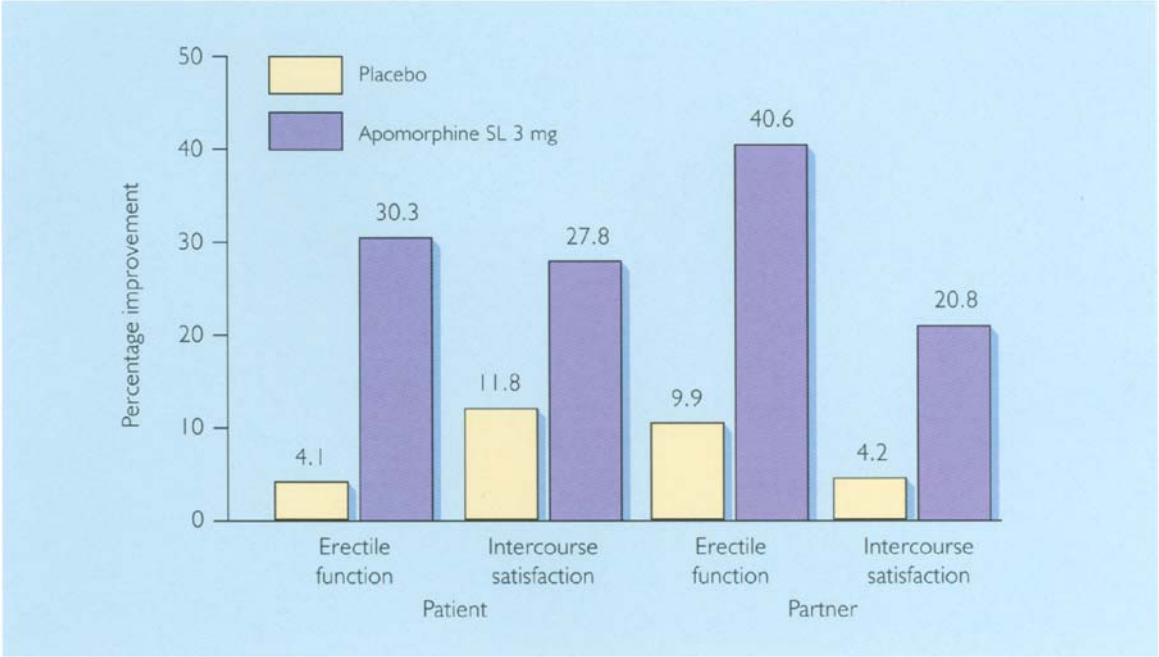


Figure 57 The efficacy of apomorphine at the 3 mg dosage, as reported by patients and their partners

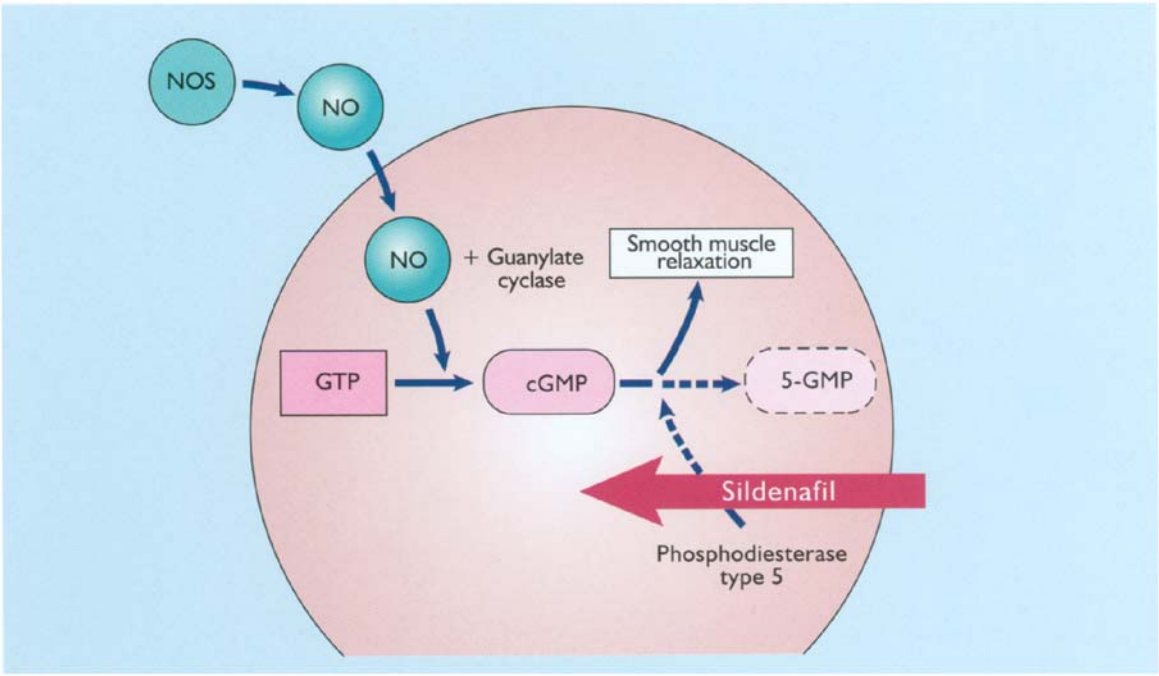


Figure 58 Mechanism of action of sildenafil (Viagra®): nitric oxide (NO) is produced by the enzyme nitric oxide synthase (NOS), found in both nerve endings and endothelial cells. NO acts as a neurotransmitter to stimulate guanylate cyclase to produce cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). cGMP in the corpora is broken down by phosphodiesterase type 5 (PDE5). Sildenafil inhibits PDE5, thus potentiating the effect of NO

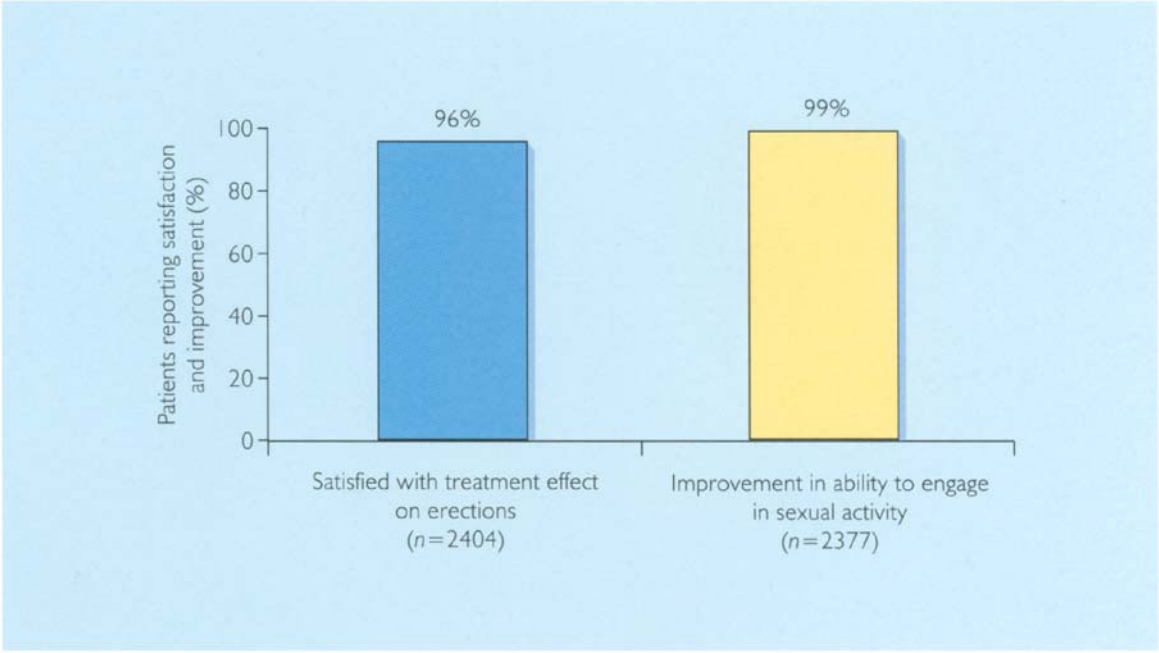


Figure 59 Satisfaction rates in men treated with sildenafil in an open-label extension study at the end of 3 years (Carson *et al*., 2002)

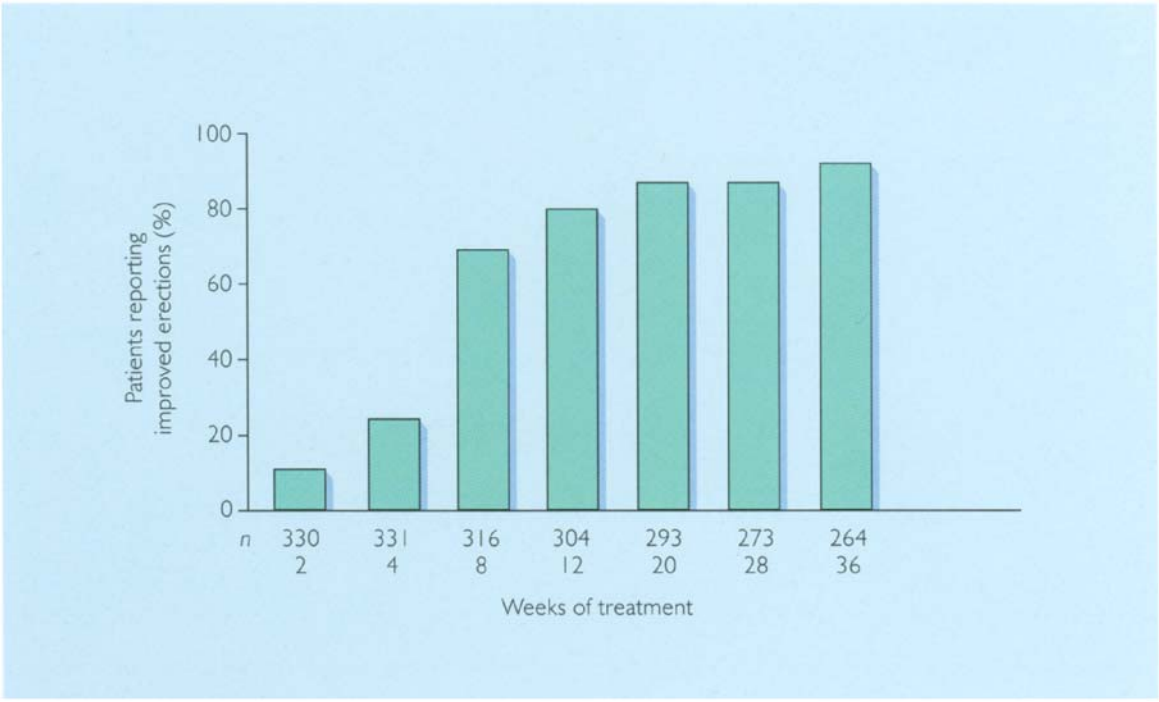


Figure 60 Percentages of patients reporting improved erections while receiving sildenafil treatment in a 36-week open-label extension study (Steers *et al.,* 2001)

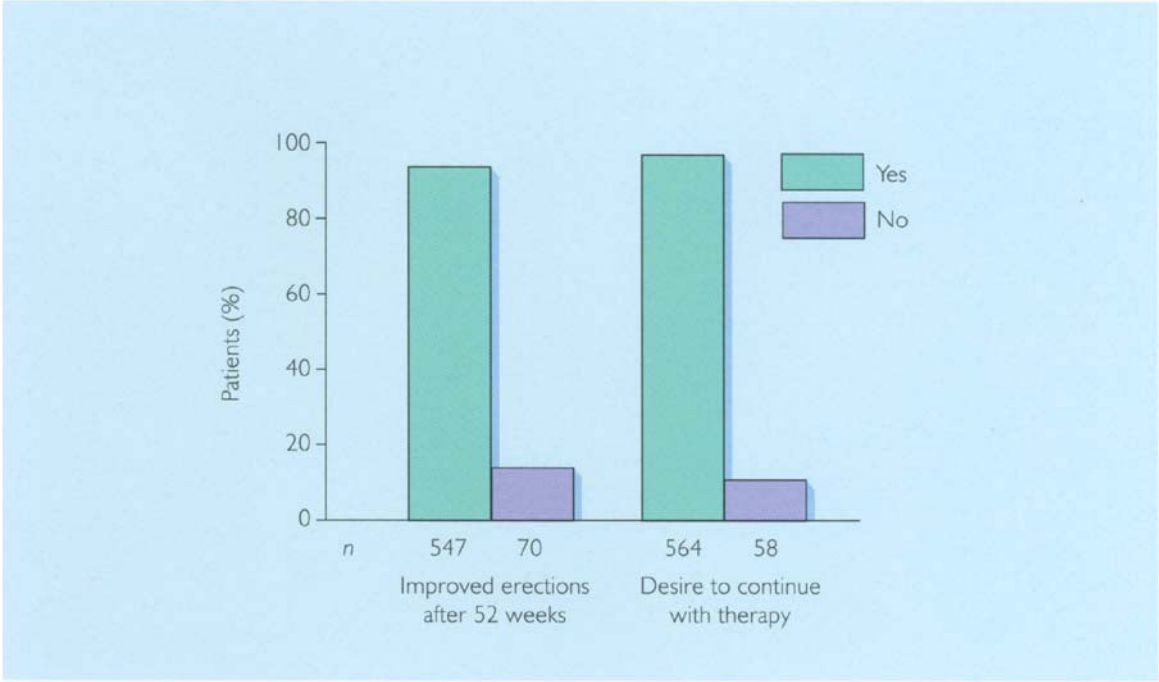


Figure 61 Percentages of patients reporting improved erections after 52 weeks of open-label treatment with sildenafil and percentages of patients wanting to continue taking sildenafil (Steers *et al.,* 2001)

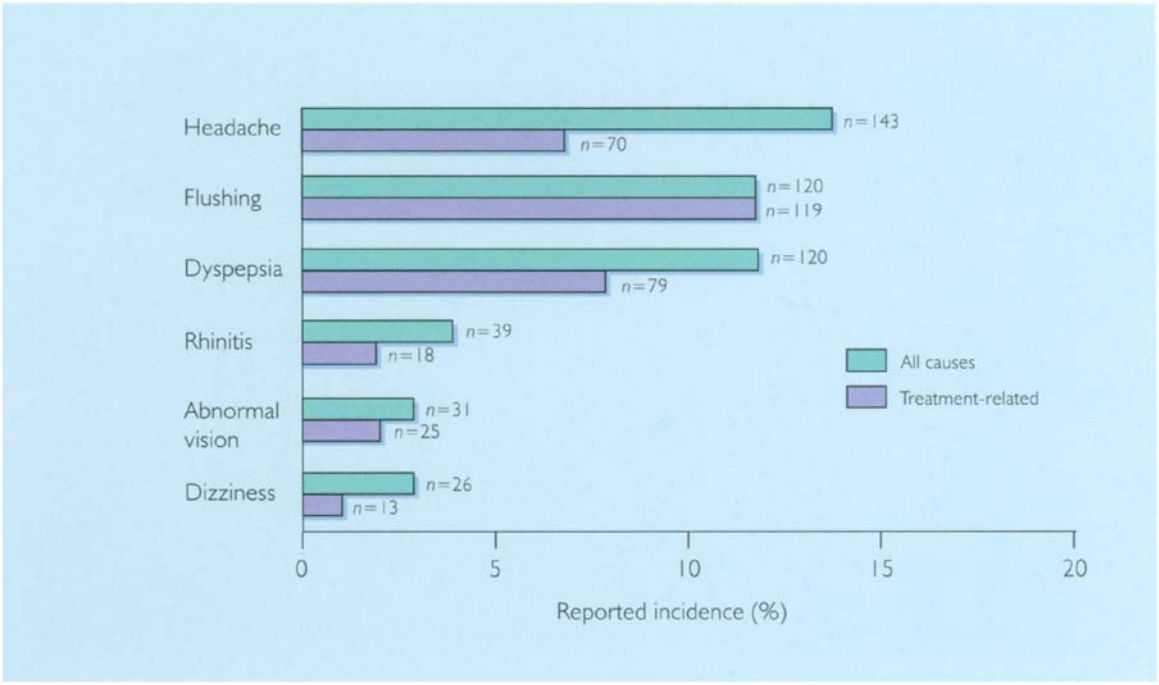


Figure 62 The most commonly occurring all-causes and treatment-related adverse events occurring during longterm open-label sildenafil treatment (Steers *et al.,* 2001)

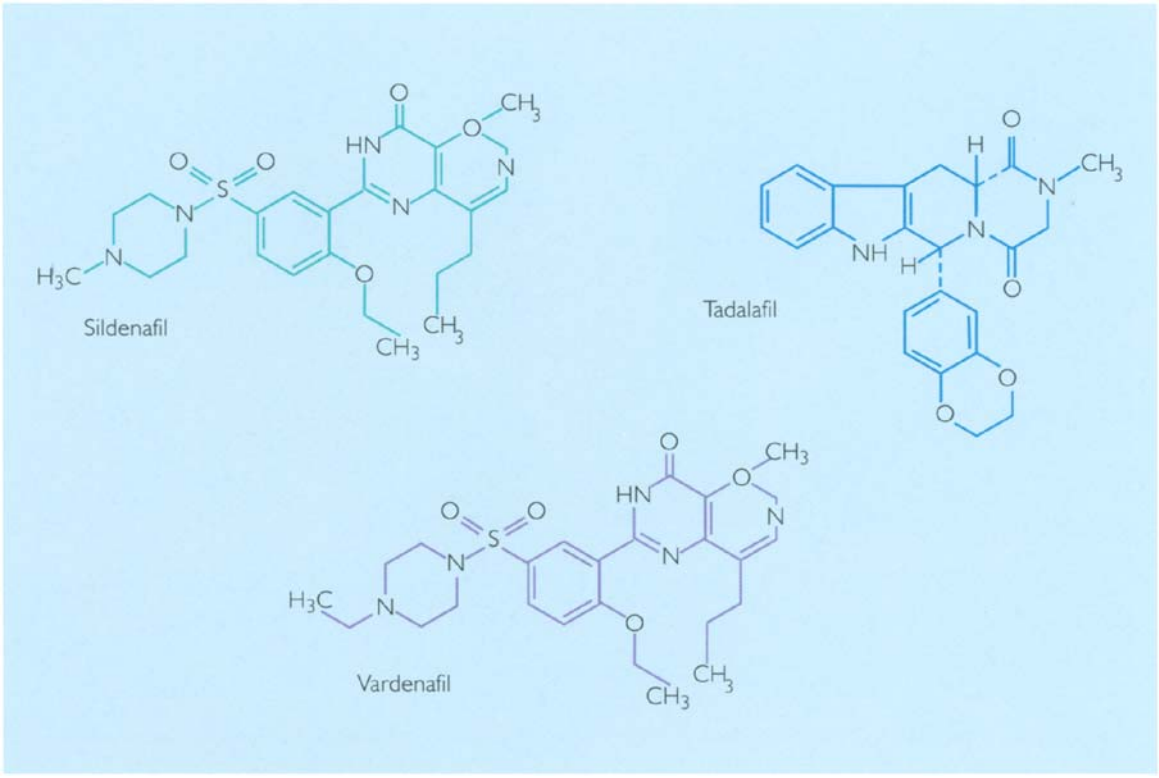


Figure 63 The chemical structures of the three phosphodiesterase type 5 inhibitors, sildenafil, vardenafil and tadalafil

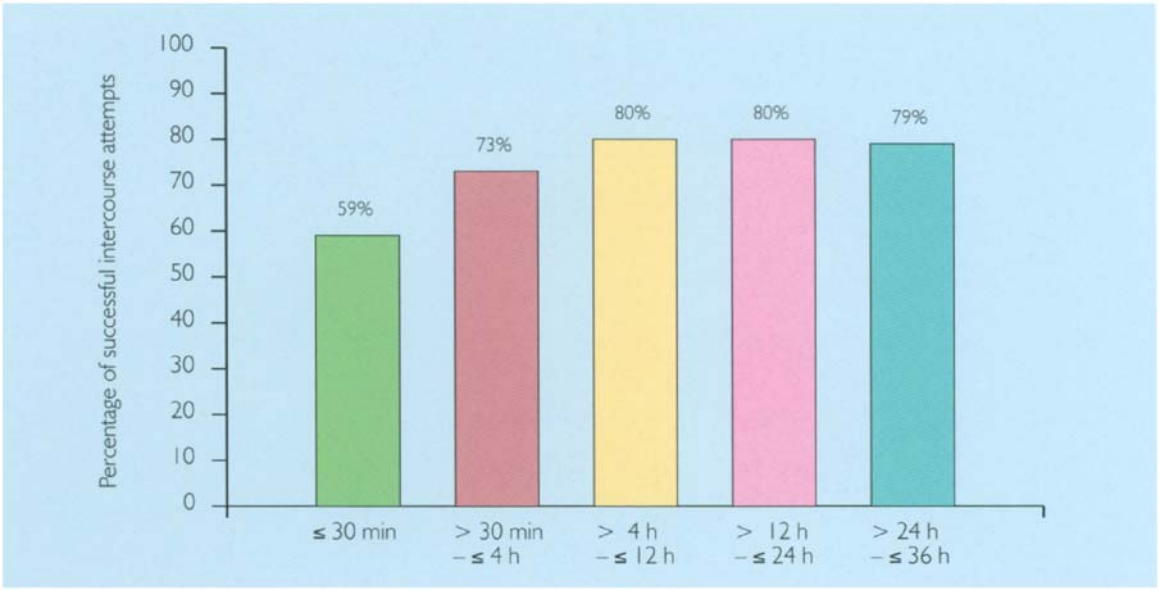


Figure 64 Effects of tadalafil on successful intercourse completion with time after dosing, as measured by Sexual Encounter Profile, question 3: 'Did your erection last long enough for you to have successful intercourse?' (Brock *et al.,* 2002)

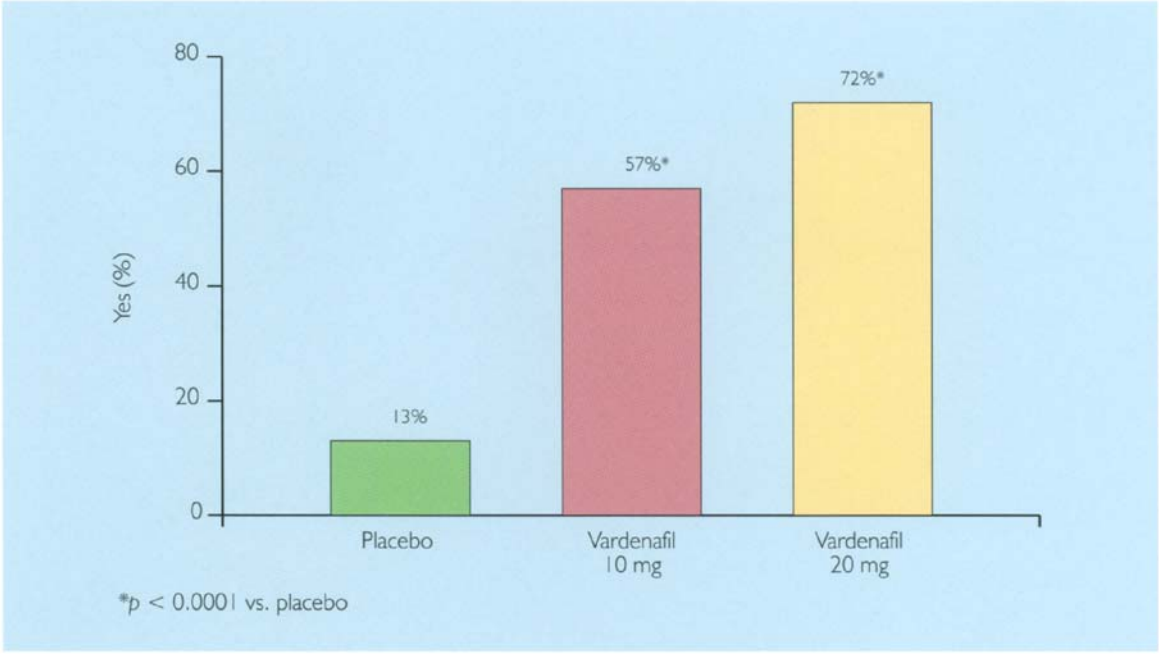


Figure 65 Percentage of diabetic men with erectile dysfunction treated with vardenafil who completed the study and reported an improvement in erections on the Global Assessment Question (GAQ) (Goldstein *et al.,* 2001)

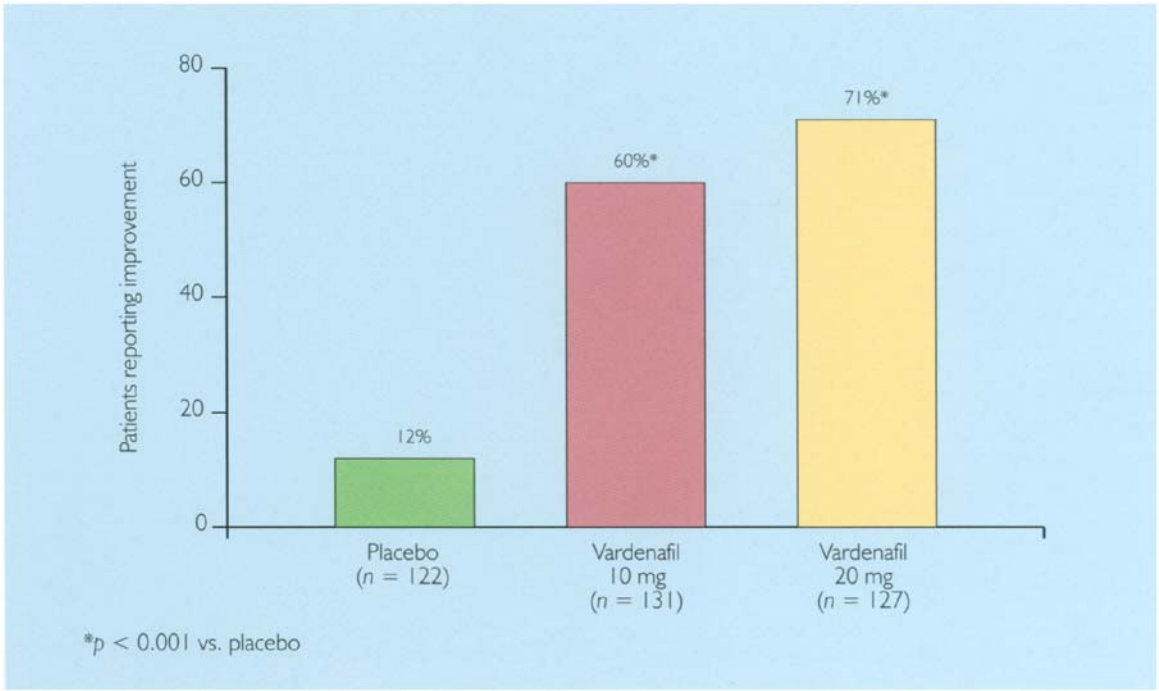


Figure 66 Vardenafil is effective in men after radical prostatectomy. Percentage of patients with bilateral nervesparing prostatectomy reporting an improvement in erection (Brock *et al.,* 2002)

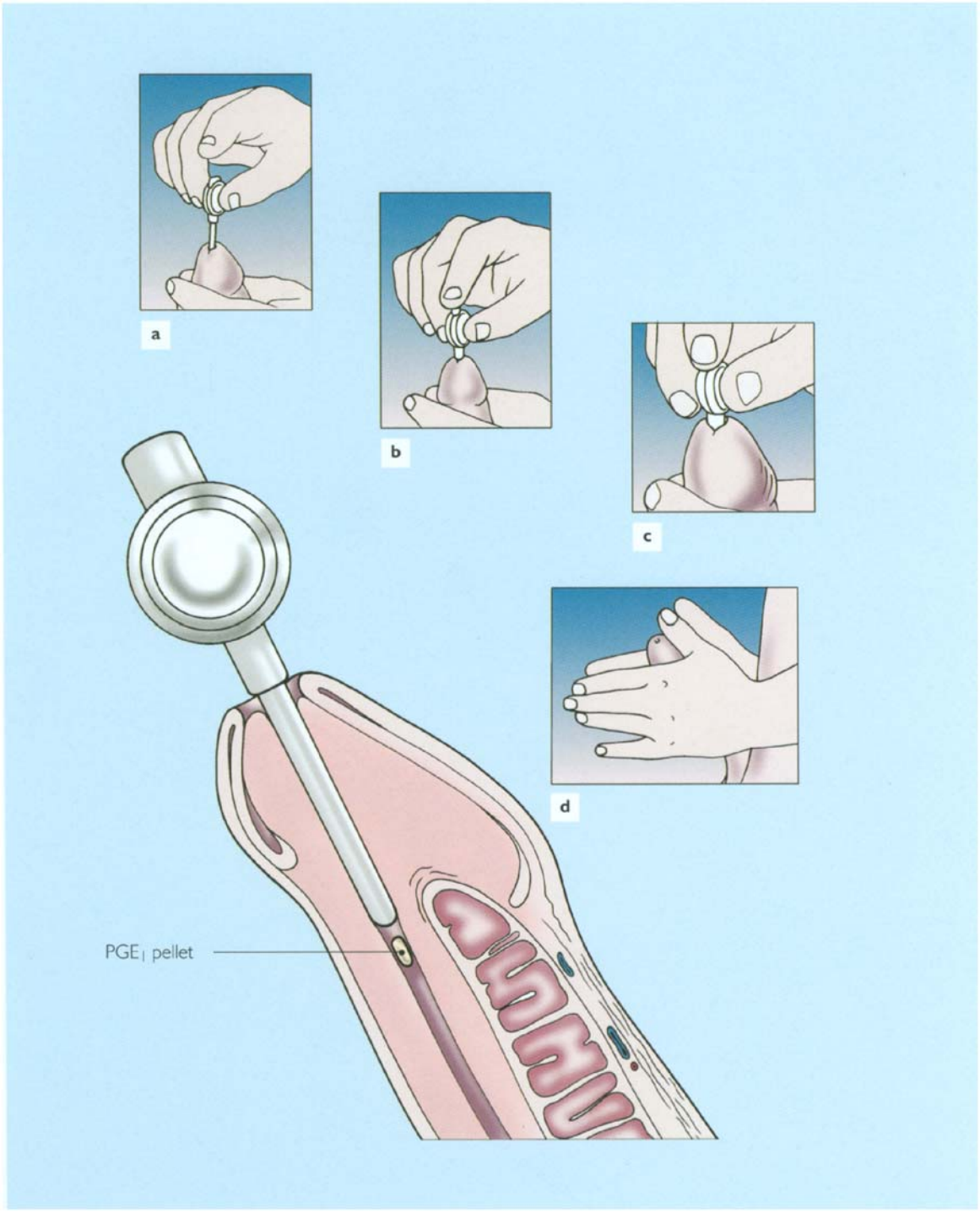


Figure 67 Medicated urethral system for erection (MUSE): using a special applicator, a 125, 250, 500 or 1000 mg suppository of prostaglandin E_1 (PGE_1) is inserted into the uethra (a-c), which has been moistened by preceding micturition. With the patient standing, the penis is rolled between two hands (d) to facilitate the absorption of PGE_1 into the corpus spongiosum and, from there, into the corpora cavernosa to enable erection

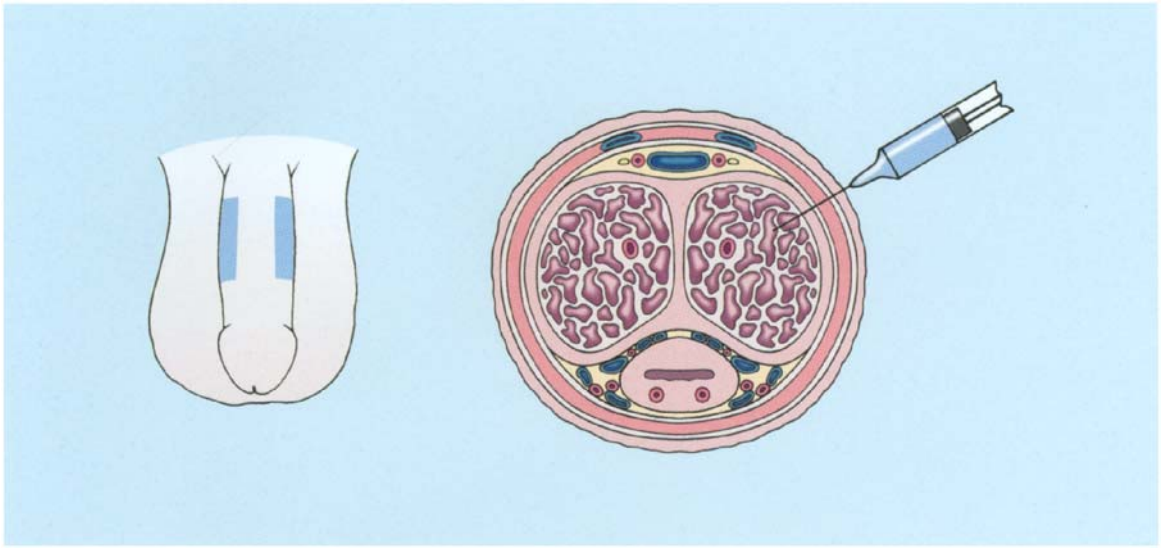


Figure 68 Intracavernous pharmacotherapy involves injection of vasoactive substances such as prostaglandin E_1, papaverine, phentolamine, vasoactive intestinal polypeptide or moxisylyte directly into the corpus cavernosum. An erection usually follows after 5–10 min and may last for up to 4 h

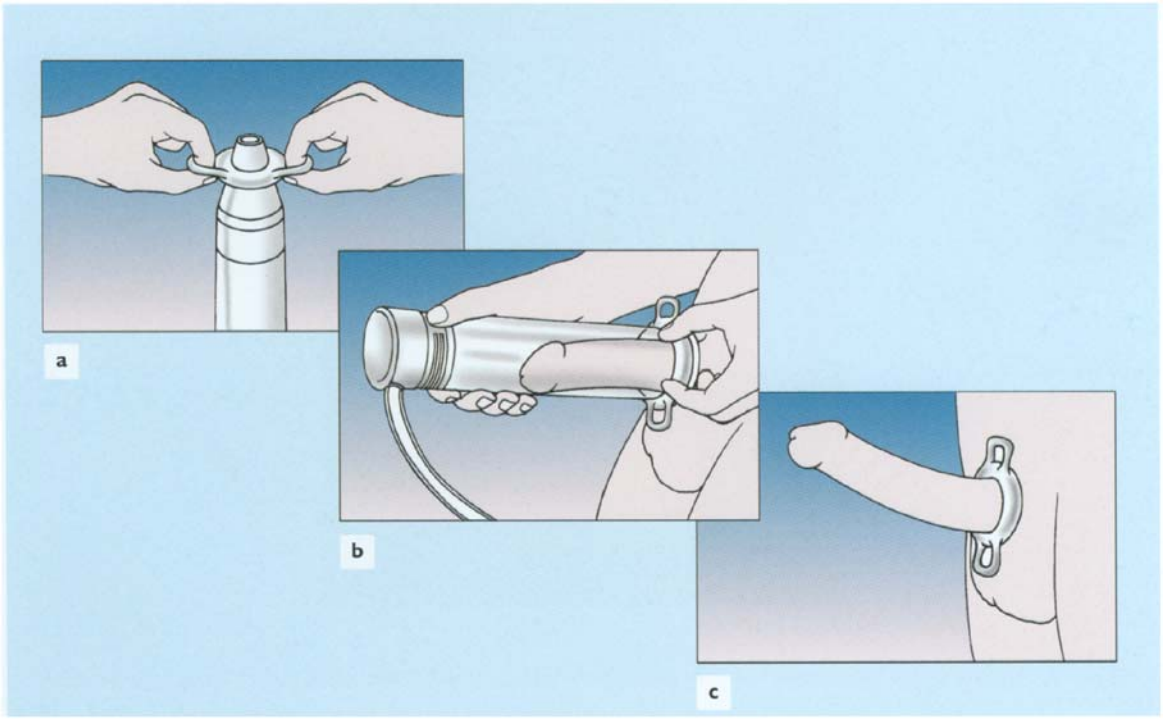


Figure 69 The vacuum device to induce tumescence is based on a simple concept. The device is lubricated with jelly around the rim to create an air-tight seal (a). A vacuum is then created, using a hand-operated or electrical pump, which draws blood into the penis, thereby inducing tumescence (b). The erection is maintained by slipping the ring off the base of the device onto the base of the penis (c)

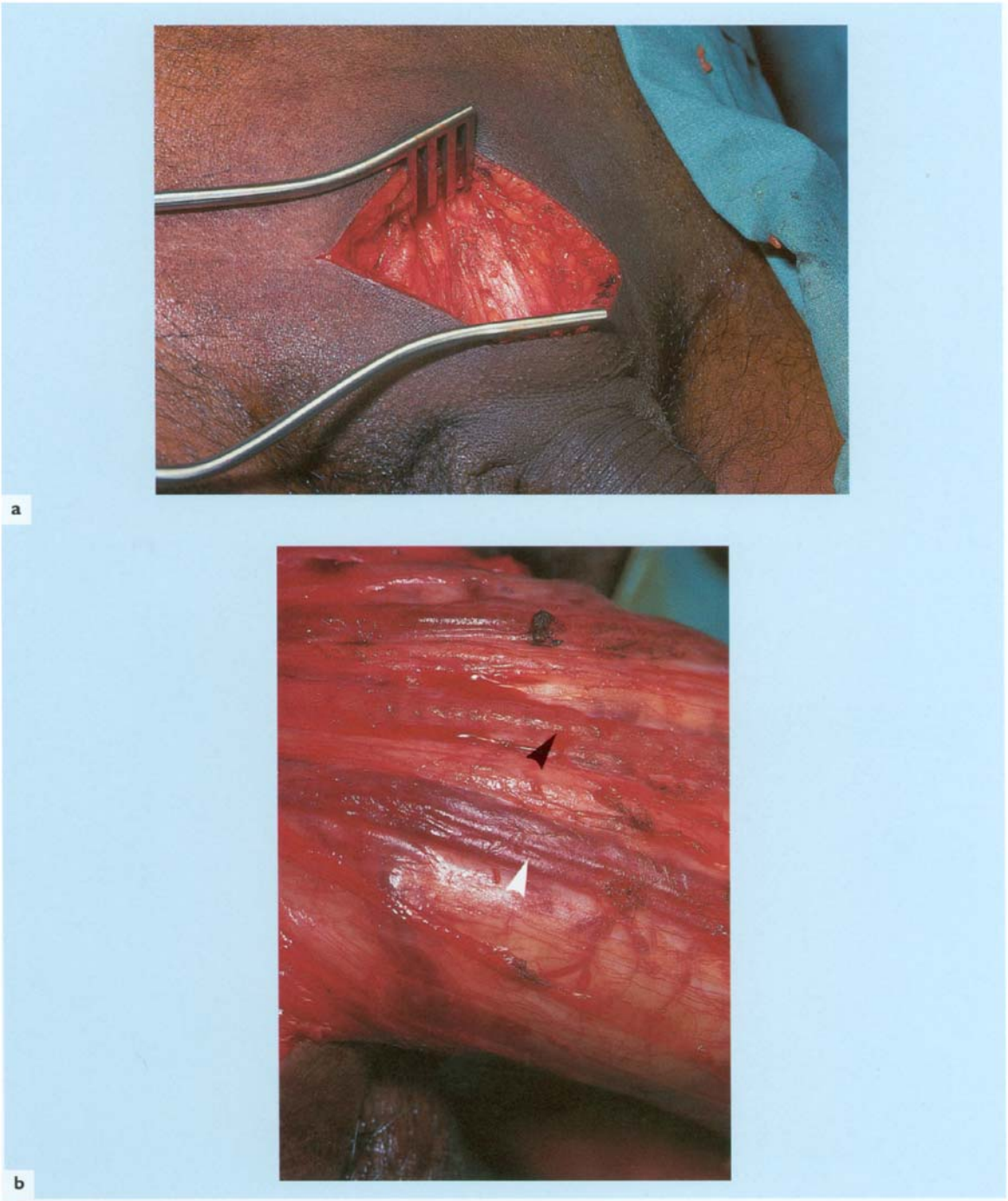
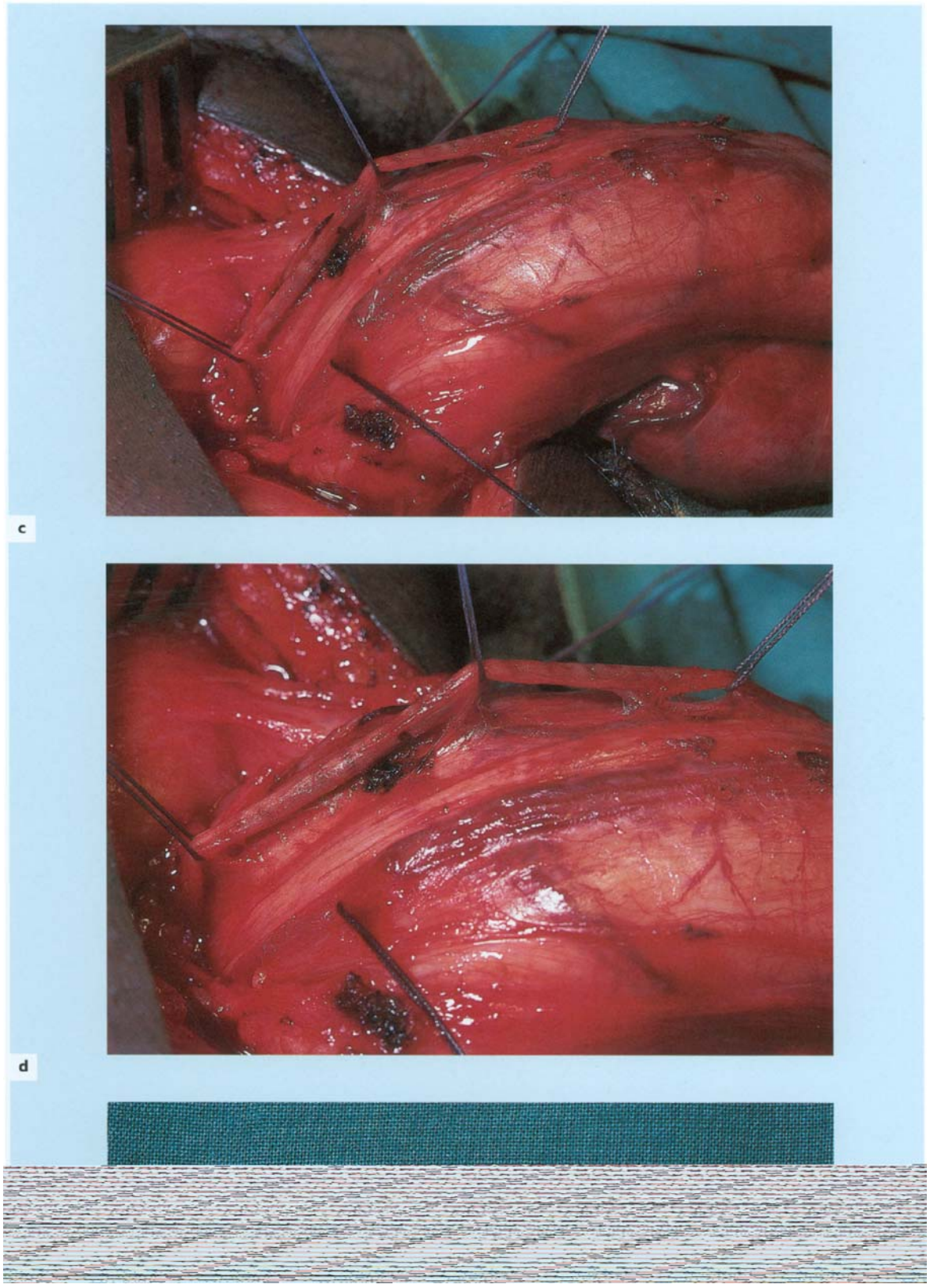


Figure 70 Correction of a venous leak into the deep dorsal vein (DDV) may sometimes be achieved by excision of a segment of the DDV: (a) a transverse intrapubic incision is made; (b) the penis is delivered into the wound, and the right (white arrow; including the dorsal artery) and left neurovascular bundles identified as well as the DDV (black arrow) lying between the two corpora cavernosa; (c) after mobilizing the DDV, the perforating vessels that drain the corpora are carefully ligated and divided; (d) the suspensory ligament is divided to allow the vein to be traced beneath the pubis; and (e) a 7-cm segment of the DDV is excised. *Continued*



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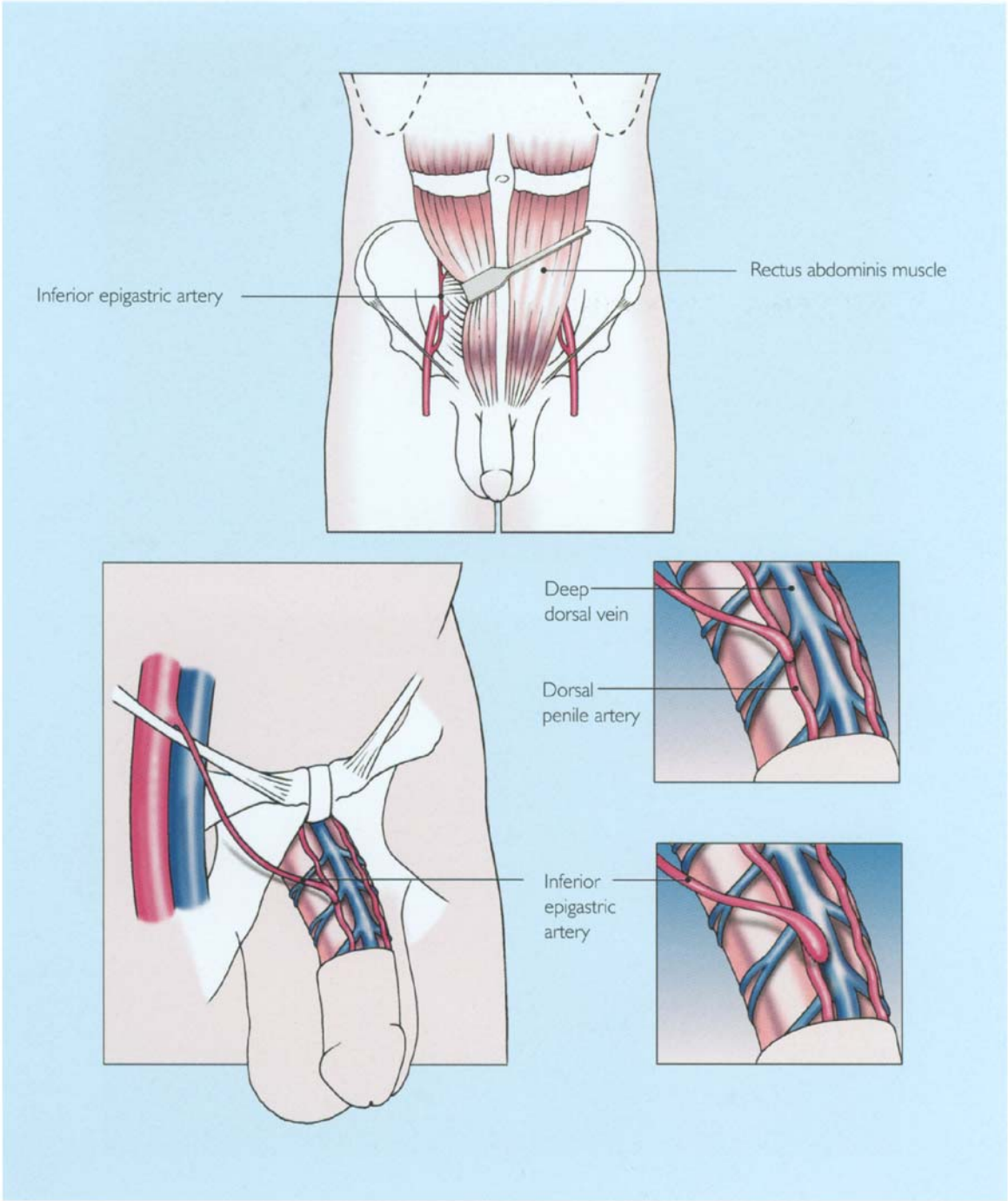

Figure 71 Arterial revascularization of the corpora may be applicable in some younger patients with localized lesions of the pudendal artery due, for example, to a pelvic fracture. A longitudinal incision is made along the line of the lateral margin of the rectus abdominis muscle. The inferior epigastric artery is mobilized and swung downwards through a tunnel to the dorsum of the penis. An anastomosis is created between the inferior epigastric artery and either the dorsal penile artery alone or the conjoined dorsal penile artery and deep dorsal vein. In the latter case, the deep dorsal vein is ligated distally to prevent glans hypervascularization

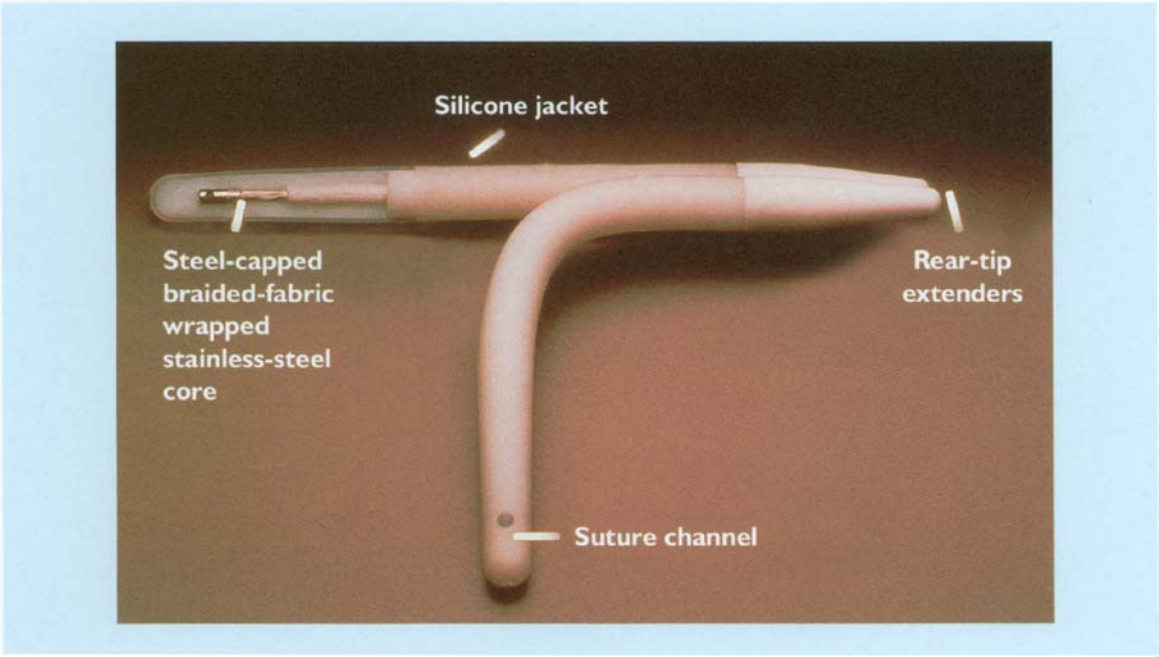

Figure 72 Semi-rigid penile prosthesis: the stainless-steel core renders the device capable of retaining its position in whichever position it is bent

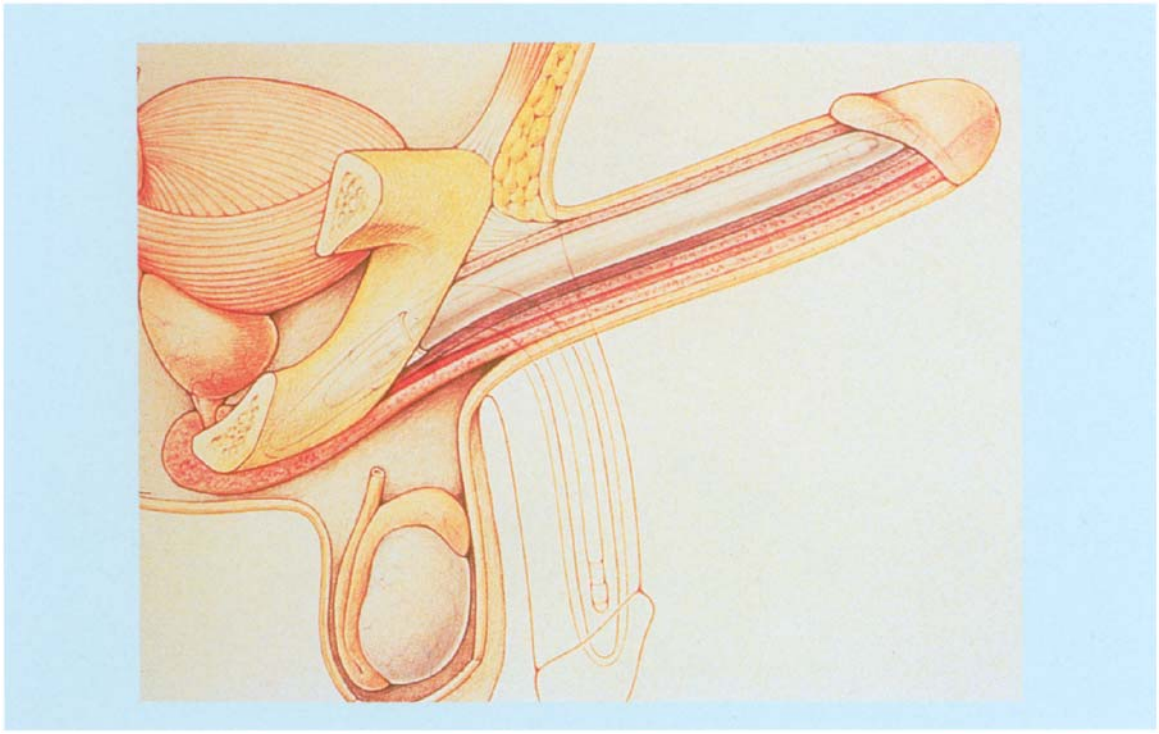

Figure 73 Semi-rigid penile prosthesis *in situ:* the lack of flaccidity may make concealment a problem, but the simplicity of the device makes malfunction a rare event

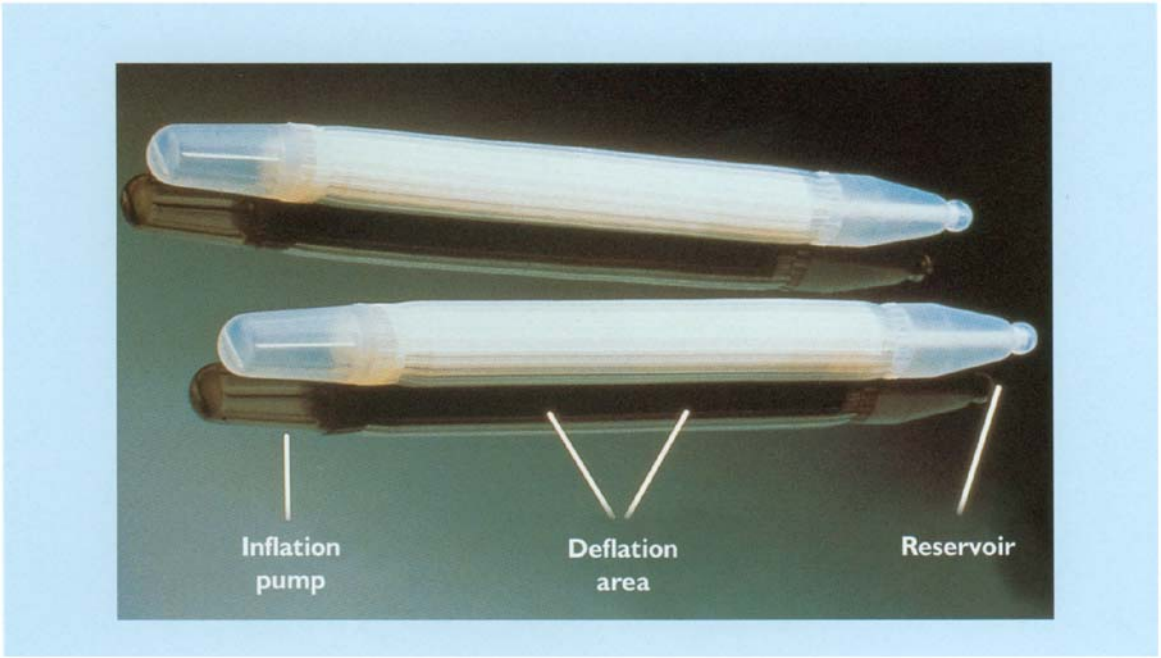

Figure 74 Inflatable one-piece penile prosthesis: this device confers some degree of flaccidity but is not always easy to inflate and deflate

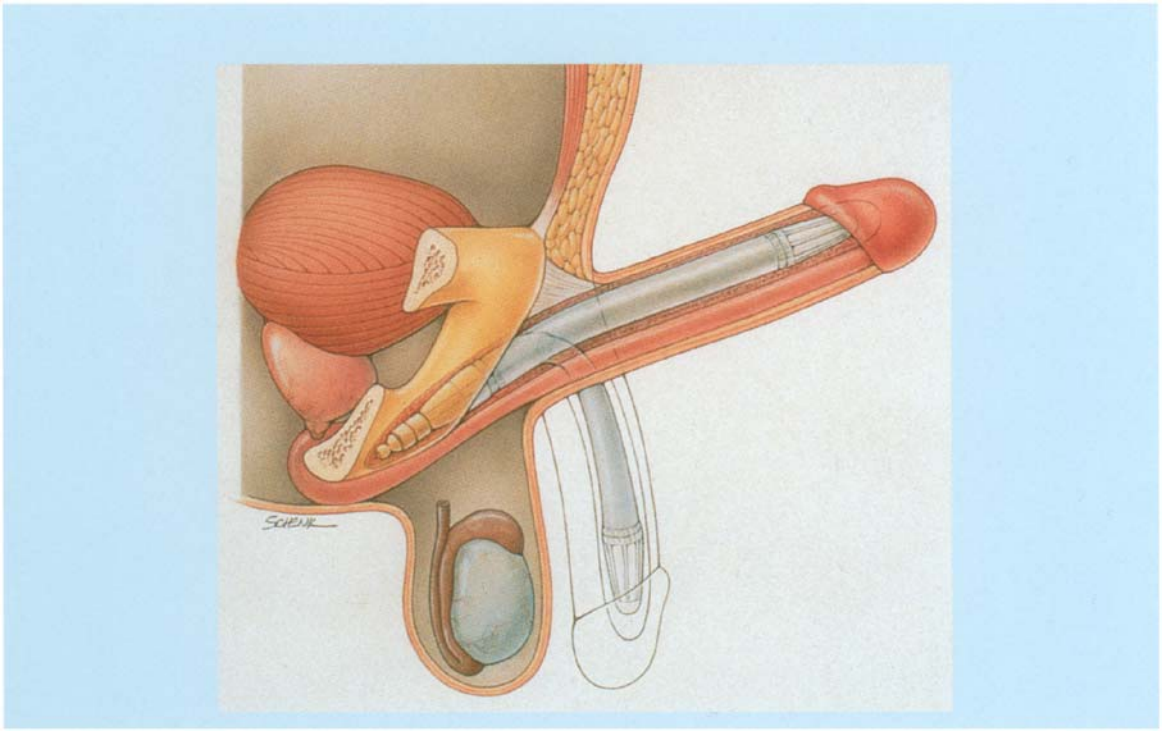

Figure 75 Inflatable one-piece penile prosthesis *in situ:* inflation is achieved by squeezing the distally located inflation pump

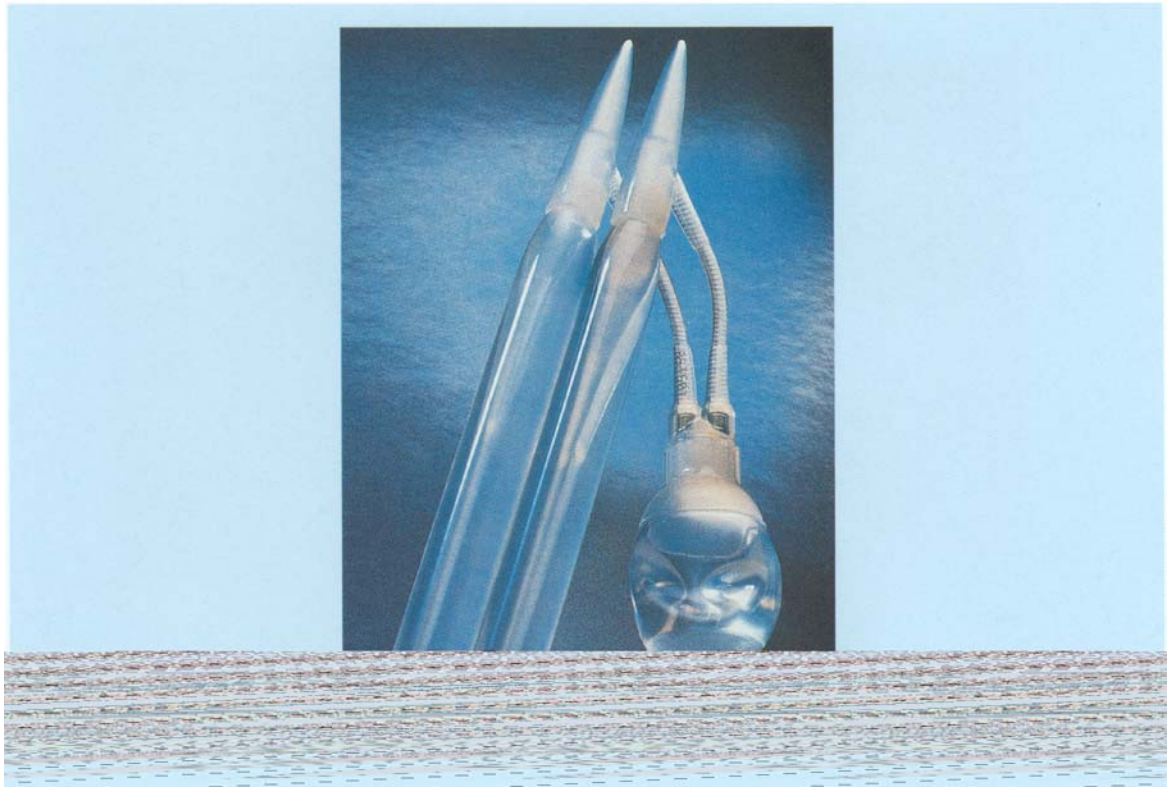

Figure 76 Two-component inflatable penile prosthesis: deflation is achieved by transfer of fluid from the two cylinders implanted in the corpora cavernosa to the reservoir located in the scrotum

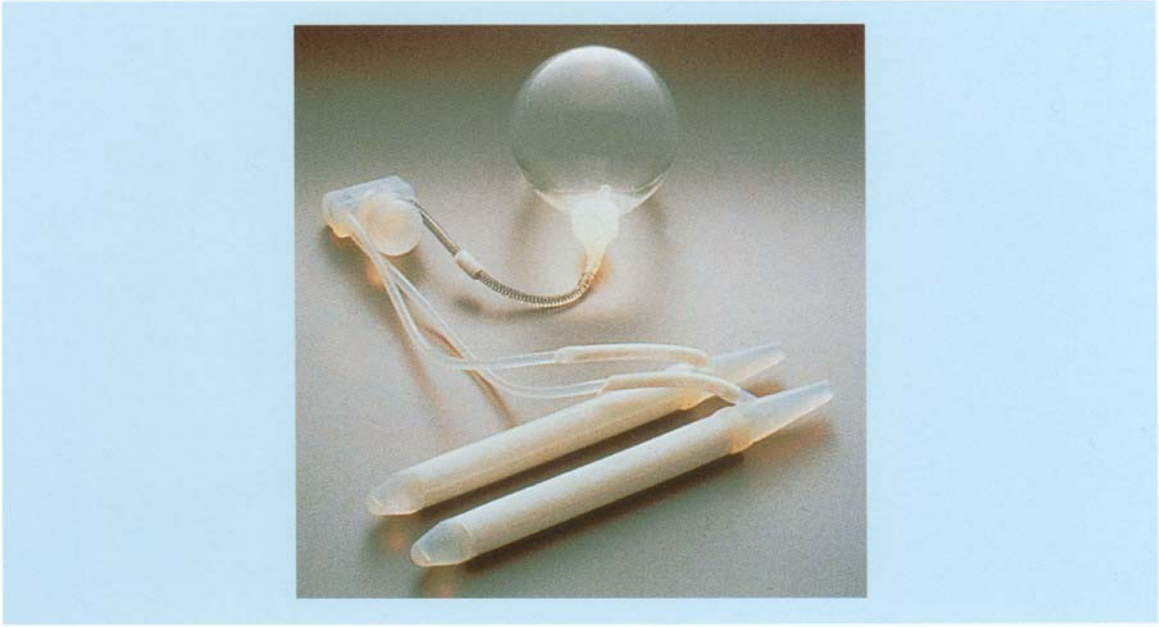

Figure 77 Three-component inflatable penile prosthesis: this device produces the most cosmetically and functionally acceptable results

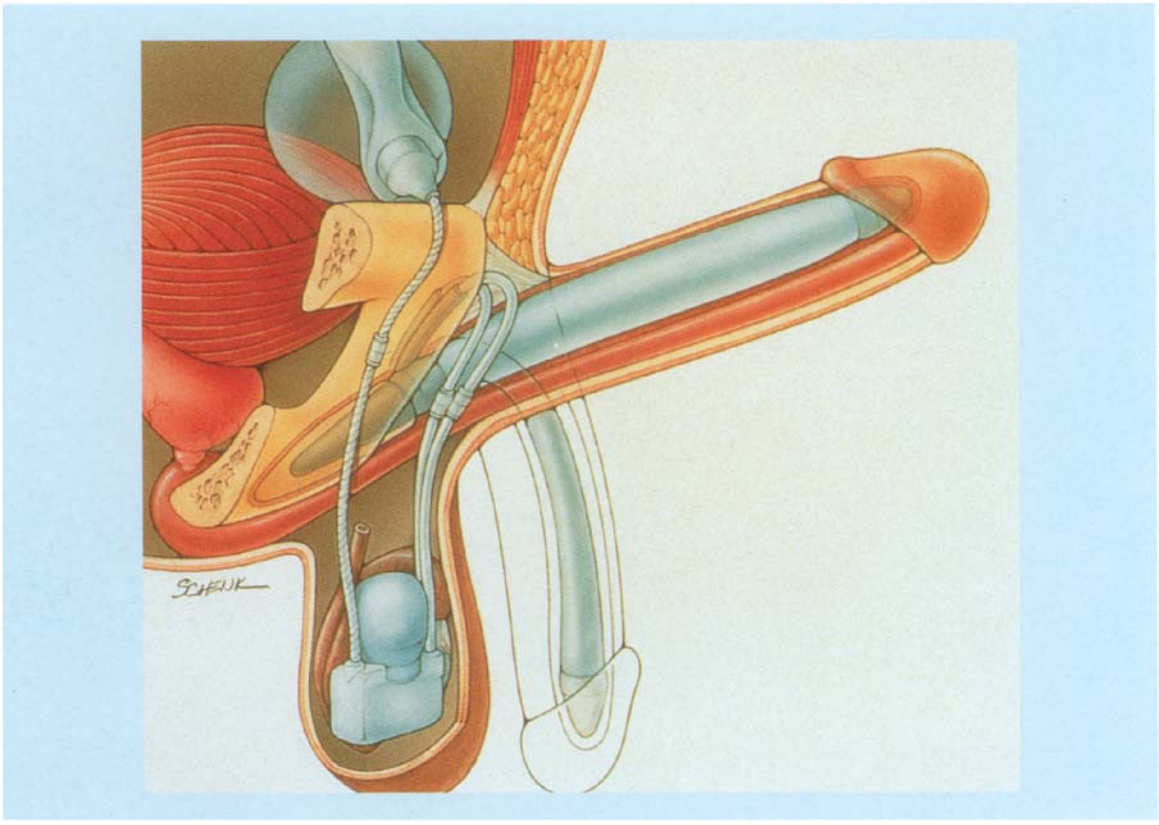

Figure 78 Three-component inflatable penile prosthesis *in situ:* a cylinder is inserted into each corpus cavernosum. The pump is placed within the scrotum and the reservoir, which may contain either 60 ml or 100 ml of saline, is implanted extraperitoneally in the prevesical space

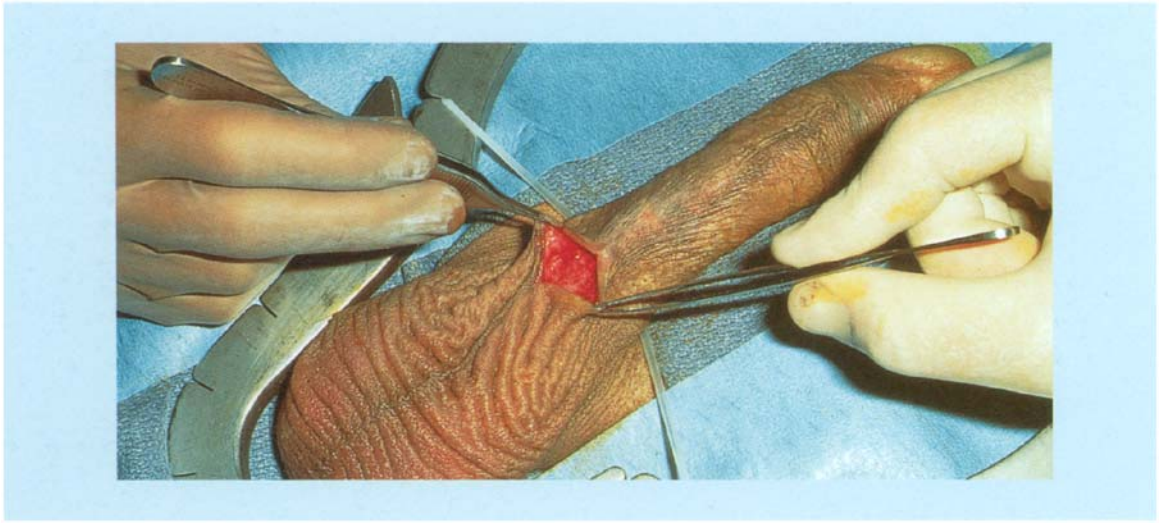

Figure 79 Surgical implantation of a three-component inflatable penile prosthesis: after scrupulous skin cleansing and administration of intravenous antibiotics, a longitudinal penoscrotal skin incision is made

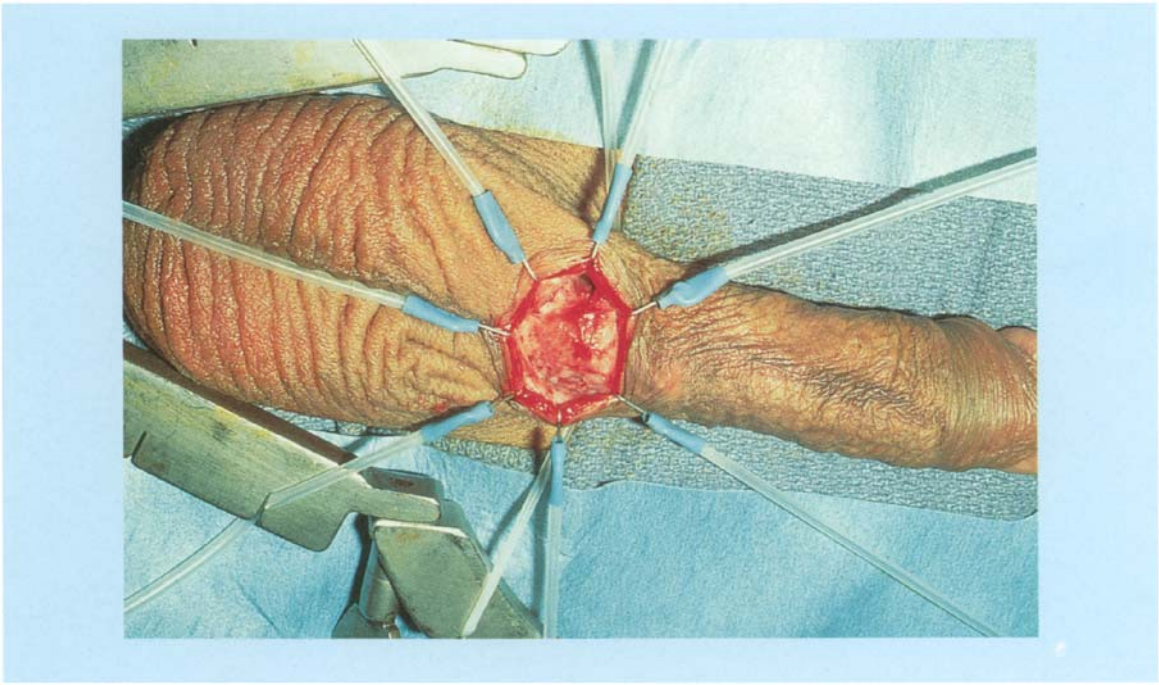

Figure 80 Surgical implantation of a three-component inflatable penile prosthesis: the incision is deepened to expose the underlying tunica albuginea of the corpora cavernosa. The corpus spongiosum, which contains the urethra, lies in the mid-line and is carefully avoided

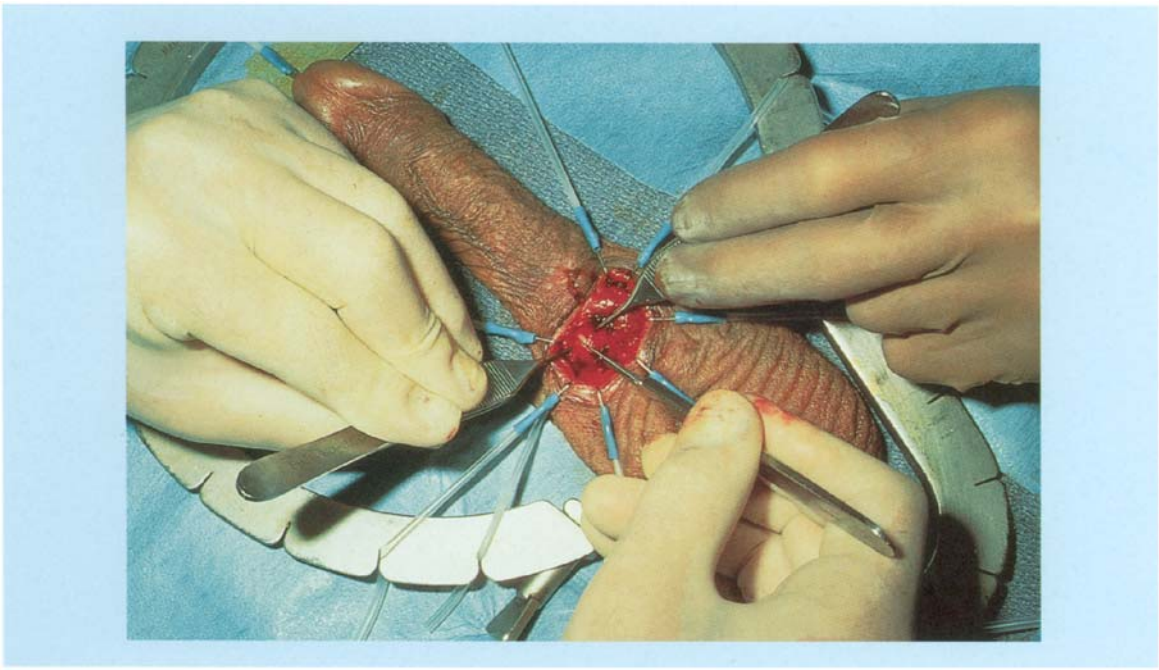

Figure 81 Surgical implantation of a three-component inflatable penile prosthesis: each corpus is incised longitudinally to expose the underlying vascular erectile tissue

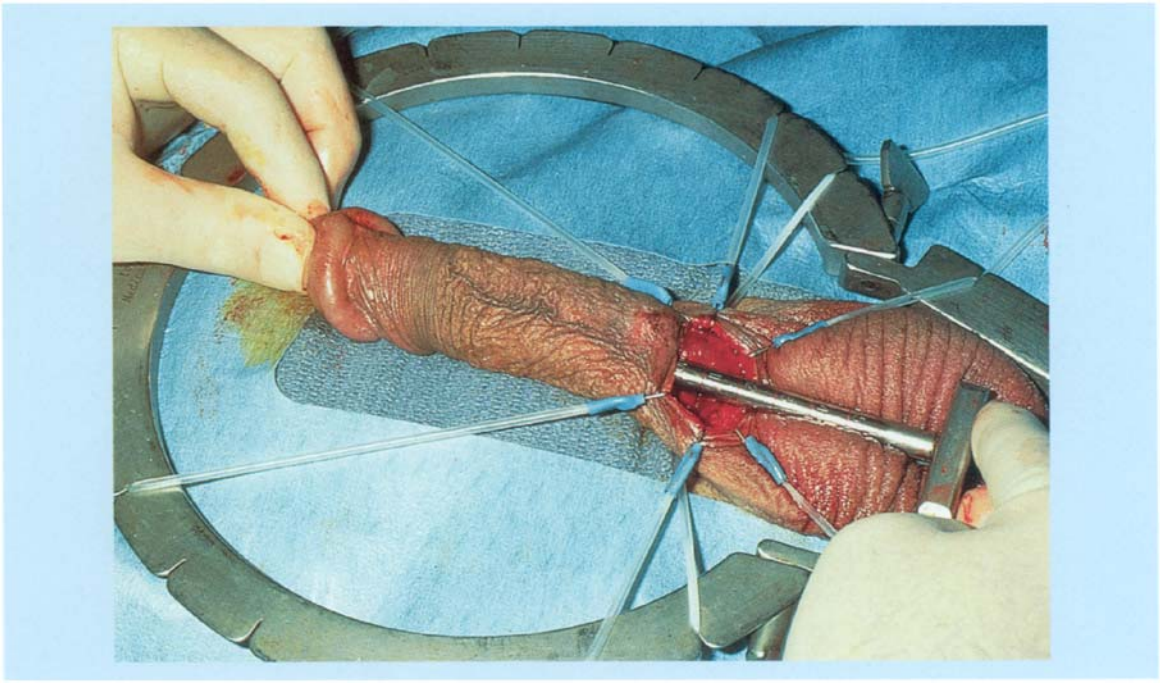

Figure 82 Surgical implantation of a three-component inflatable penile prosthesis: after dilatation of the distal corpora, their length is carefully measured

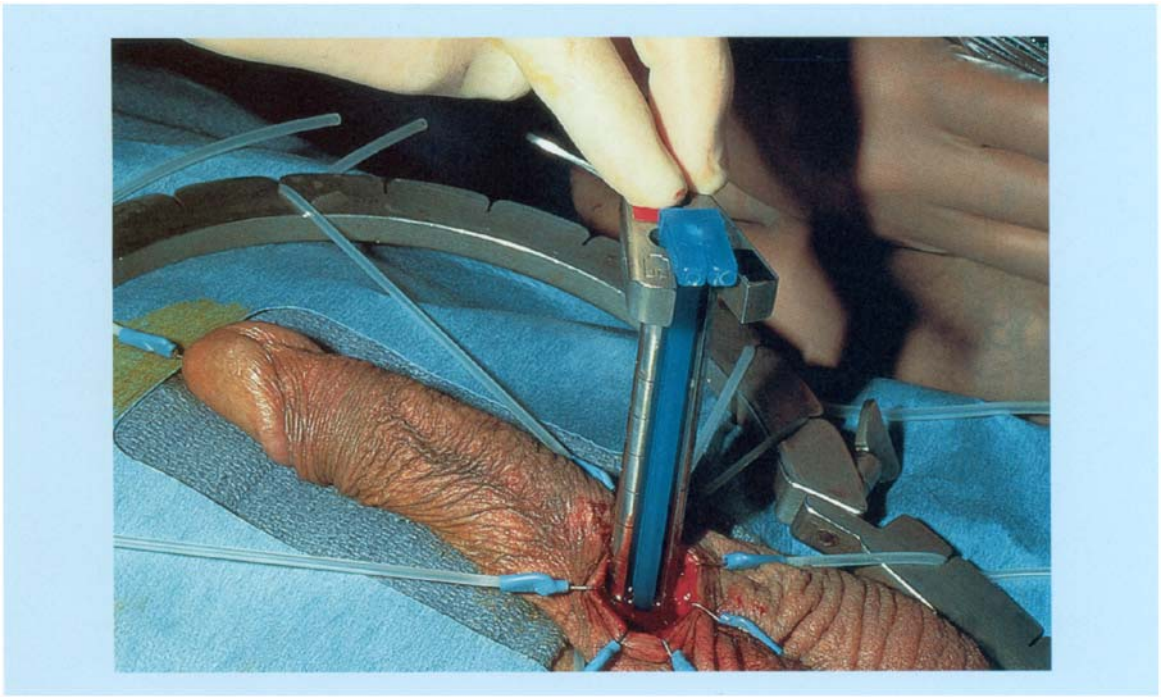

Figure 83 Surgical implantation of a three-component inflatable penile prosthesis: the proximal corporal spaces are similarly dilated and the spaces carefully measured

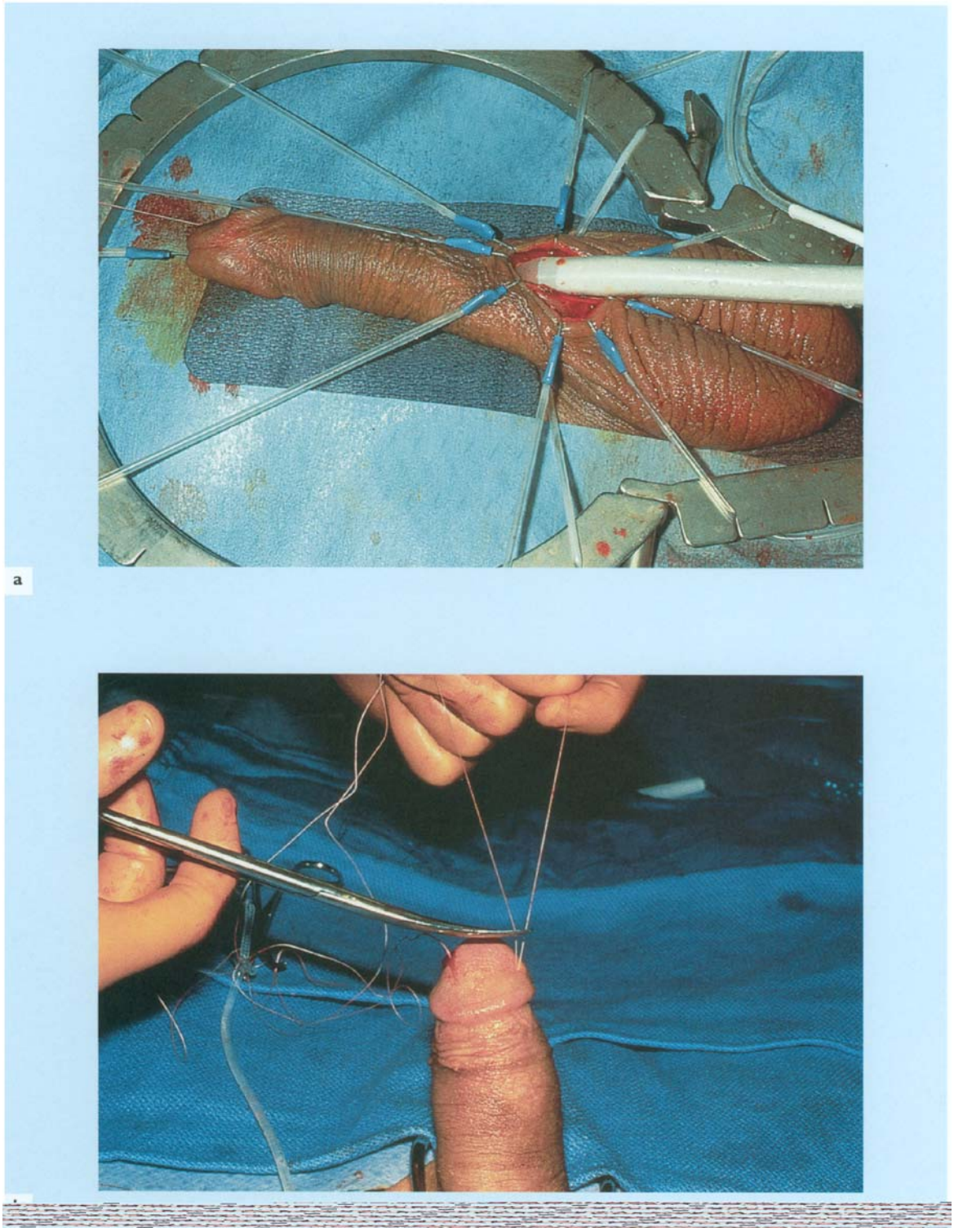

Figure 84 Surgical implantation of a three-component inflatable penile prosthesis: silicone cylinders of the correct length are implanted (a), using an attached suture brought through the glans to help locate the tip of the prosthesis distally (b)

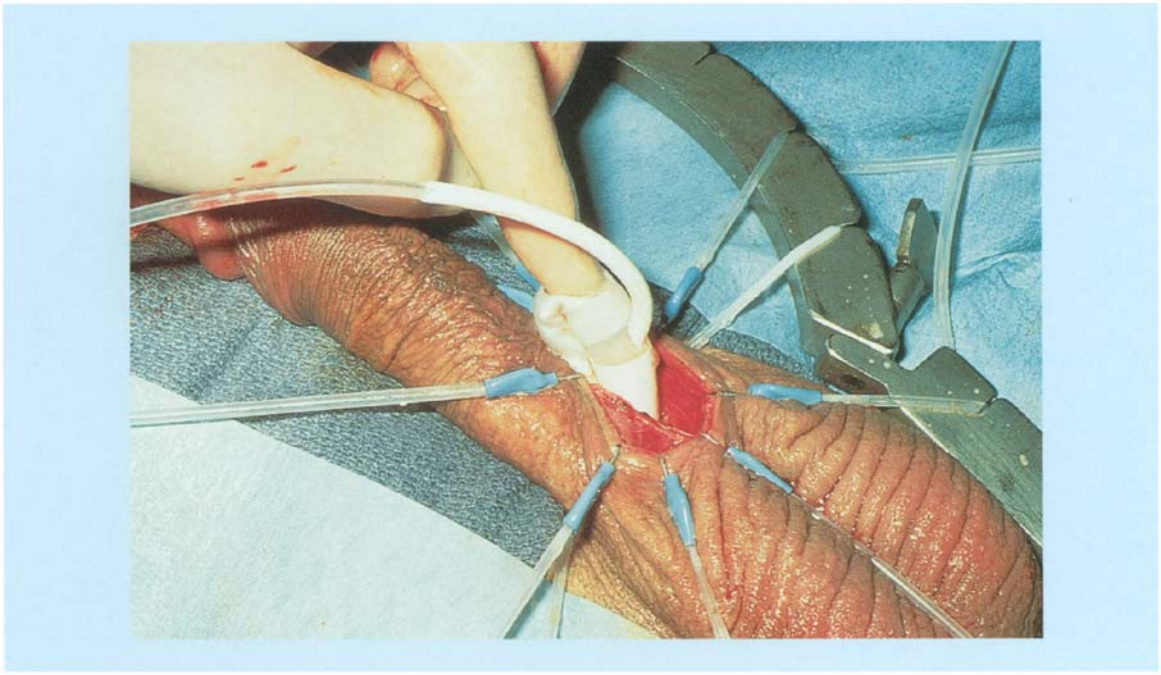

Figure 85 Surgical implantation of a three-component inflatable penile prosthesis: the proximal portion of the device with the appropriate rear tip extender is then implanted

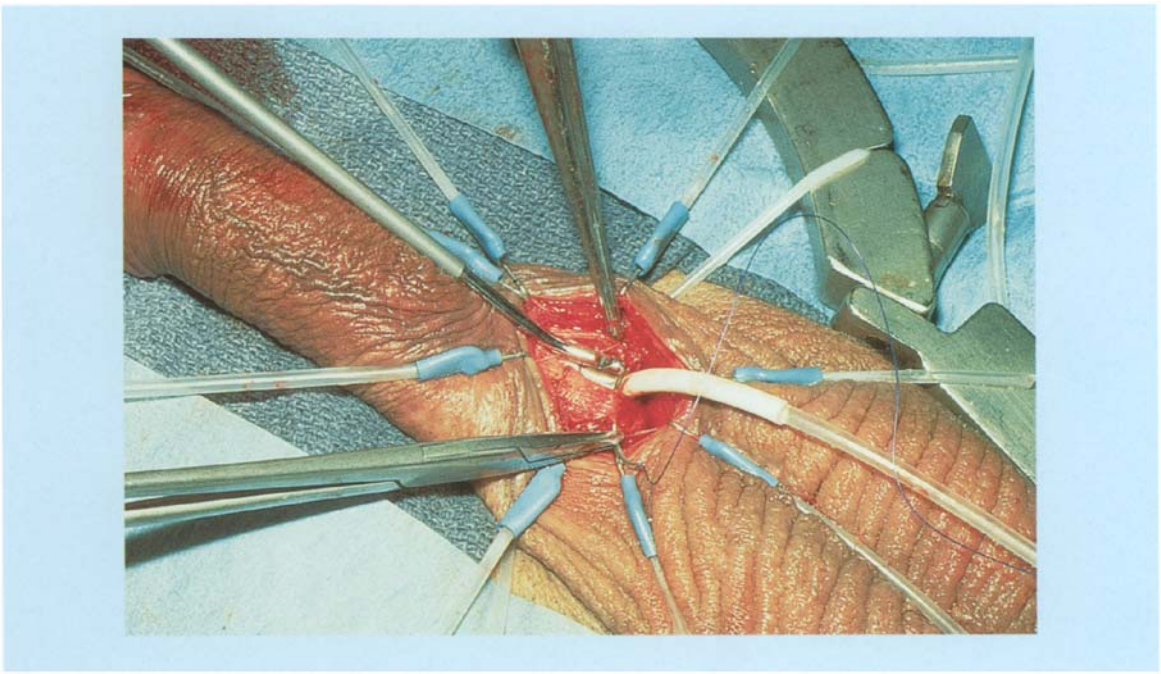

Figure 86 Surgical implantation of a three-component inflatable penile prosthesis: the corporotomy is closed while ensuring that the delicate silicone walls of the cylinders are not damaged and that the tubing to be connected to the pump is neither compressed nor kinked

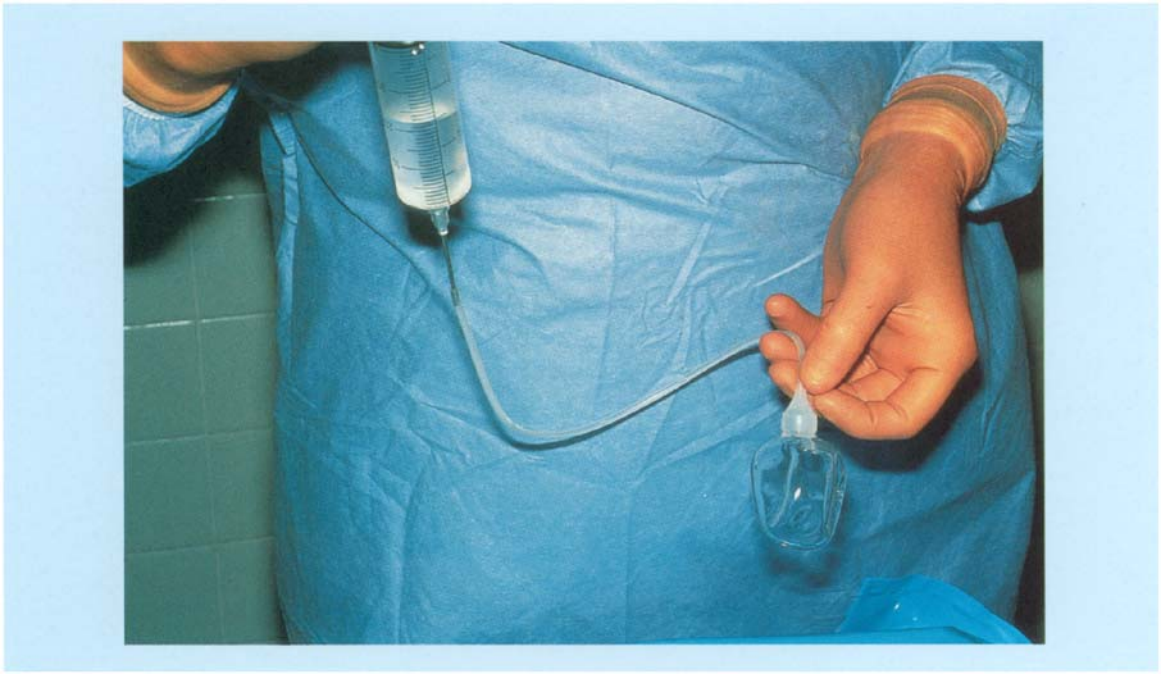

Figure 87 Surgical implantation of a three-component inflatable penile prosthesis: the reservoir is filled and emptied to remove any air bubbles, then implanted through a separate incision in the prevesical space and connected to the scrotal pump

Figure 88 Portrait of François de la Peyronie, the eminent French surgeon who gave his name to the fibrotic condition which frequently results in deformity of the erect penis

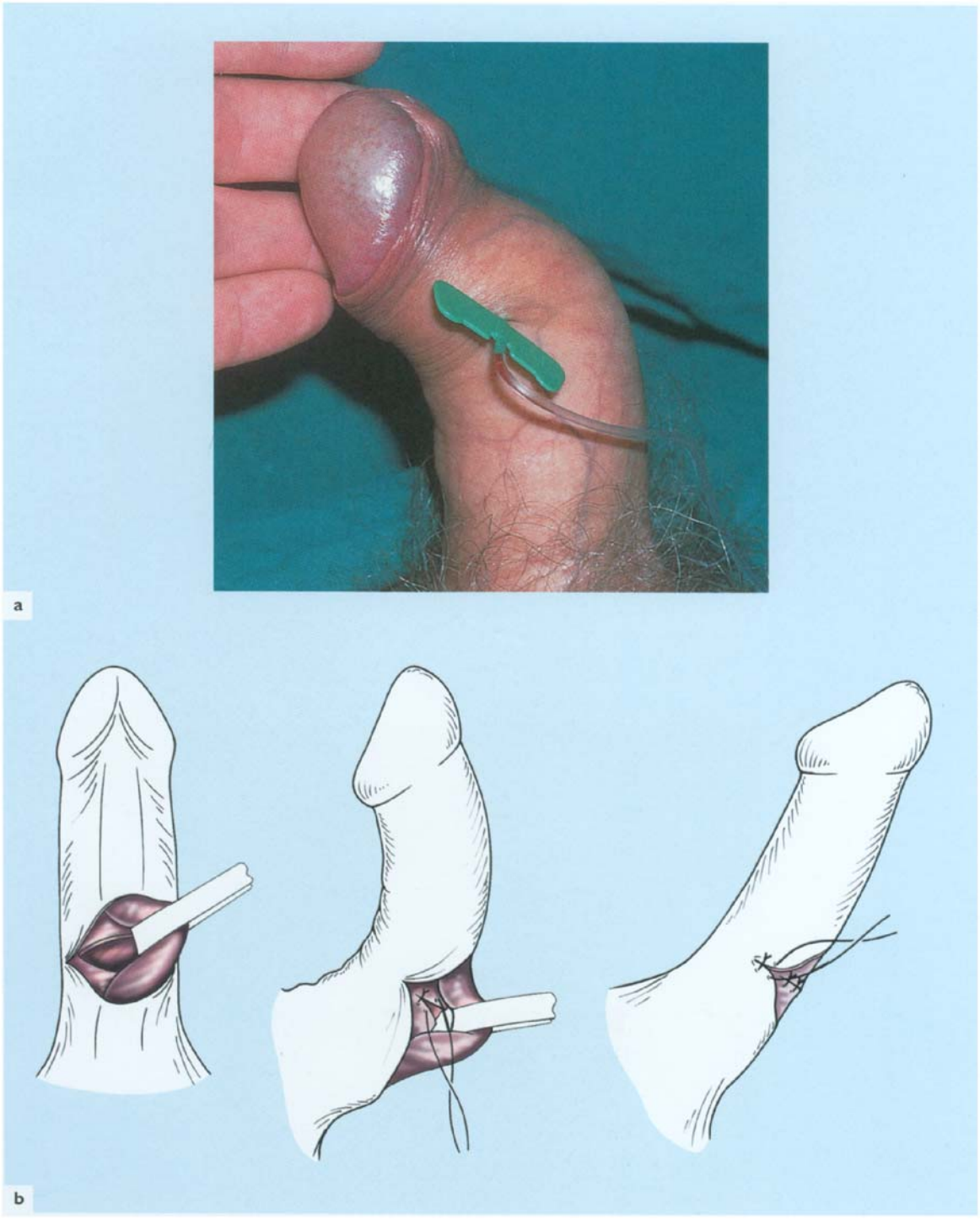

Figure 89 Dorsal penile deformity (a) as a result of a Peyronie's plaque, demonstrated by the creation of an artificial erection immediately prior to undergoing Nesbit's surgical correction procedure (b). In this procedure, the corpus spongiosum is dissected away from the corpora cavernosa, and a wedge of tissue excised from their ventral surface. Closure of the defect results in straightening, albeit with some shortening, of the penis

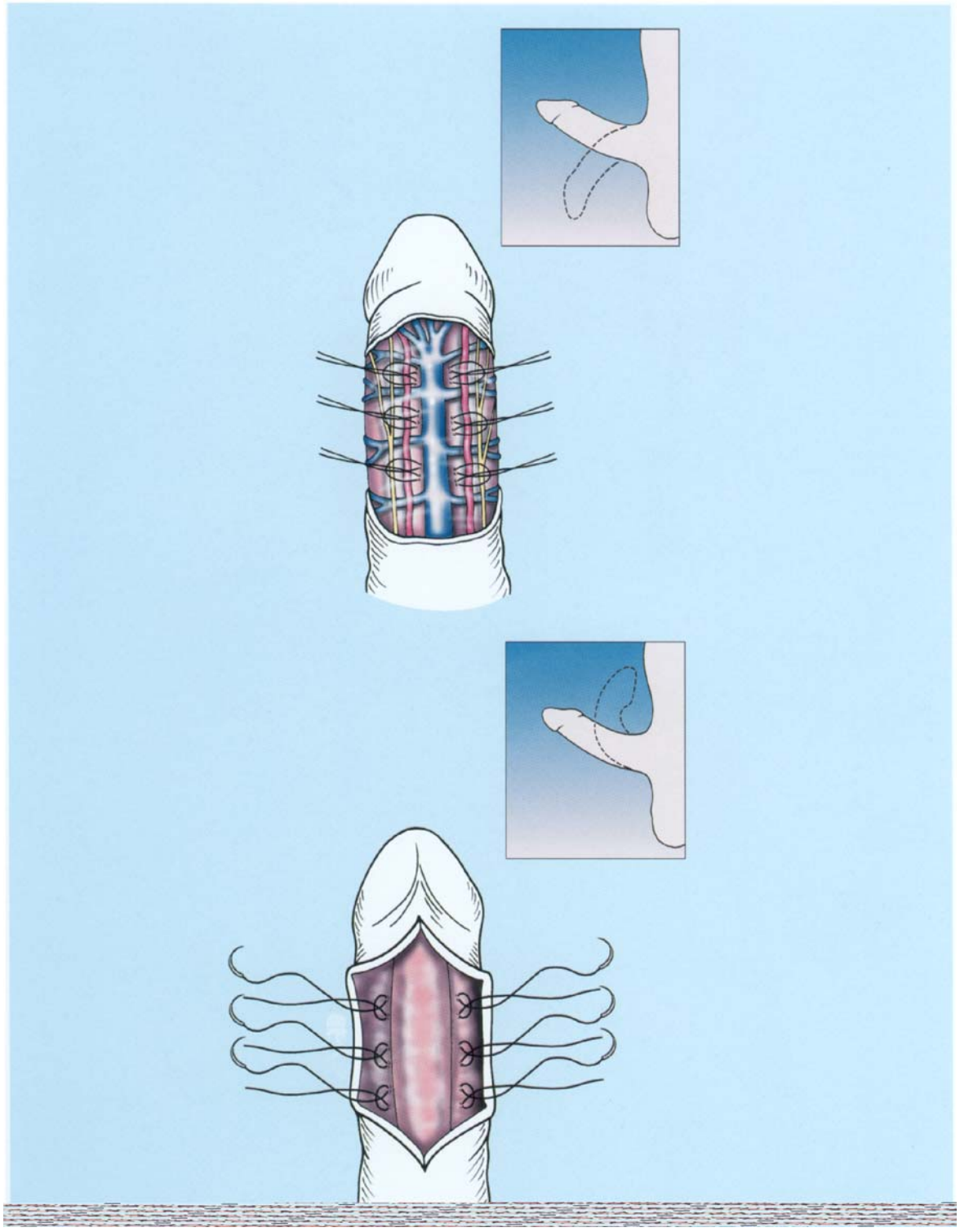

Figure 90 An alternative surgical corrective technique for Peyronie's deformity involves multiple plication of the corpora. Multiple non-absorbable sutures are placed in the tunica albuginea; this can correct either dorsal or ventral deformities

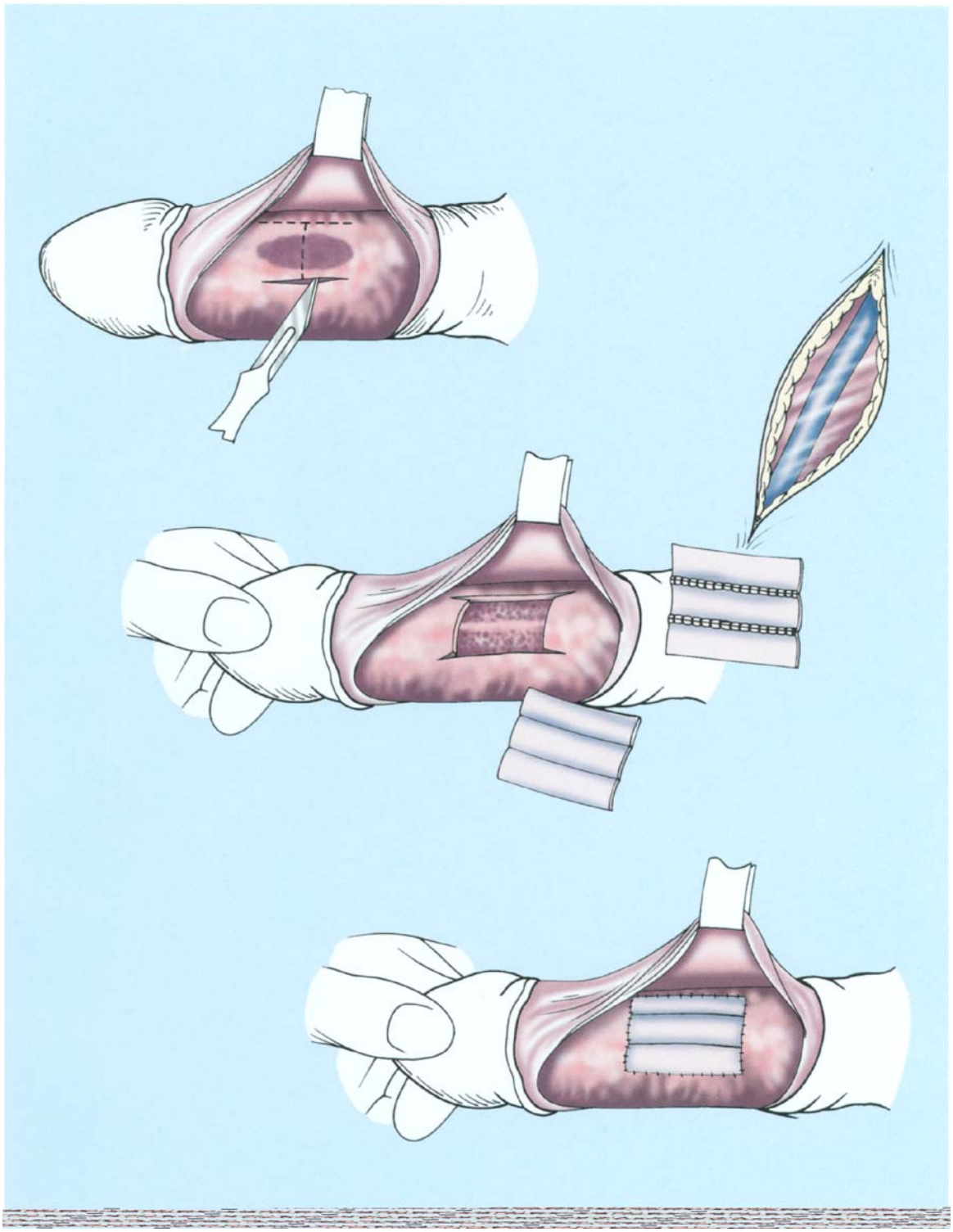

Figure 91 To avoid the inevitable penile shortening that accompanies Nesbit's operation, an alternative procedure has been described. The plaque is incised and the defect closed, using a venous segment graft. Great care must be taken not to injure the dorsal neurovascular bundles during this operation

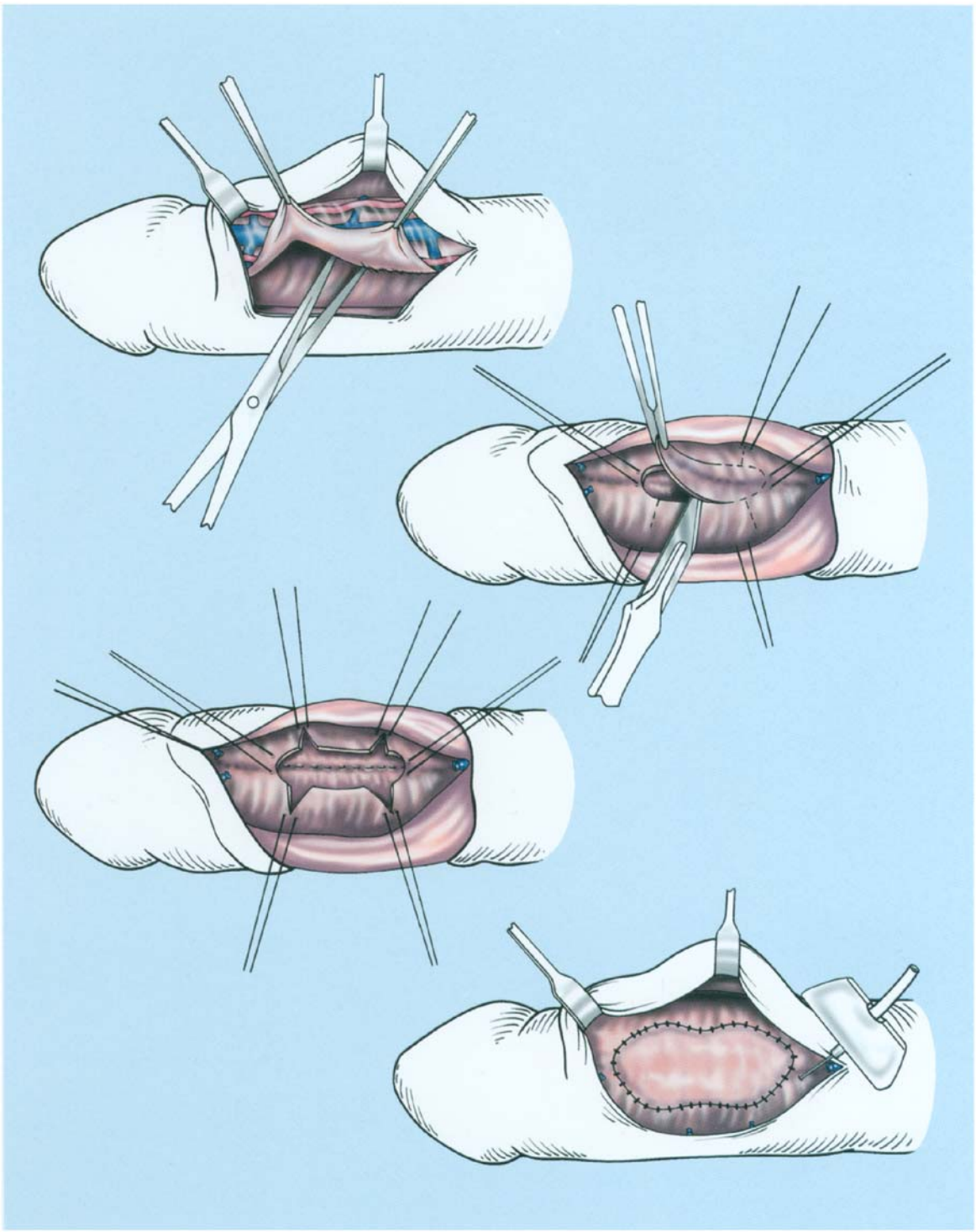

Figure 92 Another procedure to correct penile curvature due to Peyronie's disease without associated penile shortening involves dissection of the dorsal neurovascular bundles from the tunica albuginea dorsally. The plaque is then excised as shown here, using a free graft of either saphenous or deep dorsal vein to fill the defect

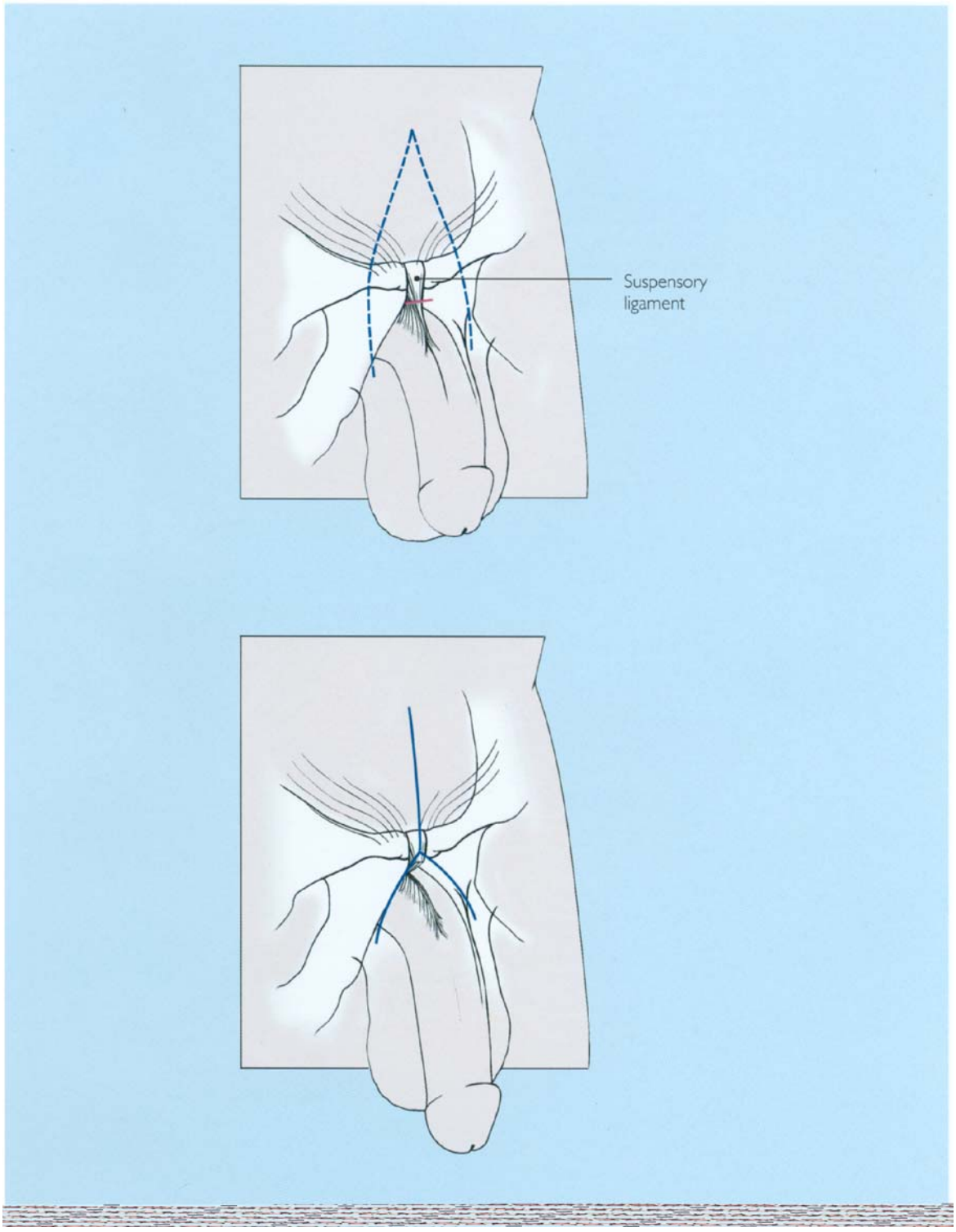

Figure 93 In this procedure to achieve apparent penile lengthening, a V-Y plasty skin incision is made to lower the penis relative to the pubis. The suspensory ligament is also divided. The result is that, although the penis appears to be longer when flaccid, there is no enhancement of organ proportions when erect

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