TEXTBOOK OF ERECTILE DYSFUNCTION

SECOND EDITION

Editors
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Second Edition

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Dedicated to my parents Culley
and Dorothy Carson and my
wife Mary Jo Carson

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Preface

While the last decade has seen enormous changes in the understanding and treatment of sexual dysfunction and erectile dysfunction, the problem of sexual dysfunction has been described since the ancients. Indeed Greek cup paintings, the Old Testament, Hindus, and ancient Chinese have all described sexual problems. Treatments from surgery, herbs, spices, and potions have all been suggested as remedies. The more modern song describing 'Love Potion Number 9' and the search for 'Spanish Fly' both detail these remedies and their promise of resolution of sexual and erectile dysfunction.

Beginning with Kinsey in 1948 and through Masters and Johnson in the 1960s, the epidemiology and behavioral treatment model has flourished before specific tested medical methods had been developed. Simultaneously, surgeons attempted to recreate the os penis of lower animal forms with surgical procedures beginning with transplanted rib cartilage and proceeding through latex to the currently used silicone elastomer. It has been just three decades since the first functional, safe, and satisfactory penile implant has been introduced.

The true revolution in treatment and patient acceptance, however, began with the marketing of the first phosphodiesterase type 5 inhibitor (PDE-5), sildenafil, in 1998. This revolution was not only scientific and medical, but also societal. Once these PDE-5 inhibitors were available, the international acceptance of the diagnosis and treatment of erectile dysfunction assumed titanic proportions. Subjects confined to the back rooms were suddenly dinner party conversation and the media were rife with reports, debates, and discussion of the treatment of erectile dysfunction and, by extension, sexual dysfunction in both men and women. That landscape continues today and the management of sexual dysfunction has enlarged from strict erectile problems to include premature ejaculation, hypogonadism, and female sexual dysfunction.

This second edition of *The Textbook of Erectile Dysfunction* marks many of those advances. While the first edition included only moderate discussion of the medical treatment of sexual dysfunction and its causes, this edition moves into a higher level of discussion with subjects such as the basic science approach to erection and sexual investigation, a more refined review of the PDE-5 inhibitors including newer agents, and a discussion of central nervous system agents, their advantages, and disadvantages. There is also a complete discussion of the surgical approach to sexual problems including priapism, Peyronie's disease, and penile implants. The authors of these chapters are chosen from among the world's experts in this growing field and are each uniquely qualified for reporting on their area of interest. This edition provides a single source for up-to-date information on sexual dysfunction from history to basic science to treatment options.

The editors would like to express their sincere appreciation to all the contributors for their time, efforts, and expertise. Without these efforts this textbook could not have become a reality. We would also like to acknowledge the assistance of the editorial staff who have taken difficult manuscripts and transformed them into complete, understandable, and readable chapters.

C Carson, R Kirby, I Goldstein, M Wyllie
October 2008

1 The history of erectile dysfunction

Sachin Agrawal and William D Dunsmuir

Introduction

Throughout antiquity, erectile function has symbolized virility and manhood. Erections are special to the human male, since in most animals copulation is quick. In the rat, erection and ejaculation are almost simultaneous reflex events. In the dog, copulation lasts around 20 seconds. Even the African ostrich, renowned for his ostentatious courtship displays, completes the act within a minute.[1] Throughout nature, strategies have evolved to facilitate penetration. Mammals like the walrus, whale, and orangutan have ossified penile shafts. This os penis, os priapi, or baculum measures up to 3.5 m. However, for some species, survival does not depend on speed. Indeed, the protraction of sex has evolved perhaps solely in humans. Erectile dysfunction has been ever-present, with modern medical practice evolving through observation, experimentation, and refinement of ancient remedies. This chapter examines its impact, tracing its history from antiquity to the present day.

The impact of impotence through the ages

Impotence has influenced society in two ways: through its association with humiliation and through its influence on the validity of marriage. 'Non-consummation' claims were frequently used for annulment, these often leveled at the male. Furthermore, humiliation was a powerful form of social control. Many men were ridiculed and destroyed by the public exposure of their impotence. By the 16th century, ecclesiastic trials were widespread. Juries comprising theologians, physicians, and midwives demanded that the accused 'prove himself'. Galleries delighted at these civic displays of voyeurism, with trial reports distributed in the thousands. So great was public exhilaration and fear generated that these courts bestowed tremendous power to the medieval Church (Figure 1.1).[2] Only the struggle for power between the Church and State in France (around 1677) led to abolition of these shameful rituals.[3] However, the relationship between law, the Church and the medical professions remained unclear. In 1896, the Illinois Supreme Court annulled a marriage on the basis of impotence, with a doctor being called to give evidence.[4] This raised an ethical dilemma regarding the professional code of confidence. The doctor eventually testified that excessive masturbation had caused impotence. In this bizarre case, the court ruled that the doctor 'oversee' the defendant's attempts at self-restraint to assess the condition's curability. The law subsequently changed, introducing the term 'naturally impotent' into the statute, making cause immaterial. To this day, impotence remains grounds for annulment.

Since ancient times, the fear of humiliation and concealment has colored the literature. In *Satyricon* by Petronius, Encolpius was damned to impotence for desecrating the rites of Priapus (the god of fertility). Having been rendered impotent, he was then humiliated by being forced into a public orgy with the priestess Quartilla.[5] Exposing the afflicted has forever been of public interest. Take the 19th century English writer and reformer, John Ruskin: his marriage was publicly dissolved on grounds of non-consummation. Ruskin suffered a mental breakdown and retreated into isolation.[6] As with so many men, the loss of potency led to the loss of self-worth. Indeed, the presumed impotence and inability of the last Spanish Hapsburg, Don Carlos II (1661–1700), to provide an heir led to the War of Spanish Succession. It is not surprising that so much time and energy has been spent in finding a cure.

Aphrodisiacs and antiquity

Aphrodisiacs derive their name from Aphrodite, the Greek goddess of love. Since antiquity they have increased sexual drive and pleasure, with many purported to help erectile function. Some may have originated by correcting nutritional deficiencies and improving health. Oysters are rich in zinc, rhinoceros horn contains calcium and amino acids, and chocolate has magnesium and phenylethylamine. Other aphrodisiacs resembled sexual organs, such as the mandrake and the penis or oysters and the ovaries. The majority heightened physical and sexual awareness, indirectly affecting erectile function. Many bizarre remedies exist, including bear's gall bladder, shark's fin, powdered lizard, snake's blood, fermented leeches (massaged into the penis), and the skin and glands of the Bufo toad (which contains bufotenine, a hallucinogenic known as chan su in Chinese medicine).[7] Man's desire has also led to many species of animals being added to the endangered list: powdered rhinoceros horn can cost $27,000 per pound,[8] and in Asia dried tiger penis soup costs $350.[9]

Figure 1.1 Medieval Church Court trial. (Reproduced courtesy of Wilma Cluness.)

The Spanish fly was probably the most dangerous aphrodisiac; it was used by the Romans and mentioned in the 15th century Arabic text *The Perfumed Garden for the Soul's Delectation*.[10] Made from dried beetle, it was actually poisonous, containing as it did cantharadin. It acted by irritating the urogenital tract, causing vasodilatation. Side-effects included infections, scarring, priaprism, and even death.

Alcohol is amongst the oldest aphrodisiacs. The Romans believed it increased libido, so much so that they forbade women from drinking it. Absinthe was considered a stimulant, extracted from wormwood; it contained thujol and thujon essential oils and other toxic compounds. It can cause blindness and neurological problems and has been banned in its original form in most of Europe since the early years of the 20th century.

Aphrodisiacs, including alcohol, amphetamines, and marijuana, increase libido and heighten sexual pleasure when used in low doses by reducing anxiety, by neuro-modulation, or by their hallucinogenic effects. Marijuana use was mentioned in Garcia de Orta's *Colloquies on the Simples and Drugs of India*.[11] Recently, cocaine has been the aphrodisiac of choice. It reduces norepinephrine reuptake within the brain, prolonging norepinephrine effects in the synapses.

While many remedies have been lost, some, including plant-based aphrodisiacs such as ginseng and yohimbine, remain popular. Many now have scientifically proven mechanisms of action. Yohimbine, an alpha-2-adrenergic receptor antagonist, is the main alkaloid from the bark of the west African tree *Pausinystalia yohimbe*. These receptors are found in the abdomen, pelvis, and sex organs and are docked with epinephrine. In a normal erection, nerve impulses displace this epinephrine, and yohimbine displaces epinephrine by interfering with this docking. Higher doses cause a rapid heart rate, high blood pressure, anxiety, and over-stimulation. Yohimbine acts as a dual aphrodisiac: it directly affects erections and it heightens arousal. Unfortunately this epinephrine release is a double-edged sword, since higher doses cause a blood shift away from genitalia, making an erection almost impossible. Cocaine and amphetamines also exhibit this feature and can lead to penile shrinkage. Recent reviews suggest yohimbine allows satisfactory erections in 30% of patients versus 14% with placebo.[12] Ambergris, a rare fat-like substance from whales, is cited in Arabic folklore as a powerful aphrodisiac. In rats it increases testosterone and copulatory behavior.[13] Opium poppies have been found to contain papaverine; its mechanism is not fully understood, but it is thought to inhibit phosphodiesterase.

In India, urological ailments were first described around 3000 BC (the Vedic period), peaking during the 9th century BC. Ayurvedic medicine was outlined in the six volumes of the *Charaka Samitha*. Susrata described systemic surgery in the *Susrata Samitha*, a text that was translated into Arabic and Latin, later forming part of European medicine as described by Hunter.[14] Both of these works described urological conditions, and *Susrata Samitha* described several surgical instruments. Ayurveda described erectile dysfunction as treatable throughout all ages. The treatment, vaji karana, involved physical, psychological, and herbal preparations. *Susrata Samitha* states that this treatment 'makes a man sexually strong as a horse (vaji) and enables him to cheerfully satisfy the heat and amorous ardors of young maidens'.[15]

In ancient Egyptian texts, the *Book of the Dead* mentions *Nymphaea caerulea* (the blue lotus) being used as a sexual adjunct and hallucinogenic in religious rituals.[16] It contains apomorphine (a centrally acting dopamine agonist that causes smooth muscle relaxation) and aporphine (which is hydroxylated to apomorphine in the body). In studies, apomorphine hydrochloride is more effective than placebo but clearly less effective than phosphodiesterase type 5 (PDE-5) inhibitors.[17] In the UK apomorphine hydrochloride was discontinued in 2005 for commercial reasons, and it will probably be confined to history. In the Ebers papyrus (prescription 663), weakness of the penis, was called 'grapo' and 37 drugs, including honey, were recommended in its treatment.[18]

Antiquity to Enlightenment

In ancient times, agriculture, animal husbandry, and human fertility were linked by religious ritual. The gods of harvest were worshiped with phallic icons, and impotent men turned to the priesthood. Ancient Greeks prayed to Aphrodite, and the Bible describes impotence as divine retribution. In Genesis, God rendered Abimelech impotent for sleeping

with Abraham's wife.[19] Folklore said that God allowed the devil power over the genitals. In medieval times, people believed that if a witch tied a knot in a strip of leather, it empowered the devil to strike a man impotent.[20] We can only guess how many women were persecuted for men's sexual failings.

Hippocrates (460–370 BC) stated that 'pneuma' (air) and 'vital spirits' flowing into the penis generated erections and that impotence was caused by imbalances between the humors (blood, phlegm, yellow bile, and black bile) and the elements (earth, air, fire, and water). He believed that sexual excess reduced potency (a theme explored many times since) and that fine cords facilitated erection, rather like a system of 'pulleys' connecting the penis and testis. Damage to these fine cords, as occurred with castration, profoundly affected erectile capability.[21] Hippocrates' teachings pervaded Western medicine until the Renaissance, when increased anatomical and scientific knowledge challenged 'classical' models. Leonardo da Vinci (1452–1519) observed that men executed by hanging developed reflex erections. Examining these, he found that they contained blood, not air.[3] In 1677, Reiner de Graaf demonstrated that injecting water into the internal iliac artery generated erections in human cadavers.[22] In 1573, Varilo stated that the ischiocavernosus and bulbospongiosus (or bulbocavernosus) muscles impeded venous return by constricting the root of the penis. Eckhard, in 1863, electrically stimulated pelvic nerves (the nervi erigentes) in a dog, inducing tumescence, thus demonstrating a neurovascular component.[23] During the Victorian period (1837–1901), impotence was widely debated (see below), and treatments included quinine, opium, digitalis, and cold salt water sponging as well as more drastic measures such as scarification of the perineum, blood-letting, and the passage of a mercury-covered boogie into the urethra.[9,24]

The 19th to mid-20th centuries

During the 19th century three schools of thought developed regarding the endocrinology, psychology, and pathology of erectile dysfunction. How these schools evolved, clashed, and fused is explored here.

The endocrine debate

The association between the testis, male behavior, potency, and fertility has probably been recognized since castration started. Neolithic tribes in Asia Minor castrated animals for domestication as early as 4000 BC. In humans, castration probably originated in Babylon in the second millennium BC, to safeguard against adultery.[25] Castration was also practiced for other reasons. The Christian priesthood (ca 3rd century AD) practiced voluntary castration to help self-imposed religious celibacy. Many civilizations regularly castrated slaves to suppress rebellion. Castration was widespread in the eastern Roman Empire, where its critical timing and effects on potency were understood. Boys castrated before puberty were recognizably 'eunchnoid', usually with docile personalities. Castrati were also infertile, making ideal guardians for the harems.

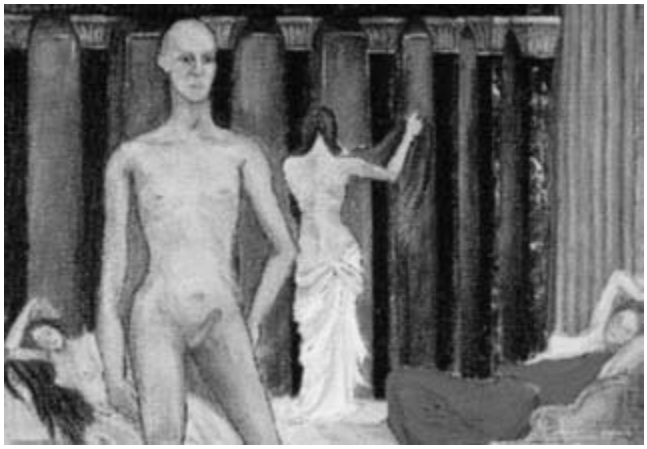


Figure 1.2 Eunuchs were sexually active in the ancient Roman harems. (Reproduced courtesy of Paula Day.)

However, the notion that castration ensured impotence was far from true. The females of the Roman harems found eunuchs made novel playmates, their sexual prowess often intact with guaranteed contraception (Figure 1.2). Additionally, early Christian choristers, gelded in their youth to ensure their voices were retained, frequently lived sexually active lives. Indeed, Italian literature is replete with stories of castrati and their sexual cavorting. Castration still occurs in India, the Middle East, and China, with its effect on potency now more clearly understood. The Hijaras are an Indian sect of males, convinced (or coerced) into castration. They function as transvestite male prostitutes, many potent, who indulge in sexual paraphilia.[26] Castration for sex crimes was practiced until recently in Europe. Heim reported that 31% of such men remained potent following emasculation and that rapists were more likely to be sexually active than homosexuals or pedophiles.[27] In prostate cancer, 19% of men who undergo surgical or chemical castration will remain potent.[28] Clearly, castration does not always result in impotence.

However, the influence of the testes on sexual behavior is more complex. Even ancient civilizations realized that it influenced potency and libido, with testicles frequently proposed as an impotence cure. Susruta (around 500 BC) advocated the ingestion of testicular tissue to treat impotence.[25] In 1889, Brown-Séquard reported himself 'rejuvenated and cured of impotence' following self-injection of aqueous canine testicular extract.[29] Berthold (in 1849) demonstrated a clear androgenic role for the testes. He castrated roosters, causing regression of the comb and wattle, but showed that transplanting testes back into the abdominal cavity prevented this.[30] Defining testicular function caused confusion for the next 100 years. The problem was twofold: crude methodology and man's desperation led to many erroneous practices. For example, despite Astley Cooper's sound scientific work (published in 1823) showing that spermatogenesis and testicular function were unaffected by ligation of the vasa,[31] Ancel and Bouin (in 1904) reported different results for the same experiments, claiming that ligation of the vas deferens caused sperm cell atrophy with concomitant Leydig cell

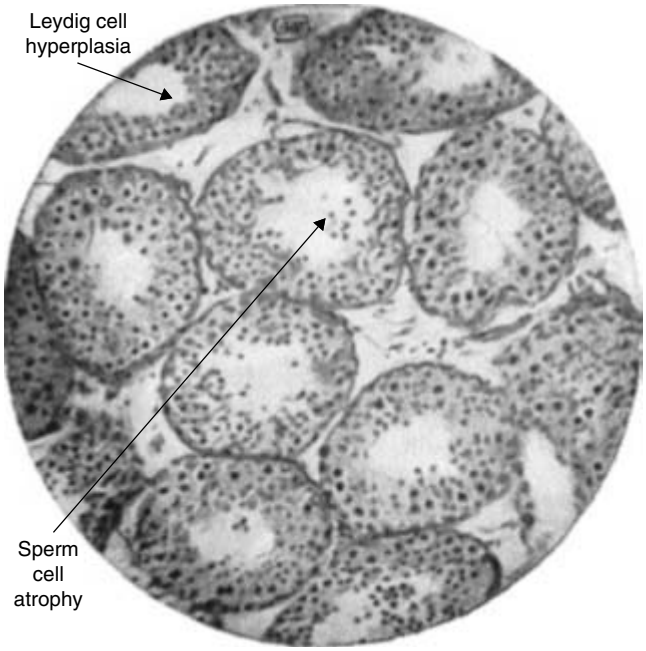


Figure 1.3 Sperm cell atrophy and Leydig cell hyperplasia, as described in C R Soc Biol (Paris) 1904; 56: 281–2.[32]

hyperplasia and suggesting that ligation might increase endogenous male hormone production, benefiting potency and health (Figure 1.3).[32]

The excitement generated from these findings led many doctors to propose this as an impotence cure. In 1917, the Austrian surgeon and physiologist Professor Steinach (1861–1944) seemingly provided evidence of marked 'rejuvenation' in aging rams after vasoligation. Encouraged, he applied this principle to humans, performing numerous procedures on impotent men. Sigmund Freud and William Yeats are thought to be amongst them.[33] More alarming were the techniques of Voronoff (1866–1951)[34] in France and Lespinasse[35] in Chicago (Figure 1.4). They transplanted testicular grafts from apes directly into the human testis or the subtunical space (Figure 1.5). In 1918, Dr Leo Stanley, a Californian prison physician, reported improving impotence. He used pressurized syringes to implant strips of testicles from goats, rams, deer, and even dead inmates' testicles. The testicles were implanted under the abdominal skin of 1000 inmates.[9,36] Despite initial claims, these techniques did not restore the 'fountain of youth' or cure impotence. In the 1930s, many clinicians challenged the credibility of the 'rejuvenists'.[37] In 1934, TE Hammond gave one of the most eloquent and ferocious challenges in the *British Journal of Urology*.[38] He reviewed his own series of castrati, men who had lost both testes through accident or tuberculosis. He reported that they were potent and questioned the role of the testicles in erectile physiology. Furthermore, in the early 20th century, castration and vasoligation were used to treat symptoms of prostate enlargement. Naturally, proponents stressed that impotence was an infrequent complication.[39,40] The lack of efficacy of both methods, on both prostatic shrinkage and erectile function, were documented long before 'rejuvenating' operations became fashionable.[41] Clearly, the profession was in a mess.

Scientific studies gradually clarified male genitourinary and reproductive physiology.[42] In 1934, WE Lower cleverly demonstrated pituitary gonadotrophic control of the testes. By creating a peritoneal anastomosis between two rabbits (coelenteral fusion), he developed an experimental model where he selectively ablated the endocrine system at different levels, conclusively showing that prostatic, erectile, and testicular function were under pituitary control (Figure 1.6).[43] Furthermore, in 1931, Butenandt[44] succeeded in isolating 15 mg of androsterone from 25,000 liters of policemen's urine. The synthesis of testosterone from cholesterol followed, performed by Ruzicka[45] in 1935. Both men shared the 1939 Nobel Prize for chemistry, spawning an industry around the development and consumption of anabolic androgenic steroids, legally and illegally. This industry's expansion enabled a greater understanding of how endocrine agents affect erectile and sexual function. Factors included dose, administration and circumstances but, in general, hormone supplementation rarely improves erectile function.[21] The overall role of androgens in erectile function is still poorly understood, but in the early 20th century, this only added to the confusion caused by the other two great controversies, the organic and psychogenic debates.

The 'organic' versus 'psychogenic' debate

During the late 19th and early 20th centuries, proponents of the 'organic' and 'psychogenic' schools frequently clashed in acrimonious debate. Sigmund Freud founded the discipline of psychoanalysis in the late 19th century. His followers explained impotence in terms of regression of unresolved conflicts. Freud believed that healthy psychological development required the experience of an Oedipus complex during infant sexual development – the erotic attachment of a child to the parent of opposite sex, coinciding with hostility towards the other parent. In later adult life, transference of these feelings to a new sexual partner could result in inner conflict and erectile dysfunction. Many psychiatrists championed psychoanalysis, but treatment was realistically available only to the rich. For most men seeking medical help, the general advice was 'resensitization' through long periods of abstinence. Excessive masturbation was cited by many doctors as a cause, creating great anxiety among the youth, who feared they would 'fail' in later life.[46] In 1927, psychoanalysts that reported repressed sexuality caused over 95% of cases of impotence[47] and designed special anti-masturbatory devices (Figure 1.7). In 1934, New York psychiatrists effectively declared 'open war' with urologists. In a statement, they urged general practitioners not to refer patients to urologists, and fuelled a bitter debate that raged in the medical literature. Psychiatrists accused urologists of charlatanism, and urologists defended their practice with elaborate descriptions of the pathology they claimed to observe.[48]

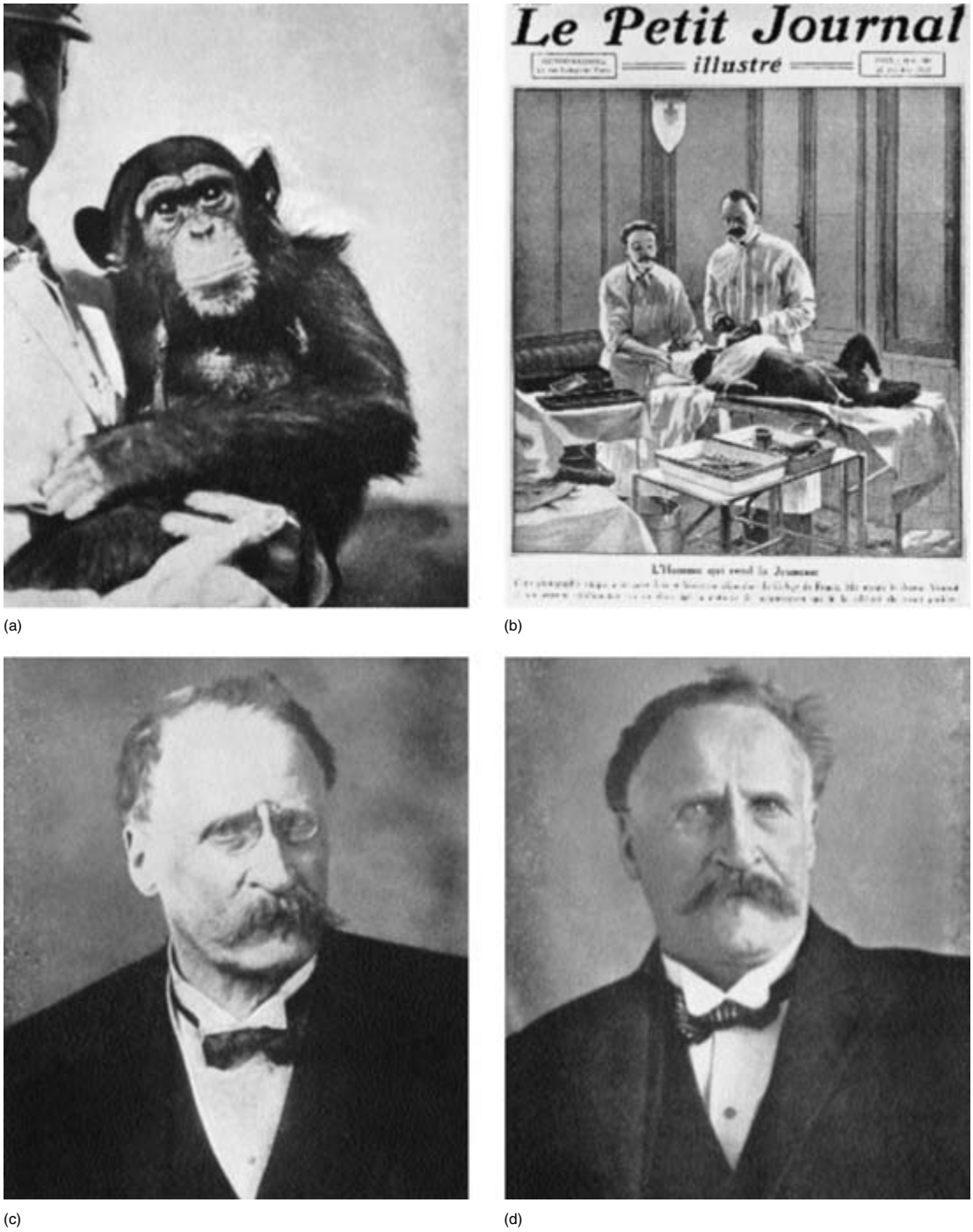


Figure 1.4 (a) Voronoff with his monkey. (Reproduced from Chadwick AJ, Mann WN, eds. Hippocratic Writings. London: Penguin, 1987, with permission.) (b) Voronoff performs testicular transplantation from a monkey to man. (c, d) As witnessed by his countenance, an elderly man is markedly rejuvenated following testicular transplantation. (Reproduced from Voronoff S. Rejuvenation by Grafting. London: George Allen and Unwin, 1925, with permission.)

Thomas Curling's classic publication in 1878 summarized factors thought to be important.[49] He described numerous pathologies, venereal disease in particular, and was probably amongst the first to connect impotence, diabetes, and Peyronnie's disease. More importantly, he described the cystoscopic appearances of the verumontanum. Many urologists frequently observed inflamed swellings of this posterior urethral structure in patients with erectile failure. Wolbarst reviewed 300 cases of impotence and claimed that 87% of patients had pathological posterior urethral changes.[50] Max Huhner eloquently summarized its significance in 1936, mounting a sterling defense of urological practice.[51] Huhner described perpetual prostatic 'irritation' caused by these urethral swellings, resulting in a constant desire for

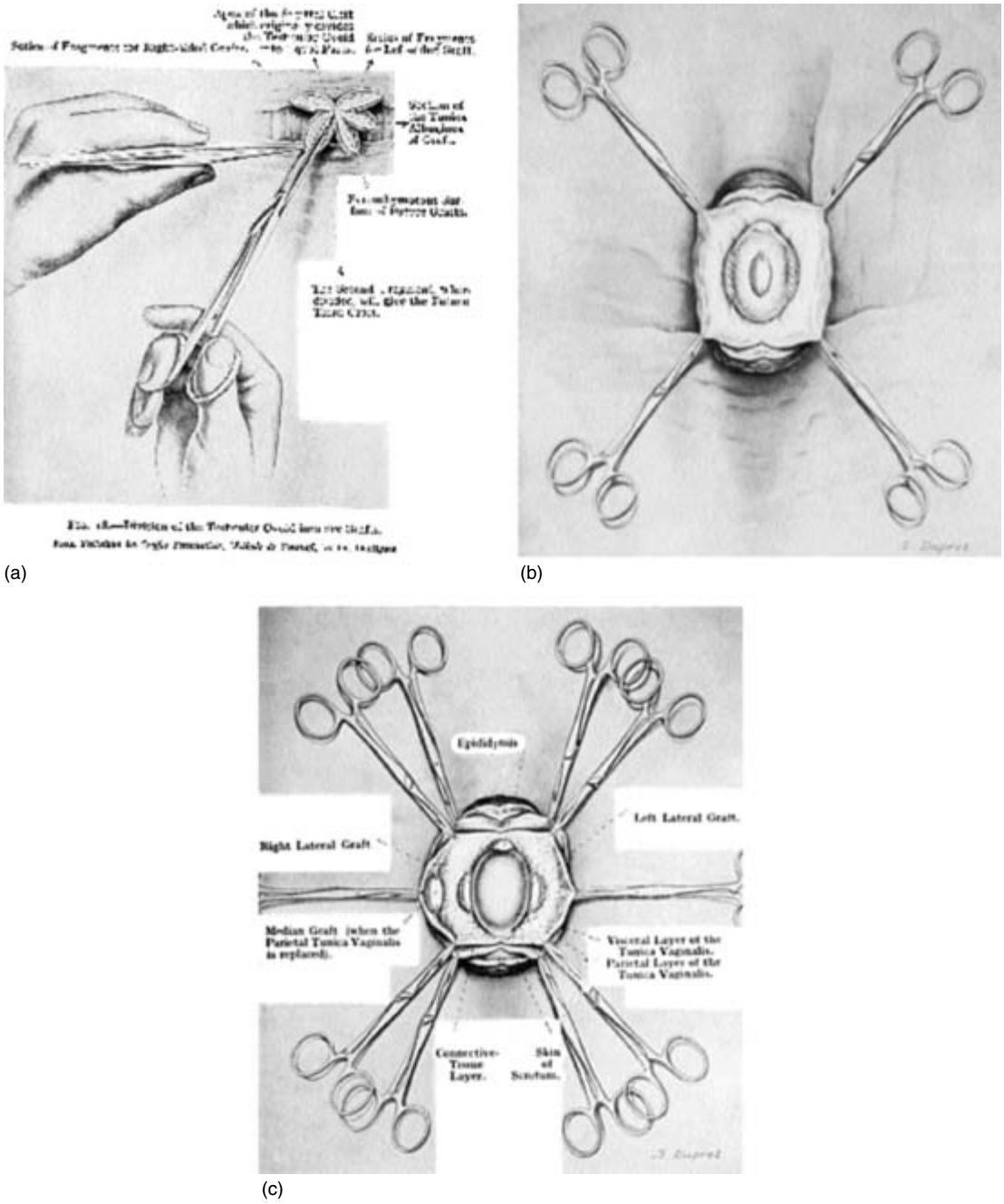


Figure 1.5 (a, b) Direct grafting into the tunica albuginea. (c) Grafting into the subtunical space. (Reproduced from Voronoff S. Rejuvenation by Grafting. London: George Allen and Unwin, 1925, with permission.)

sexual excess. Men would indulge too frequently in coitus or masturbation and desensitize their erectile centers, causing impotence (Figure 1.8).[51] Common urological treatments included cauterization of the posterior prostatic urethra along with the urethral instillation of cantharides.[51] Psychiatrists including Hammond[52] and urologists like Curling[49] attempted to resensitize erectile centers. They applied faradic electrical current to the penis, prostatic urethra, and spinal cord (Figure 1.9).

Most treatments were disappointing. Psychoanalysis, aphrodisiacs, vasoligation, testicular grafting, forced abstinence, and desensitization (by whatever method) helped but a few people. More practical devices such as suction pumps and penile supports (scaffolds) were introduced in the 20th century (Figure 1.10). Many were patented, and some sold by the thousand.[53] Various surgical techniques were tried. Wooten,[54] in 1902, advocated dorsal vein ligation to retard outward penile blood flow. Lilienthal championed this in the 1930s.[51] Further attempts to impede outflow included ischiocavernosal muscle plication by Lowsley and Bray (1936)[55] (Figure 1.11). Despite claims of great success, this last-named procedure has passed into obscurity,

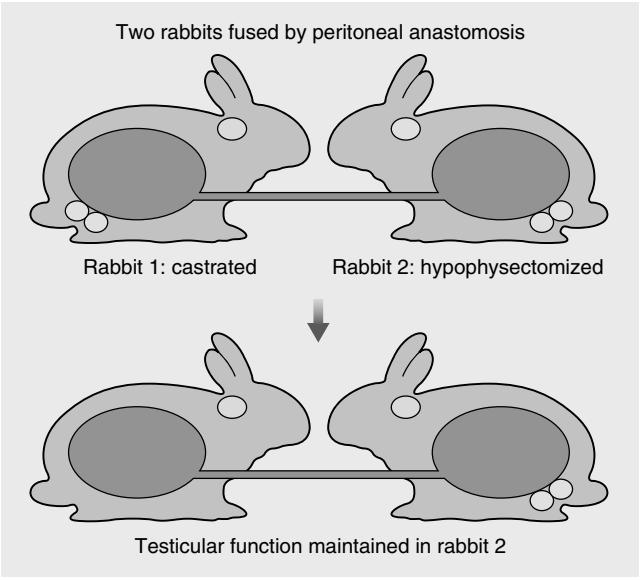


Figure 1.6 The ingenious coelenteral fusion model of WE Lower.[43]

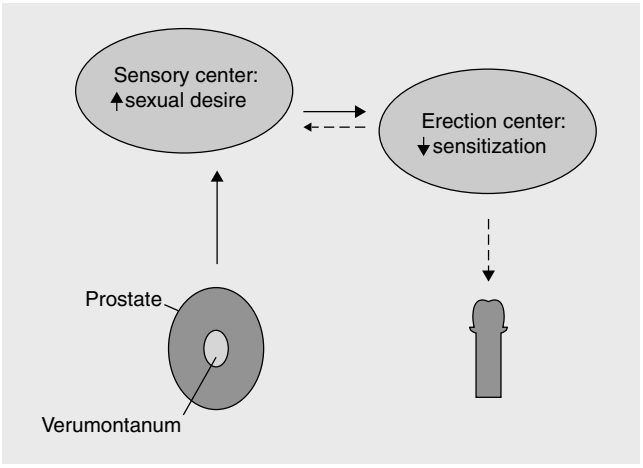


Figure 1.8 Perpetual prostatic irritation resulting in desentization of the erectile centers. (Adapted from J Urol 1936; 36: 770–84, with permission.)

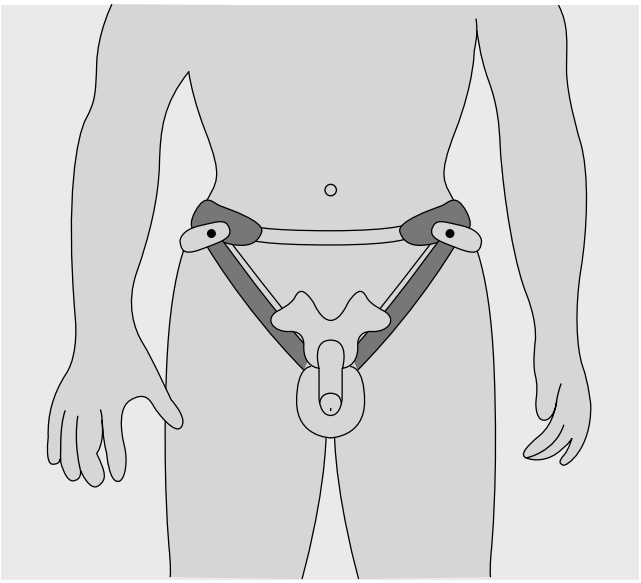


Figure 1.7 Anti-masturbatory device.

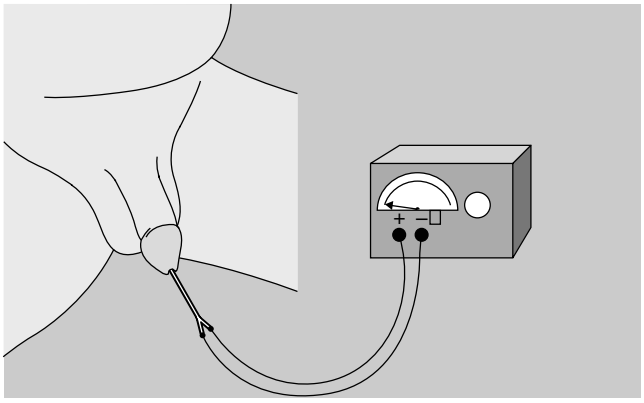


Figure 1.9 Faradic electrical desensitization of the verumontanum.

though dorsal vein ligation has drifted in and out of fashion ever since.

Plastics, prosthetics, pumps and pills

During the Second World War, many pilots and soldiers lost genitalia through burns and land mines. This saw plastic surgical penile reconstruction develop in the post-war period. Gills and Borgoras were the pioneers, the latter using rib cartilage in 1936 to allow successful micturition and intercourse.[56]

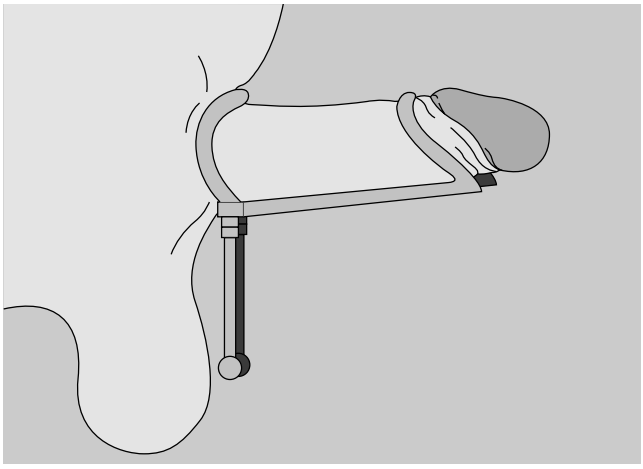
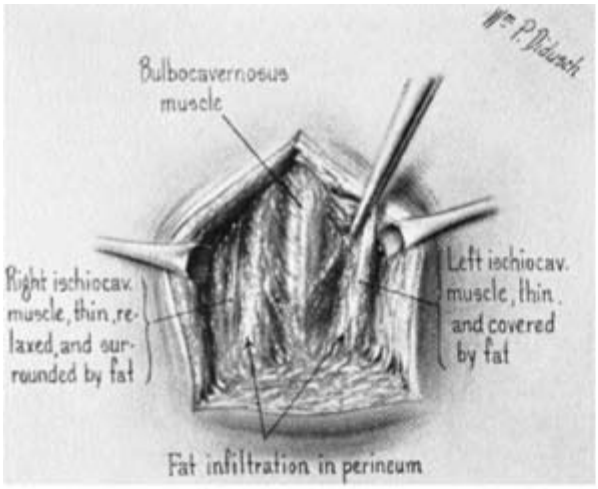
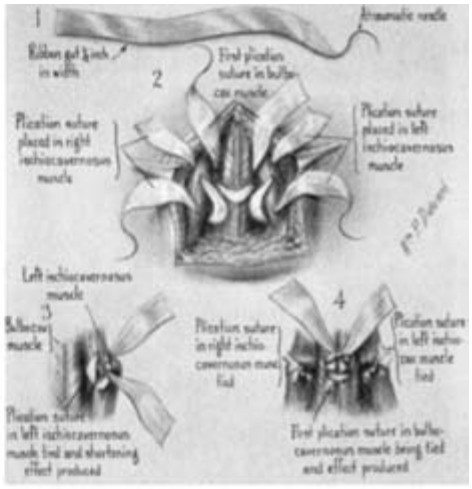


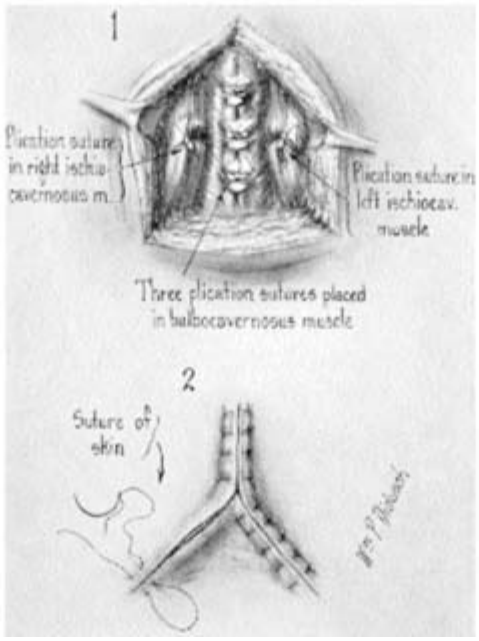
Figure 1.10 Penile scaffold.



(a)



(b)



(c)

Figure 1.11 (a, b) Ischiocavernosal muscle plication of Lowsley and Bray. (c) Plication is complete. (Reproduced from Zentralbl Chir 1936; 63: 1271–6, with permission.)

In 1948 Bergman fashioned a new penis over an autografted rib cartilage (Figure 1.12).[57] These techniques were extended to treat impotence, but had limited success, owing to eventual cartilage reabsorption. However, they heralded prosthetic implant surgery. In 1964, Loeffler reported the insertion of acrylic rods into the penis to treat impotence.[58] Beheri independently performed 700 cases in Egypt in 1966.[59] The original technique described the rods being placed between the tunica and Buck's fascia, but they were later placed intracavernosally because the initial technique caused pain. Subsequently, numerous and more sophisticated devices have been designed and are commonly used, including newer self-erectable prostheses.

The post-war period was also a time of changing attitudes. Male sexual dysfunction had previously been taboo and free discussion had been repressed. Lesley Hall remarked that even sad heroes of 20th-century literary works – Hemingway's Jake Barnes in *The Sun Also Rises* and DH Lawrence's Clifford Chatterley in *Lady Chatterley's Lover* sustained impotence as unfortunate victims of war.[6] People were uncomfortable identifying with men who had lost their 'manliness'. The Kinsey Report (1948) highlighted the widespread prevalence of this problem.[60] Attitudes changed slowly, but openness evolved, with more men seeking help.

The 1960s and 1970s heralded the arrival of Masters and Johnson[61] and Helen Kaplan[62] and a renaissance of

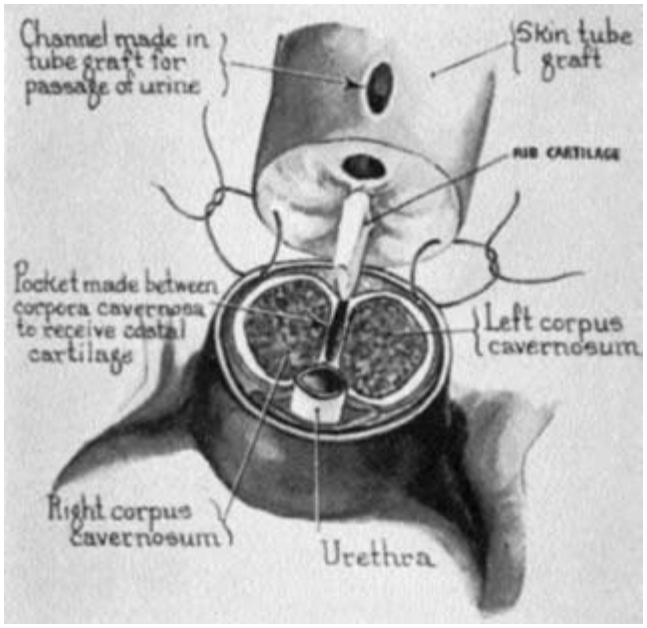


Figure 1.12 Autograft of rib cartilage. (Reproduced from JAMA 1948; 59: 1174–80, with permission.)

'new sexual therapies'. In 1982, Virag[63] and Brindley[64] introduced the effective intracavernosal agents, papaverine and phentolamine, respectively. In the 1970s, Geddings Osbon created the ErecAid, noting that vacuum devices could cause an erection. The prototype was based on a bicycle pump; currently a number of models are available, providing good results.[9] Prostaglandins and other agents have recently been added to the therapeutic armory. The development of erectile tissue-specific PDE-5 inhibitors has made effective oral agents a reality. Sildenafil citrate, the first PDE-5 inhibitor, was released by Pfizer in 1998; it originated as a drug for heart failure but was observed to cause erections. Newer PDE-5 inhibitors, such as vardenafil and taldenafil, have subsequently been introduced.

The history of erectile dysfunction is ongoing and new chapters are being written, with newer therapies replacing older ones. Increasingly, surgeons, physicians, and psychologists work together in multidisciplinary teams to tackle the multifactorial nature of erectile dysfunction. A great deal has been achieved since the days when men prayed to Aphrodite for deliverance. Many causes have been identified and defined. However, for those affected, the feeling of destruction remains, with solutions still imperfect and limited.

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2 The history of the International Society for Sexual Medicine

Ronald W Lewis and Gorm Wagner

Biennial meetings and structure of the organization

The founding of the International Society for Sexual Medicine can be traced back to a couple of meetings that were held in 1978 and 1980. Dr Adrian Zorgniotti, a urologist with a vision for the future for sexual medicine, became aware of some unique reports on the work of a vascular surgeon, Vaclav Michal (Prague, Czechoslovakia), regarding his success stories on restoration of erectile function in patients having pelvic vascular reconstruction. These surgeries had led him to propose revascularization of the corpora cavernosa directly by anastomosis of the inferior epigastric artery to the corpus tissue.[1] Zorgniotti, along with his colleague Dr Guiseppe Rossi, decided to host a meeting at their home institution, Cabrini Medical Center, in New York City, in the fall of 1978. Two other groups were also invited to be a focus of the meeting. Dr Jean François Ginestié (Montpelier, France) was the main presenter for two radiologists who had developed exquisite internal pudendal arteriography studies; and Gorm Wagner (Copenhagen, Denmark) was the presenter for a multidisciplinary group involved in unique diagnostic tests for erectile dysfunction (ED). The interest was so keen after this meeting that it was decided to reassemble after 2 years to see where the science would go. Some of the presentations at this meeting led to the publication of a book, *Vascular Impotence: Proceedings of the First International Conference on Corpus Cavernosum Revascularization.*[2]

The second meeting, entitled The Second International Meeting on Corpus Cavernosum Revascularization, took place in October 1980 in Monaco. At this meeting the group of international physicians and scientists focused on alternatives to vascular surgery for ED. A series of articles that focus on the meetings of this society is being prepared by the authors of this book chapter. The first such article, dealing with the details of these first two meetings, called 'The Beginnings', will be published in the *Journal of Sexual Medicine.*[3] The breath of developing science in this field can be found in the subjects discussed at these meetings, which included:

- Doppler evaluations of penile arteries
- Unique blood flow measurement by clearance method in the human corpora cavernosa
- Incorporation of visual sex stimulation in the evaluation of ED
- Measurement of bulbocavernosal latency test
- Early effects of oral atropine, alpha-blockers, and beta-blockers on human penile erection
- Techniques and pitfalls of phallography (which would become cavernosography)
- Anatomic basis of the corpora cavernosa
- Pudendal arteriography
- Microvascular surgery techniques
- The results of treatment of other vascular disease in the pelvis as it relates to postoperative sexual dysfunction
- A very unusual case of a congenital shunt between the corpora cavernosa and the glans of the penis
- Some of the early problems with surgery for arterial vascularization
- A discussion of the drainage system of the penis and how that might be involved with erection
- Complications of the then current vascular surgery.

Zorgniotti and Wagner planned a closed symposium at the meeting in Monaco, inviting key physicians and surgeons involved in cutting-edge research in the field of ED in order to develop agendas for intensified research in this field, possible co-operative research protocols, and areas for future meetings. At the close of the meeting in Monaco, Wagner invited the next meeting to be held in Copenhagen 2 years later.

In their frequent correspondence, Wagner and Zorgniotti continued discussing a name for this developing group. They had truly become the nucleus for these international meetings and at the 1982 meeting in Copenhagen, Denmark, the group decided on a name for the organization: The International Society for Impotence Research (ISIR). The meeting in Copenhagen was still labeled as the Third International Symposium on Corpus Cavernosum Revascularization.

It was at the Copenhagen meeting that the idea of an international biennial meeting was solidified, and it was decided that the 1984 meeting would be held in Paris, France. It was to be hosted by Dr Ronald Virag, a vascular surgeon who had been very active in developing unique techniques for corpus cavernosum revascularization, which he had initially presented at the meeting in Monaco. He was the first to call this biennial meeting the World Meeting on Impotence, and hence his meeting was the first with such a title. He also published a book after the meeting with papers requested and received that represented data presented at the meeting.[4]

Table 2.1 Biennial Meetings of the Society

Symposia on Corpus Cavernosum Revascularization		
Year	**Place**	**Major host**
1978	New York	Adrian Zorgniotti
1980	Monaco	Adrian Zorgniotti and Gorm Wagner
1982	Copenhagen	Gorm Wagner
Symposia on Corpus Cavernosum Revascularization World Meetings on Impotence Research		
Year	**Place**	**Major host**
1984	Paris	Ronald Virag
1986	Prague	Vaclav Michal
1988	Boston	Robert Krane and Irwin Goldstein
1990	Rio de Janeiro	Pedro Puech-Leao and Sydney Glina
1992	Milan	Eduardo Austoni
1994	Singapore	Ganesan Adaikan
1996	San Francisco	Tom Lue
1998	Amsterdam	Eric Meuleman
2000	Perth	Carolyn Earle and Bronwyn Stuckey
World Conferences of the ISSIR or ISSM		
Year	**Place**	**Major host**
2002	Montreal	Jeremy Heaton
2004	Buenos Aires	Edgardo Becher
2006	Cairo	Khaled Dabees

Table 2.2 Officers of the Society

Presidents	
Vaclav Michal	1978–1986
Adrian Zorgniotti	1986–1988
Gorm Wagner	1988–1994
Robert Krane	1994–1998
Ronald Lewis	1998–2000
Sydney Glina	2000–2002
Jacques Buvat	2002–2004
Ganesan Adaikan	2004–2006
Ira Sharlip	2006–2008
Presidents-elect	
Ronald Lewis	1996–1998
Sydney Glina	1998–2000
Jacques Buvat	2000–2002
Ganesan Adaikan	2002–2004
Ira Sharlip	2004–2006
John Dean	2006–2008
Secretary–treasurers	
Ronald Lewis	1992–1996
Jacques Buvat	1996–2000
Secretaries	
Ira Sharlip	2000–2004
Edgardo Becher	2004–2008
Treasurer	
Eric Meuleman	2000–2006
Luca Incrocci	2006–2008

The fifth meeting was held in Prague, Czechoslovakia, in 1986 in honor of Dr Michal. It would be the Fifth Symposium on Corpus Cavernosum Revascularization and the Second World Meeting on Impotence. Injection therapy was highlighted, both at the Paris meeting and at the Prague meeting, with a new agent – prostaglandin E1 – and this received attention at the Prague meeting from Singapore, Japan, and Vienna. Thus, one of the main functions of this society was established – a biennial international meeting at which to share scientific advances in the field. Table 2.1 lists all of the meetings of the Society from 1978.

It is interesting to point out there are only three current members of this society who have attended all of the biennial meetings since 1978 and that each of them has served this society as president: Gorm Wagner (Copenhagen) – president from 1988 to 1992; Ronald Lewis (beginning attendance from New Orleans, Louisiana; then Rochester, Minnesota; now Augusta, Georgia) – president from 1998 to 2000; and Ira Sharlip (San Francisco, California with a brief stint in New Orleans, Louisiana) – president from 2006 to 2008. Table 2.2 lists the presidents, secretaries, and treasurers of the Society.

Highlights of growth of the organization include the following milestones. At the 1992 meeting the first official by-laws of the organization were adopted and the terms of office for the officers were more clearly defined. The office of secretary–treasurer was established at this meeting, originally for a term of 6 years but this was later changed to a 4-year term; Dr Ronald Lewis was elected as the first secretary–treasurer. At the 1994 meeting in Singapore, Dr Robert Krane from Boston was elected president. Dr Krane was one of the major people (along with his young colleague, Irwin Goldstein) responsible for the first meeting of this organization in the USA in 1988 – he worked to develop the ISIR as a parent organization for the developing regional organizations, including the European Society for Impotence Research, founded in 1995 (the future European Society for Sexual and Impotence Research, and then the European Society for Sexual Medicine), the Society for the Study of Impotence, founded in 1994 (to become the Society of Sexual Research of North America and then the Society of Sexual Medicine of North America), the South and Central American Society founded in 1990, which joined ISIR in 1997 (SLAI – Sociedad LatinoAmericana para el Estudio de la Impotencia, later to become the Latin American Society for Sexual Medicine); and he worked towards limited affiliations with the Asian Pacific Society for Impotence Research,

founded in 1987, and the developing African Society for Impotence Research, founded in 1997.

There was a sharing of profits from the 1994 meeting in Singapore (hosted by Dr Ganesan Adaikan) with ISIR. At the meeting in 1996 in San Francisco, California (hosted by Tom Lue and his group from the University of California, San Francisco) the first papers on a possible emerging new oral therapy for ED were presented. The group from San Francisco presented to ISIR a portion of the profits for the specific purpose of sponsoring a new award – the Tanagho Prize (see below).

At the 1998 meeting held in Amsterdam in the Netherlands, a professional organization assisted Dr Eric Meuleman in the arrangements for the meeting. The leaders of the society were so impressed that Status Plus of the Netherlands became the official business office of the society. The Dutch group hosting the 1998 meeting made a donation of $75,000 to the Adrian Zorgniotti Research Fund of the ISIR.

Dr Lewis, while he was secretary of the organization from 1992 to 1994, suggested that the office of president-elect be established and that the term of the president be limited to a 2-year stint from one biennial meeting to another. The office of secretary was also changed to a 4-year term. The by-laws were changed to reflect these changes, which allowed more of the developing leaders in the field to serve the Society as president. During his term as secretary–treasurer, Jacques Buvat consolidated the bank accounts of the organization under our registered name, as ISIR, in 1998.

At the meeting in 2000, hosted in Perth, Australia (chaired by Carolyn Earle and Dr Bronwyn Stuckey), the first sessions on female sexual dysfunction were made part of the program. In an effort to solidify this for the future, the name of the organization was changed to the International Society for Sexual and Impotence Research (ISSIR), a bridging name between the old and the final new name.

For the 2002 meeting a professional congress organizer was directly contracted by the ISSIR executive at the suggestion of the local organizer, Dr Jeremy Heaton. As a result, the largest ever contribution to the treasury from a biennial meeting of the ISSIR was made. However, it was decided that our own business office would be more efficient at running future scientific biennial meetings, and thus the 2004 meeting, held in Buenos Aires, Argentina and hosted by Dr Eduardo Becher, was run by Status Plus, our business office in the Netherlands.

During Jacques Buvat's term as president and Ira Sharlip's term as secretary, an industrial partnership board was created. The members of the industrial advisory board made significant financial contributions as unrestricted funds to the international Society, with the purpose that these funds be distributed among the four regional affiliates that participated in the plan. The European Society of Sexual Medicine decided to remain independent of this plan. In 2001 the ISSIR presented a special symposium during the European Society for Sexual and Impotence Research meeting in Rome, Italy, in order to show solidarity with its affiliated organizations. The title of the symposium was 'Molecular Mechanisms of Erectile Function'. The speakers were Dr Robert Furchgott, the 1998 Noble Prize recipient, who discovered that the nitric oxide molecule is a messenger for vital functions in the body; Dr Donald Maurice, a key researcher in phosphodiesterase physiology; and Dr Clinton Webb, a prominent smooth muscle physiologist. At the 2003 fourth biennial meeting of the African Society of Sexual and Impotence Research, the meeting was preceded by a full-day ISSIR meeting that covered three topics: education, priapism, and the influence of lifestyle on ED.

At the 2004 meeting in Buenos Aires, the society officially changed its name to the International Society for Sexual Medicine (ISSM), following the lead of two of its affiliates, which had earlier changed their names to the European Society of Sexual Medicine and the Society of Sexual Medicine of North America.

Publications and communications

The second major function of the international society has been the publication of a journal, which began in 1989, just 11 years after the first meeting in New York. The first editors were Drs Gorm Wagner and Bill Furlow (Mayo Clinic, Rochester, Minnesota). They served as co-editors-in-chief from 1989 to 1992. In 1992, Furlow resigned as editor-in-chief and was replaced by Dr Arnold Melman as the new co-editor-in-chief, along with Wagner, until 2002, leaving the journal with an impact factor of 2.7. The journal, entitled at first *The International Journal of Impotence Research*, started as a four-times-a-year publication, published and owned by Smith–Gordon and Co of London, UK. In 1995, the journal was purchased from that company by Stockton Press. Stockton Press was merged with Nature Publications Group in 2000 and thus the journal came into the ownership of this publisher. In 2003 Irwin Goldstein assumed the office of editor-in-chief of the journal, after the newly appointed Publication Committee headed by John Pryor of London interviewed a strong slate represented by this candidate and three others for the position.

In 2003, it was decided by the leadership of the ISSIR that the journal would be better suited for ownership by the Society. An attempt was made to enquire about sale of the current *International Journal of Impotence Research* to the ISSIR but Nature Publishing Group was not interested in this offer. The ISSIR then entered into a contract with Blackwell Publishing House to publish a new journal, to be called the *Journal of Sexual Medicine*. ISSIR would retain ownership of this journal and Blackwell would be the publishing partner. The entire editorial team of the *International Journal of Impotence Research* moved to the new journal, which became the official journal of the ISSIR and subsequently the ISSM and all of the five regional affiliates. In addition, in 2006 the journal became the official journal of the International Society for the Study of Women's Sexual Health. It has become the dominant journal in sexual medicine, a monthly journal from 2008; it has a recently announced first impact factor of 4.676. This was impressive from a three-volume start in 2003 to a six-volume journal for the years 2004–2007. In 2008 the journal became a monthly publication. This factor placed the journal fourth in terms of impact factor for all urological and related journals, with the *Journal of the American Society of Nephrology*, *European Urology*, and *Kidney International* as the only such journals ahead of it; the highest impact factor for journals in the andrology category were 2.183 and 2.137. In addition to Irwin

Goldstein, there are nine associate editors: Gloria Buchmann from New Brunswick, New Jersey; Ian Eardley from Leeds, UK; Annamaria Giraldi from Copenhagen, Denmark; Wayne Hellstrom from New Orleans, Louisiana; Mario Maggi from Florence, Italy; Chris McMahon from Sydney, Australia; James Pfaus from Montreal, Canada; Caroline Pukall from Kingston, Canada; and Ira Sharlip from San Francisco, California.

In August 1998, Jacques Buvat, editor, presented the first issue of the 'Newsbulletin' of the ISIR. This was to serve as a newsy communication of the happenings and events of the parent ISIR as well as the affiliates, with information concerning the officers of those organizations and summaries of meetings regarding sexual medicine. As an example of the latter function the first issue contained a take-home message of sexual medicine issues presented at the 93rd Annual Meeting of the American Urological Association in San Diego, California in 1998, prepared by Tom Lue. Luca Incrocci, who joined the editorial committee of the 'Newsbulletin' in the May 2000 issue (issue 3), and who assumed the title of associate editor in June 2001, became the new editor-in-chief of the 'Newsbulletin' with issue 9, in October 2002. Dr Hussein began to report on summaries of activities of discussions on ISSIR list in the April 2002 issue. Issue 12, in December 2003, marked the Netherlands publication of this communication.

In 2000, the new president of the ISSIR, Dr Sydney Glina, established a website committee. Jacques Buvat was named chairman of this committee. Alexandre Gilbert, the new web administrator, presented the new design of the website in issue 7 of the 'Newsbulletin' in December 2001. Dr Gregory Broderick became chairman of the website committee in the fall of 2002. At the biennial meeting of the ISSIR (during which the Society became the ISSM) in Buenos Aires, the website committee and the 'Newsbulletin' committee were combined into a single communications committee to be co-chaired by Jacques Buvat and Luca Incrocci.

During Jacques Buvat's term as president of the ISSM he had the vision to create a standards committee. This committee, under the leadership or Dr Hartmut Porst of Germany and the co-chairman of the standards committee Jacques Buvat, took on the herculean task of developing a book as a work-product of this committee's efforts to update current knowledge and present standards in the field of sexual medicine for both sexes. This 28-chapter volume was published in 2006 and represents 'a focused consonance between clinical problems and contemporary scientific literature', in the words of Ira Sharlip, the president of the ISSM in the year that the volume was published.[5]

Scientific awards and research

The ISIR recognized that it should award cutting-edge research with awards at the biennial meetings. Tables 2.3, 2.4, 2.5, and 2.6 list the recipients of these awards over the years. At present the ISSM has four permanent prizes.

- The Jean François Ginestié Prize of US$2500 was first awarded in 1984. It is funded by the family of Dr Ginestié, a French pioneer in the field of ED (who performed the first arteriographies of the pudendal arteries). This prize is awarded for the best paper on basic science.

Table 2.3 Jean François Ginestié Prize winners

1984	Herbert Newman, USA
1986	P Ganesh Adaikan, Singapore
1988	William D. Steers, USA
1990	KM Azodzei, USA
1992	Geng-Long Hsu, Taiwan
1994	Gerald Brock, Canada
1996	Kwangsung Park, USA
1998	Gyung-Woo Jung, Korea
2000	Annamaria Giraldi, Denmark
	Kanhan Chitaley, USA
2002	John Mulhall, USA
	Trinity J Bivalacqua, USA
2004	B Musicky, USA
2006	T Mostafa, Egypt

Table 2.4 Newman–Zorgniotti Prize winners

1988	C Persson and KP Junemann, Germany
1990	Christian Steif, Germany
1992	no award
1994	S Krishnamurti, India
1996	no award
1998	Michael J Metro, USA
2000	Kwangsung Park, Korea
2002	Clifford Bleustein, USA
2004	P Teloken, Brazil (male sexual dysfunction) Ridwan Shabsigh, USA (female sexual dysfunction)
2006	AL Burnett, USA

Table 2.5 Tanagho Prize winners

1998	Hong-Zhan Wang, USA
2000	Yosikauzu Sato, Japan
2002	Biljana Musicky, USA
2004	K Park, Korea
2006	B Shrilatha, Singapore

- The Zorgniotti–Newman Prize of US$1000 was first awarded in 1988. It is funded by the Zorgniotti Research Fund, itself funded by voluntary donations of ISIR members as well as by a donation from the Dutch organizers of the eight biennial ISIR Meeting, from the profits of this congress. It honors two other famous pioneers in the field of ED, both founders of the ISIR, and is awarded for the best clinical paper.
- The Tanagho Prize of US$1000 was first awarded in 1998. It is funded by the Tanagho Fund, made up of the benefits

Table 2.6 ISIR Poster Prize winners	
1990	JA Moreno, USA
1992	RS Pickard, UK
1994	J Bernabi, France
1996	Hunter Wessels, USA
1998	Yi Tang, France
2000	MA Khan, UK
2002	Michael Di Santo, USA
2004	S Ückert, Germany (basic science, female)
	K Park, South Korea (basic science, male)
	R Shabsigh, USA (clinical, female)
	P Teloken, Brazil (clinical, male)

of the San Francisco ISIR Meeting (1996). It awarded for the best innovative research.
- The Poster Prize of US$1000 was first awarded in 1990 and is awarded for the best poster.

A female sexual dysfunction prize was announced at the 2002 biennial meeting in Montreal, Canada (Table 2.7).

At the meeting in Amsterdam in 1998, the ISIR presented the first pre-conference symposium. At the same meeting Pfizer Inc made a $50,000 unrestricted educational grant to support young investigators in the field. This was to be divided into five $10,000 grants and to be administered by a panel that reviewed submitted grant applications, chaired by Dr Robert Krane. There were four grant awards announced at the 2000 meeting in Perth, Australia:

- Dr Trinity Bivalacqua, Tulane University, New Orleans, Louisiana – Gene transfer of eNOS and nNOS
- Dr Yutian Dai, Medical College of Georgia, Augusta – Effects of RHO kinase inhibition
- Dr Kwangsung Park, Chonnan Medical University, Kwanjiu, Korea – Effect of hyperglycemia on vaginal function
- Dr John Mulhall, Loyola University, Maywood, Illinois – Analysis of ED as a predictor of coronary arterial disease.

There were six awards in 2001:

- Dr Hunter C Champion, The Johns Hopkins Hospital, Baltimore, Maryland – Role of arginase in aging-associated ED: influence of *in vivo* gene transfer
- Dr Taben M. Hale, Queen's University, Kingston, Ontario, Canada – Development of a new therapeutic strategy in sexual dysfunction: pharmacologically targeting vascular remodeling
- Dr Noel N Kim, Boston University School of Medicine, Boston, Massachusetts – Does chronic phosphodiesterase type 5 (PDE-5) inhibition increase PDE-5 activity and attenuate penile erectile function?
- Dr Jonathan Man, Guy's and St Thomas' Hospitals, London, UK – Is ED, *per se*, characterized by generalised increased oxidative stress and endothelial dysfunction?
- Dr Mahadevan Rajasekaran, UCSD Medical Center, San Diego, California – Role of RHO-kinase pathway in hypertension-related male ED?

Table 2.7 Female Sexual Dysfunction Prize winners	
2002	Kathleen Connell, USA
2004	S Ückert, Germany
2006	no award

- Dr Xiaogang Jiang, University Hospital, Copenhagen, Denmark – Uninterrupted 24-hour registration of corpus cavernosum electromyography with a portable recording system.

Another six awards were given in 2002:

- Dr Derek Bochinski, University of California, San Francisco – Comparison of the effect of three combinations in the nerve freezing ED rat model
- Dr Kelvin P Davies, Albert Einstein College of Medicine, Bronx, New York – Changes in global gene expression accompanying ED in diabetics
- Dr Jas Kalsi, Wolfson Institute for Biomedical Research, London, UK – Effect of nitric oxide-independent vasorelaxant agents on cavernosal smooth muscle
- Dr Steven R. King, Baylor College of Medicine, Houston, Texas – Steroidogenic acute regulatory protein's role in libido
- Dr Guiting Lin, University of California, San Francisco, California – Embryonic stem cells therapy for neurogenic ED
- Dr Ricardo M Munarriz, University School of Medicine, Boston, Massachusetts – Is PDE-5 expression, phosphorylation, or activity regulated by steroid hormones in the penile corpus cavernosum smooth muscle?

The first International Consultation on ED was organized by Dr Saad Khoury and convened in July 1999 in Paris, under the co-sponsorship of the World Health Organization and the Union Internationale Contre le Cancer. This consultation was chaired by A Jardin and co-chaired by G Wagner. Its mission was to develop recommendations for the diagnostic evaluation and management of ED. Recommendations for that meeting were based on a thorough review of the available literature and the subjective opinion of 128 recognized global multidisciplinary experts representing 29 countries and serving on 18 committees. This meeting was co-sponsored by ISIR and the Société Internationale d'Urologie. A book was produced from this effort.[6] This meeting led to the second consultation held in Paris in 2003, again co-sponsored by ISSM and expanded to cover sexual disorders in both men and women. A second book was published in 2004.[7]

Summary

The organization that was to become the International Society for Sexual Medicine had its beginnings less than 30 years ago and its first focus was possible revascularization surgery for ED. This organization blossomed at a time when the majority

of sexual medicine was considered to be in the province of psychological problems. Not long after the first meeting in 1978, other scientific, diagnostic, and therapeutic elements of sexual medicine were placed under more scientific scrutiny. The early founders of the organizations were particularly interested in looking at anatomical and physiological processes that explain normal sexual function as well as pathological dysfunction. This focus led to the decision to have biennial meetings to share cutting-edge findings in the field of sexual medicine. As molecular biology techniques were used to explain other disease processes, the group of scientists who made up this organization easily moved into this more intense scientific evaluation. Not only was the scrutiny afforded to problems of ED, but the members of the organization rapidly realized and expanded into all fields of sexual medicine, so that the organization became the International Society of Sexual Medicine.

The sharing of information on a biennial basis led to the wish to establish a journal to be able to disseminate higher science that was occurring in sexual medicine. However, the field of education was not confined to members of the Society; rather, a new effort was made to educate other healthcare practitioners about sexual medicine; in addition, an effort to help educate the general public in matters of sexual medicine became even a greater focus for the organization.

The Society has continued to be a truly international organization that brings together investigators in various disciplines across the world to define more clearly the biology of sexual medicine. Long-term friendships are forged and scientific enquiry is not only encouraged, but has become the lifeblood of the organization. The attempt of this chapter is to place a historical perspective on how the organization has changed and to introduce some of the key players that have helped nurture and develop it.

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3 Epidemiology of erectile dysfunction

Peter Boyle

Introduction

There is a centuries-old tradition that 'impotence' is a consequence of witchcraft or satanic magic.[1] In European culture, the issue is of masculinity with the capacity for a strong erection symbolic of the strong man. Bancroft[2] reviews the history of impotence and the historical literature. The frequency of impotence has not been well investigated until recently and one of the major difficulties is the sensitivity of the information, with respondents tending to give unreliable replies.[3] For example, Marsey et al.[4] investigated the occurrence of impotence in a large cohort of men who had undergone vasectomy, together with an equally large control group. Hidden among questions about many aspects of health and well-being were questions about impotence. These produced incidence estimates of approximately 17 new cases per 100,000 man-years.[4] This is slightly lower than the incidence rate of bladder cancer in the same community and difficult to believe. The epidemiological investigation of impotence has also been held back by the lack of a clear and common definition of the condition.

Impotence is the persistent failure to develop and maintain erections of sufficient rigidity for penetrative sexual intercourse. The disorder is common enough, from all accounts, but there are few reliable data available about the population prevalence. Many patients, and even their doctors, are still very reluctant to discuss such problems and, consequently, a large proportion of both the public and the medical profession are ignorant about available treatment options.[5]

The general terminology used to describe this condition has been moving away from the highly emotive term impotence towards a more widely descriptive term erectile dysfunction (ED). Today it is recognized that the causes of ED are frequently multiple, with psychological, neurological, endocrinological, vascular, traumatic and iatrogenic components described. Very little high-quality epidemiological investigation of ED has been undertaken and completed, so that the relative importance of each of these groups of causes to the overall burden of impotence in the community is unknown at present. There are incomplete indications of a precise role of environmental or lifestyle factors in the development of impotence, although smoking, hypertension, hyperlipidemia, diabetes mellitus and the presence of vascular disease have been proposed as potential risk factors.[5] Research on ED proceeded for many years in parallel among the psychological community and the medical community and it was only after the two groups began serious interaction that true progress was made. Neither group would admit the importance of issues in the other's domain as a cause of this problem: surgeons pronounced that 80–90% of impotence is caused by physical, not psychological, problems,[6] whereas sex therapists have to come to terms with the fact that many men with erectile dysfunction, possibly as many as 50%, have physical abnormalities that contribute to their erectile problems.[1]

The epidemiology of ED is so poorly understood that to entitle a chapter 'Epidemiology of erectile dysfunction', giving the indication that there was some certainty about any statements, is a little presumptuous. In this chapter, the author discusses some of the epidemiological data available, puts it in some perspective and outlines the basic requirements necessary to understand more completely the epidemiological picture.

Erections and the causes of dysfunction

Sexual arousal is a function of great evolutionary antiquity and is often best understood by specialists in research on human nature, such as sociobiologists. Sexual arousal in men is, in some important respects, quite different from sexual arousal in women, particularly with regard to the stimuli and experiences that are optimally exciting.[7] Sexual arousal to erotic stimuli diminishes as initially highly exciting stimuli lose their ability to create arousal with habituation. This has also been shown in laboratory animals, where the male quickly tires of the same partner but whereby rates of intercourse are quickly restored if a fresh partner is found.[8] Farm animals, such as bulls and rams, have a marked preference for novel females: for example, rams introduced to the same partner have a much longer time to ejaculation (around 17 minutes) compared with rams introduced to different partners at the same rate (around 2 minutes).[9] Thus, it could be possible that factors such as habituation could play a part in the development of ED although there are physiological mechanisms as well as psychological mechanisms that must be kept in mind in the potential etiology of erectile dysfunction.

In simple terms, erection of the penis depends on the adequate filling of the paired corpora cavernosa with blood at systolic pressure (or even slightly above).[5] Erection occurs when the tonically contracted cavernosal and helicine arteries relax, increasing blood flow to the lacunar spaces and resulting in engorgement of the penis. Relaxation of the trabecular smooth muscle of the corpora cavernosa is mediated by acetylcholine, which acts on endothelial cells causing them in turn to release a further non-adrenergic non-cholinergic carrier of the relaxation signal. The strongest suspect for this second carrier is currently nitric oxide, although other candidates, particularly vasoactive intestinal polypeptide, cannot be entirely ruled out at present.[10]

Thus, the search for etiological factors in erectile dysfunction has certain clues to begin with: factors that interfere with the filling of the corpora cavernosa, with the blood flow to the lacunar spaces, or with the production and regulation of nitric oxide (or other carriers of the relaxation signal) are prime suspects for any etiological investigation.

Erectile dysfunction is not always, however, the failure of some mechanical or biochemical process: sexual function cannot be considered on its own without bearing in mind the concept of sexuality. The human sexual response is a complex, multifaceted phenomenon that is not completely, or nearly, understood by anyone at present. Problems with potency are frequently multi-factorial in origin.

In nervous or anxious men, increased sympathetic tone and raised circulating catecholamine concentrations may interfere with the mechanisms of smooth muscle relaxation underlying erection. Psychogenic impotence is self-perpetuating: each failure increases the associated anxiety levels and frequently can lead to the continual failure to have erections. This is the commonest cause of intermittent erectile dysfunction in young men, although it is usually secondary to organic dysfunction from middle age onwards.[11]

Free serum testosterone concentrations fall progressively with age, while erectile dysfunction increases in frequency. Falling testosterone levels are associated with a loss of libido and reduced frequency of erections,[5] although the straightforward restoration of circulating androgen levels often does not restore sexual function. This underlines, once again, the complex nature of male sexual function and the interplay with sexuality.

Although endocrinological impotence frequently is a consequence of poorly understood processes, neurogenic impotence often can have a precise cause attributed. Several neurological disorders can impair erectile function, although it is unusual – but not completely unknown – for impaired erectile function to be the sole manifestation of diseases or disorders of the nervous system. Peripheral neuropathies, most frequently associated with alcoholism or diabetes, are associated with impotence.

Probably the most important causes of erectile dysfunction are impaired blood flow to the penis or excessive leakage from the penis; frequently, both are present. In older men, reduced blood flow into the penis due to atherosclerotic lesions of the internal iliac, pudendal and cavernosal arteries is the most common cause.[11,12] With large increases taking place in the aging population,[13] vascular impotence will take on ever-increasing importance in urological practice.

Basic epidemiological considerations

The most useful definition of epidemiology is that it is the scientific study of the distribution and determinants of disease in humans.[14] From this evolve the two components of descriptive epidemiology – the description of disease incidence, mortality and prevalence by persons, place and time – and analytical epidemiology – the search for determinants of disease risk that may serve to increase prospects for prevention.

Determination of disease frequency, the first step towards geographical and temporal comparisons, relies on a definition (or at least on a working epidemiological definition) of the disease or condition under investigation. ED shares with the other common urological condition of benign prostatic hyperplasia (BPH)[15] the absence of a unifying definition of which the sensitivity and specificity can be determined. This is a fundamental problem that requires resolution. It should also be a priority to establish a system of classification, after determination of the severity and 'cause' of erectile dysfunction.

Many questionnaires have been developed in the hope of achieving this (among other goals),[16] although many have suffered from being too long and fussy with detail. Recently, two questionnaire-based symptom scales have been developed[17,18] that employ modern concepts of psychometric methodology and that attempt to overcome the inherent difficulties experienced with earlier attempts. The brief Sexual Function Index (SFI)[17] covers the domains of sexual drive, erection, ejaculation, perceptions of problems in each of these areas and overall satisfaction in a total of nine questions. The International Index of Erectile Dysfunction (IIEF)[18] has been developed and covers in 15 questions the domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. The similarity of these two instruments, both developed on the basis of detailed statistical analysis, is very reassuring. Time is necessary to observe which comes into the forefront of international usage, although the shorter version of O'Leary and his colleagues[17] has its attractions, if all other things are equal (i.e. if the questionnaires perform similarly).

A particular problem surrounds the probability of a man declaring his impotence and, to a large extent, this can be influenced by aspects of sexuality. There will be couples who accept the reduction in sexual activity and potency as a natural consequence of aging (and many may, in fact, be pleased and relieved). In similar circumstances, others will be extremely concerned and upset. Such facets of sexuality will have a strong influence on who comes to the doctor or who admits to the interviewer that they have erectile dysfunction. Frequency of self-reports is not to be trusted and consequently will bias any epidemiological study that would investigate the etiology of the phenomenon. Solstad and Hertoft[19] interviewed 100 men who had previously completed a questionnaire regarding erectile dysfunction: whereas less than 4% of all men who completed the questionnaire (16 of 439) reported erectile dysfunction, among the 100 men from the initial sample who were subsequently interviewed, nearly 40% reported some kind of sexual dysfunction. Interestingly, only 7% found their problems abnormal for their age and only 5% indicated that they would seek treatment for their problems.[19]

Descriptive epidemiology of erectile dysfunction

The reported frequency of erectile problems in completely unrepresentative samples is very similar. For example, Sanders[20,21] reports an analysis of responses to two surveys published in *Woman* magazine: 7% of men reported themselves to have erectile problems compared with 8% of women who made the same report. Frank et al.[22] studied 100 married couples and reported that 7% had difficulty in getting an erection; the same figure (in a study of 58 men) was reported by Nettelbladt and Uddenberg.[23] Even although the figures are all so similar, this may just reflect the effects of the same major biases that have been outlined above.

Many of these (and similar previous) reports on the frequency of erectile dysfunction are of very limited value, being based on poor epidemiological methodology and likely to be biased in directions that are frequently difficult for the reader to determine; these should be discarded immediately. Even in many recent reports, the methods for obtaining study populations have differed, the definitions of impotence have varied widely from study to study, and stratified information of prevalence by age has frequently been omitted completely or has been unreliable owing to the small numbers of subjects in each of the age classes. These are catastrophic failures from the point of view of comparison of rates. However, some limited data are available regarding the occurrence of ED.

Among 1180 men attending a medical outpatient clinic, Slag et al.[24] observed that 34% reported impotence to their interviewers. These were attendees at a medical outpatient clinic and may differ from the general population in having over-representation of diabetes, hypertension and other vascular diseases.

Erectile dysfunction is the most common presenting symptom among men attending sexual problem clinics. For example, in Edinburgh, over a 3-year period, over one-half of all men presenting at this clinic reported erectile dysfunction as their main complaint. The next most common complaint was premature ejaculation,[25] which was reported by 13% of the men. Of these men, over one-half (52%) had some other condition that contributed to their erectile dysfunction: 32% arterial, 21% neurological, 29% urological and 19% diabetes mellitus.[25] In a similar clinic in Singapore, 72.5% of men attending the Sexual Dysfunction Clinic at Toa Payoh Hospital had erectile dysfunction due to organic causes with the remaining 27.5% of patients having erectile dysfunction due to psychogenic causes.[26] Of the patients with organic impotence, in 81% of cases this could be attributed to the effects of diabetes and vascular disease.[27]

In a small study (212 family practice patients) with a young mean age (37 years), 27% of men, on detailed questioning, reported being impotent.[27] The small sample and the young average age argue strongly against the representativeness of these findings to a community, however.

Morley[28] determined the prevalence of impotence to be 27% in men of more than 50 years of age undergoing a general health screening. In terms of size of the sample and the mean age of the men, this sample is better than most. However, it is still hindered by the lack of definition of the term impotence and is potentially biased, for reasons associated with the discussion in the previous section.

Diokno and colleagues included questions about sexual activity and its correlates in a clinic examination, whose participants were identified by a household survey of a probability sample of Washtenaw County, Michigan, USA. Men were aged 60 years and over and were questioned with regard to medical, epidemiological and social aspects of aging.[29] Of married men, 73.8% reported that they were sexually active (whereas the corresponding figure for married women was 55.8%), with levels decreasing with age. Overall, 35.3% of men included in this sample reported that they were impotent.

Feldman and his colleagues conducted the most useful and comprehensive study of the epidemiology of impotence until the present time.[30] The study sample consisted of respondents to the Massachusetts Male Aging Study (MMAS): this was a cross-sectional, random sample survey of health status and related issues in men aged between 40 and 70 years. The MMAS was conducted between 1987 and 1989 in 11 randomly selected towns in the Boston area of Massachusetts, USA. Of 1709 respondees, 1209 men provided complete responses and constitute the sample on which the findings were based. Although the 419 men excluded did not differ from the study sample with respect to all essential variables, a 2/3 non-response rate to sexual questions should be a cause for some hard cynical questioning. A total of 291 men did not respond because they had no sexual partner, and this could bias the prevalence downward. Discriminant analysis was employed to create an impotence scale of nil, minimal, moderate and complete impotence, which was accorded to each individual in the survey.[30]

Between the fifth and seventh decades, the probability of complete impotence almost tripled, from 5.1% to 15% (Figure 3.1); 60% of men were potent in their fifth decade, whereas only 33% were potent at 70 years.[30]

Of 1680 men who participated in the (free) Prostate Cancer Awareness Week and who were invited to complete a self-administered questionnaire containing questions on urinary symptoms, impotence, quality of life and age, 1517 answered the questionnaire, a response rate of 90.3%.[31] A total

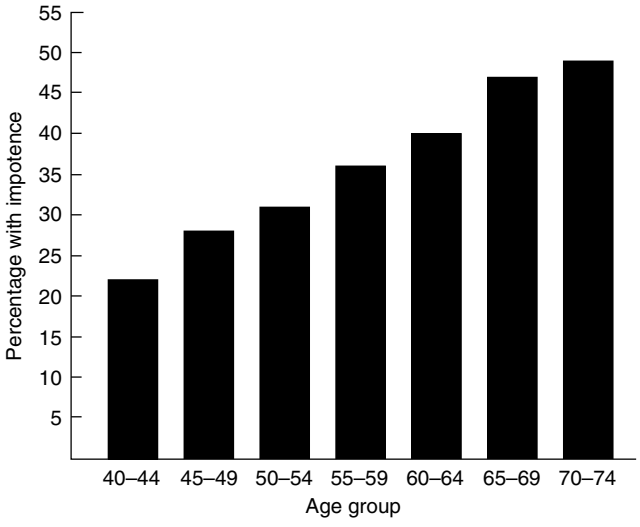

Figure 3.1 Probability of complete or moderate impotence in Massachusetts Male Aging Survey.[30]

of 129 men (7.7%) had not had any erections during the previous 12 months. Of subjects who reported that they had experienced erections during the previous 12 months, 12.4% had had erections on less than one occasion in five when sexually stimulated during the last month. There was a striking association between the frequency of varying degrees of impotence and age.

Sexual function was assessed in the prospective Olmsted County Study of Urinary Symptoms and Health Status Among Men, involving a random sample of men living there.[32] The prevalence of sexual problems and erectile dysfunction increased with age. Comparison of men aged 70–79 years with men aged 40–49 years indicated that older men were more worried about sexual function (46.6% vs 24.9%), had worsened performance compared with a year ago (30.1% vs 10.4%), expressed extreme dissatisfaction with sexual performance (10.7% vs 1.7%), had an absence of sexual drive (25.9% vs 0.6%) and reported complete erectile dysfunction when sexually stimulated (27.4% vs 0.3%).[32] Age did not appear to be an independent determinant of this dissatisfaction; rather, this could be accounted for primarily by the age-related increase in erectile dysfunction, decreased libido and their interaction.

Prior to Jonler et al.[31] and Feldman et al.,[30] Kinsey et al.[33] had found impotence to be an age-dependent disorder with a prevalence of 1.9% at 40 years and 25% at age 65.[33] All three studies share the common feature of being based on selected population subgroups. The trends with age, and the high prevalences at older ages, are comfortingly similar, not only to themselves but also compared with other surveys of this area.[22,34–38]

Despite the methodological inadequacies in each of these studies, to some degree or another, it is clear that impotence is a very common condition in men and one in which the prevalence is strongly linked to aging. The prevalence probably now exceeds 2% in the fifth decade, rising to 25–30% by the middle of the seventh decade, as estimated by Furlow in 1985.[39] Good data are still required, particularly by ethnic group and at older ages. No data are available for impotence among men aged 75 or over, of whom substantially over one-half may be affected.[5]

Determinants of erectile dysfunction in men

Until the early 1980s, it was commonly held that psychogenic causes were the etiology in up to 90% of cases of erectile dysfunction.[40–42] Current thinking favors arterial changes as the key factor in the largest proportion of impotence,[5,12,24,43] with alterations in the flow of blood to and from the penis the single most important cause. Some studies have indicated that there may be evidence of a role for certain cardiovascular risk factors in determining the risk of impotence, including tobacco, hypertension, diabetes mellitus and hyperlipidemia.

Cigarette smoking has been implicated as an independent risk factor for (vascular) impotence.[44] In the MMAS, among subjects with treated heart disease the age-adjusted probability of complete impotence was 56% for current smokers, compared with 21% in current non-smokers.[30] Among treated hypertensives, those who currently smoked cigarettes had an elevated probability of complete impotence (20%), whereas the non-smokers (8.5%) were comparable to the general sample (9.4%). Feldman et al.[30] also found that drug effects were exacerbated by current smoking, which increased the age-adjusted probability of complete impotence in those taking cardiac medication (from 14 to 41%), using antihypertensive medications (from 7.5 to 21%) and using vasodilators (from 21 to 52%). However, in this study an overall effect of current smoking was not noted,[30] with complete impotence present in 11% of smokers and 9.3% of non-smokers. Among current smokers, the probability of impotence demonstrated no dose dependency with current smoking or lifetime cigarette consumption.

Diabetes is widely recognized to be associated with impotence. A review of seven prevalence surveys found rates of erectile dysfunction ranging from 35% to 59% among diabetics.[45] The association with increasing prevalence with age is also found. For example, Figure 3.2 contrasts the prevalence of erectile dysfunction in diabetic and non-diabetic men,[1] and clearly demonstrates the differences between diabetic and non-diabetic men in terms of prevalence of erectile dysfunction as well as the striking association with age in both groups. Similar prevalences have been reported recently[46,47] and, additionally, erectile dysfunction in diabetic men has been associated with the presence of severe diabetic retinopathy, a history of peripheral neuropathy, amputation, cardiovascular disease, a higher glycosylated hemoglobin, use of antihypertensive drugs and a higher body mass index.[46] It would appear that tighter glycemic control and careful selection of antihypertensive medication could prove beneficial in the avoidance of erectile dysfunction in diabetic patients.[46]

In the MMAS, the age-adjusted probability of complete impotence was three times higher in men who reported having treated diabetes than in those without diabetes. In studies of diabetic patients, there have been consistent findings of high prevalences of impotence, with estimates ranging between one-third and one-half and, occasionally, up to three-quarters.[48,49] It has been reported that impotence in diabetics increases from 15% at age 30–34 to 55% at age 60 years.[50] It has been reported that impotence occurs at an earlier age in

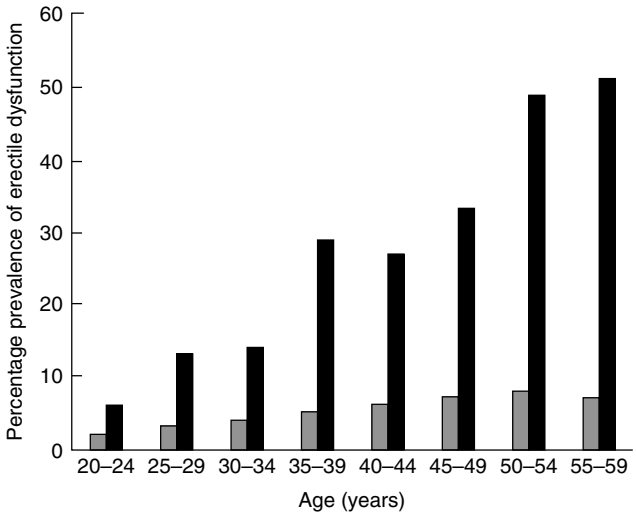

Figure 3.2 Prevalence of erectile dysfunction in diabetic (right columns) and non-diabetic (left columns) men. Data have been abstracted from reference 1.

men with diabetes than in men in general, both in type I and type II diabetes.[51,52]

Vascular disease is the aspect of diabetes most widely held to be responsible for associated impotence. The association of impotence with vascular disease appears to be quite consistently reported. Impairment in the hemodynamics of erection has been demonstrated in men with a number of vascular diseases: in a group of men aged 31–86 with myocardial infarction, 64% were impotent,[53] and 57% of men in a study of coronary bypass surgery were found to be impotent.[54] Similar excesses of impotence have been demonstrated in men with peripheral vascular disease[55] and cerebrovascular accidents.[56] It has also been reported that impotence was increased among patients with arthritis,[57] although Feldman noted that the same association in the MMAS study was confined to smokers.[30]

The effect on sexual function of lifestyle factors related to cardiovascular disorders such as alcohol consumption has been reported to be either slight[30] or unclear.[58,59] There is no consistent evidence suggesting that obesity *per se* is associated with impotence.[30,58,59] A high level of total cholesterol or low level of high-density-lipoprotein cholesterol (HDL-C) may result in arteriosclerosis and induce erectile dysfunction by arterial insufficiency. Wei et al.[60] reported the relation between serum cholesterol and erectile dysfunction among blood samples obtained from the Cooper Clinic in Dallas, Texas, USA. The study included a total of 3250 men aged 26–83 years (mean age reported to be 51 years) without erectile dysfunction at the first visit and who had a further clinic visit between 6 and 48 months following.[60] Erectile dysfunction was reported by 71 men (2.2%) during this period and every mmol/liter increase in total cholesterol was associated with 1.32 times the risk of erectile dysfunction (95% confidence interval [CI] 1.04, 1.68). Men with an HDL-C measurement over 1.55 mmol/liter (60 mg/dl) had 0.30 times the risk (95% CI 0.09, 1.03). Men with total cholesterol over 6.21 mmol/liter (240 mg/dl) had 1.83 times the risk (95% CI 1.00, 3.37) of that of men with less than 4.65 mmol/liter (180 mg/dl). These differences remained essentially unchanged after adjustment for potential confounding factors (Figure 3.3).[60]

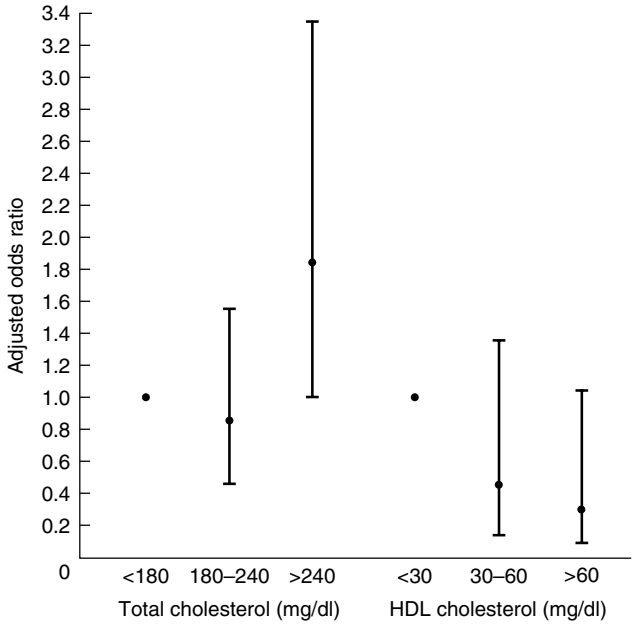

Figure 3.3 Relative (and 95% confidence interval) risk of erectile dysfunction by levels of total cholesterol and high-density-lipoprotein (HDL) cholesterol. Data abstracted from reference 60.

Feldman et al.[30] reported that the probability of impotence varied inversely with HDL-C. For younger men, aged 40–55 years, the age-adjusted probability of moderate impotence increased from 6.7% to 25% as HDL-C decreased from 90 to 30 mg/dl. In older subjects, aged 56–70 years, the probability of complete impotence increased from near zero to 16% as HDL-C decreased from 90 to 30 mg/dl. No association with total cholesterol was found in this study.[30]

Impotence is often reported following radical prostatectomy, although preservation of the neurovascular bundles helps to reduce the frequency of the condition. Quinlan et al.[61] reported 600 radical retropubic prostatectomies from the Johns Hopkins Hospital of which 503 men were potent preoperatively.[61] Three factors were found to be related to the return of sexual function postoperatively, namely age, clinical stage of the tumor and surgical approach – i.e. whether the neurovascular bundles were preserved or excised. In young men, aged less than 50 years, potency was similar in patients who had both neurovascular bundles preserved (90%) and in those who had one neurovascular bundle widely excised (91%). In men over 50 years, sexual function was better in men who had both bundles preserved than in men in whom one neurovascular bundle was widely excised ($p < 0.05$). When the relative risk of impotence was adjusted for age, the risk of postoperative impotence was twofold greater if there was capsular penetration or seminal vesicle invasion, or if one neurovascular bundle was excised ($p < 0.05$). In contrast, the proportion of men who stated that they were impotent following transurethral resection of the prostate (TURP) for BPH (24%) was essentially similar to the preoperative impotence rate (22%).[62] Previous anecdotal reports of an association between TURP and erectile dysfunction may have arisen because of patients' confusion in equating retrograde ejaculation with erectile dysfunction.[63]

Of 40 patients with aorto-iliac occlusive disease (AIOD) scheduled for surgery, 31 were given questionnaires and penile dynamic color Doppler ultrasonography.[64] Five of the 31 who volunteered were found to be potent (16%) and the remaining 26 (84%) were found to have erectile dysfunction. This was found to be entirely arteriogenic in 8% of cases, purely venogenic in 23% of cases and a combination of arteriogenic and venogenic in 53%. Following surgery, 20 patients returned for evaluation and erectile function was found to have improved in seven patients. Of these patients, six (of nine) had undergone endarterectomy and one (of 11) had undergone reconstruction.[64]

The association between impotence and taking medication is still controversial in many instances, as many of these associations have been based on case reports and personal case series. Morley[28] noted that 16 of the 200 most widely prescribed drugs in the United States were associated with impotence and that 1/4 men in a medical outpatient population were reported to have drug-induced erectile dysfunction.[24] The frequency of erectile dysfunction was found to be slightly elevated in men receiving finasteride, a 5-alpha-reductase inhibitor used in the treatment of BPH.[65,66] Erectile

dysfunction has been associated with a wide range of antihypertensive preparations, including diuretics, sympatholytics, beta-adrenoceptor-blocking agents and vasodilators.[67,68] Unfortunately, many of these reports are from studies where the presence of impotence was not ascertained before the trial began and, in most of the studies, it is difficult to separate the effect of the treatment from the effect of the disease. The one exception appears to be doxazosin, an alpha-adrenergic receptor blocker used in the treatment of hypertension and BPH, which was shown in a four-arm study to enhance sexual function.[69]

Psychological factors directly involved in the development of impotence have been very poorly studied from the etiological point of view. It has not been common practice to include psychological assessments in prospective studies and, in retrospective surveys, it is difficult to avoid the effect similar to confounding by indication, wherein men who become impotent then become depressed and exhibit other psychological traits.

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Conclusions and recommendations

With the 20th century has come a wide range of diseases of affluence and aging, including appendicitis, myocardial infarction, osteoporosis and old age. Prior to age 40, impotence is a relatively uncommon disorder but the prevalence rises in such a way that the majority of men over 70 years of age may suffer from erectile dysfunction. Although 100 years ago this was of little consequence in public health terms, today life expectancy approaches 80 years in the most developed countries. Although ED does not kill, it is a major contributor to a reduced quality of life and to the consequent psychological sequelae of many aging men.

The epidemiology of erectile dysfunction is very poorly researched and incompletely understood, although several aspects of the epidemiology are clear, at least in qualitative terms. Most importantly, despite the presence of all possible methodological failings in the available studies, the prevalence of the disease in aging men is very high. The etiology of erectile dysfunction is classified into several major subheadings; whereas psychogenic impotence was held, only 20 years ago, to account for over 80% of cases, today it is widely accepted that the commonest cause, and the explanation for the majority of cases, is the vascular changes commonly found in aging men. In particular, erectile dysfunction appears to be common in diabetic patients and in men with clearly defined, serious vascular disease. A number of risk factors for vascular disease appear to be related to the risk of impotence, including cigarette smoking and serum cholesterol levels, particularly HDL-C. Erectile function also appears to be very sensitive to unrelated drug therapy effects.

Smoking is the largest single source of preventable mortality worldwide today. Smokers have great difficulty in stopping the habit, although it is very tempting to speculate that if it could be demonstrated that smoking cessation reduced the probability of becoming impotent, then men might be more motivated to give up this noxious habit and improve the expected duration as well as the quality of their lives.

There are a number of priorities in epidemiological research on erectile dysfunction. First, it is necessary to develop standard instruments to determine with certain sensitivity and specificity the presence, frequency and nature of erectile dysfunction in men; there have been important developments in this field in the recent past. Subsequently, this should be used to determine variations in the occurrence of erectile dysfunction, be it internationally, temporally or in special groups of the population; this is now ongoing. There is an urgent need to have a better understanding of the etiology of erectile dysfunction: risk factors need to be identified more clearly so that prevention possibilities can be investigated. In this line, it would be interesting and useful to have urgent information on whether the cessation of cigarette smoking or lowering HDL-C levels could lead to a reduction in the probability of developing impotence. A positive effect of cholesterol-lowering drugs on nocturnal penile tumescence has been observed and, given the association now developing between cardiovascular disease and decreased nocturnal penile tumescence,[70] this could lead to the prioritization of this research line as one important way forward towards prevention. However, this line of etiological and preventive research appears to have stalled and is developing only very slowly at present.

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4 Anatomy of erectile function

William O Brant, Anthony J Bella, and Tom F Lue

Introduction

The penis is essentially a tripartite structure, with bilateral corpora cavernosa and the midline ventral corpus spongiosum and glans, all three of which are surrounded by loose subcutaneous tissue and skin that can be moved freely over the erect organ (Figure 4.1). The cavernosa function as the main erectile bodies, while the spongiosum contains the urethra. The length of the penis is highly variable, especially in the flaccid state, since it is dependent on the degree of contraction of the cavernosal smooth muscle tissue. There is considerably less variation in length of the fully erect penis, with one study demonstrating a good correspondence between erect length and stretched penile length, as measured from the pubopenile junction to the meatus.[1] This length was found to be an average of 12.4 cm.

Skin and fascia

Penile skin is continuous with that of the lower abdominal wall and continues over the glans penis; there it folds back on itself and attaches at the coronal sulcus. The folded portion is known as the prepuce.

There are two fascial layers. The more superficial is the dartos fascia, continuous with Scarpa's fascia of the abdomen. It continues caudally as the dartos fascial layer of the scrotum and Colles' fascia in the perineum. The deeper fascial layer is Buck's fascia, which covers the corpora cavernosa and the corpus spongiosum in separate compartments, including coverage of the deep dorsal vein as well as the dorsal neurovascular bundles. Buck's fascia attaches to the perineal membrane proximally and to the coronal sulcus distally, where it fuses with the tips of the corpora. The fundiform and suspensory ligaments attach to the pubic symphysis and Buck's fascia, and allow the erect penis to achieve a horizontal or greater angle.

Tunica albigunea

The corpora are surrounded by tunica albigunea, a strong structure of heterogeneous thickness and anatomy, the purpose of which is to both provide rigidity of the erectile bodies as well as to function in the veno-occlusive mechanism. The tunica albigunea consists of two layers, the outer of which is oriented longitudinally whereas the inner layer consists of circular fibers. The inner layer contains struts that course the cavernosal space and serve to augment the support provided by the intracavernosal septum. The corpus spongiosum lacks both the outer layer as well as the struts.

There is variability in the thickness and strength of the tunica albigunea in various locations. Thickness ranges from approximately 0.8 mm at the five o'clock and seven o'clock positions (just lateral to the corpus spongiosum) to 2.2 mm at the one o'clock and eleven o'clock positions.[2]

Corpora cavernosa

The paired corpora cavernosa originate separately underneath the ischiopubic rami, then merge as they pass under the pubic arch. The septum between them is incomplete in humans, although complete in some other species. They are supported by several fibrous structures, including the surrounding tunica albigunea, the intracavernous struts radiating from the inner layer of the tunica albigunea, and perineural, periarterial fibrous sheaths. The spongy inner portion of the corpora consists mainly of interconnected sinusoids separated by smooth muscle trabeculae, which are surrounded by collagen and elastic fibers. These sinusoids are larger centrally and smaller towards the periphery. The corpus spongiosum and its distal termination in the glans penis is similar in internal structure to the corpora cavernosa except that the sinusoids are larger, there is a lack of outer layer of the tunica albigunea, and the tunica albigunea is absent in the glans.

Associated musculature

The paired ischiocavernosus muscles originate from the ischial tuberosity, cover the proximal corpora, and insert into the inferiomedial surface of the corpora. These muscles are innervated by the perineal branch of the pudendal nerve and allow the corpora cavernosa to obtain much higher intracorporal pressures than would be possible with arterial pressure alone. The bulbospongiosal muscle originates at the central perineal tendon, covers the urethral bulb and corpus spongiosum, and inserts into the midline. This muscle is innervated by a branch of the perineal nerve and assists in the ejaculation of semen.

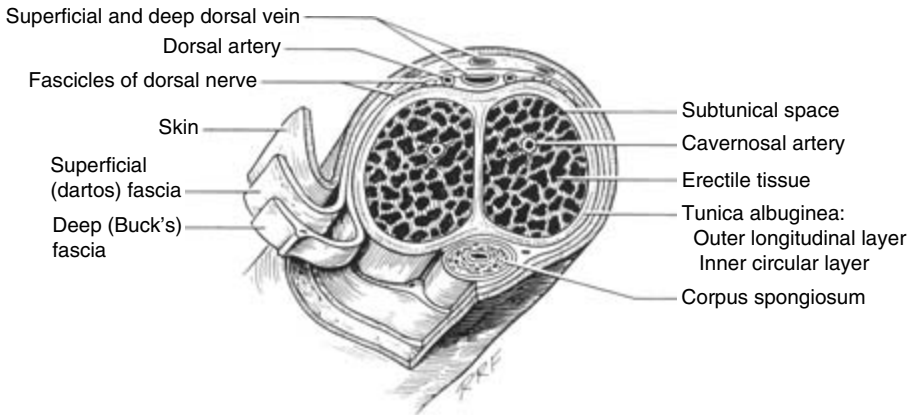

Figure 4.1 Cross-sectional anatomy of the penis. With permission from the American Urological Association AUA Update Series, volume 13, lesson 2; 1994.[6]

Penile vascular anatomy

The main source of blood supply to the penis is usually through the internal pudendal artery, a branch of the internal iliac artery (Figure 4.2). In many instances, however, accessory arteries arise from the external iliac, obturator, vesical, or femoral arteries, and they may occasionally become the dominant or only arterial supply to the corpus cavernosum.[3] Damage to these accessory arteries during radical prostatectomy or cystectomy may result in vasculogenic erectile dysfunction (ED) after surgery.[4,5] The internal pudendal artery becomes the common penile artery after giving off a branch to the perineum. The three branches of the penile artery are the dorsal, bulbourethral, and cavernous arteries. The cavernous artery is responsible for tumescence of the corpus cavernosum and the dorsal artery for engorgement of the glans penis during erection. The bulbourethral artery supplies the bulb and corpus spongiosum. The cavernous artery enters the corpus cavernosum at the hilum of the penis, where the two crura merge. Distally, the three branches join to form a vascular ring near the glans. Along its course, the cavernous artery gives off many helicine arteries, which supply the trabecular erectile tissue and the sinusoids. These helicine arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection.

The venous drainage from the three corpora originates in tiny venules leading from the peripheral sinusoids immediately beneath the tunica albuginea (see Figure 4.2). These venules travel in the trabeculae between the tunica and the peripheral sinusoids to form the subtunical venular plexus before exiting as the emissary veins. Outside the tunica albuginea, the venous drainage is as follows:

1. The skin and subcutaneous tissue drain through multiple superficial veins that run subcutaneously and unite near the root of the penis to form a single (or paired) superficial dorsal vein, which in turn drains into the saphenous veins. Occasionally, the superficial dorsal vein may also drain a portion of the corpora cavernosa.
2. In the pendulous penis, emissary veins from the corpus cavernosum and spongiosum drain dorsally to the deep dorsal vein, laterally to the circumflex vein, and ventrally to the periurethral vein. Beginning at the coronal sulcus, the prominent deep dorsal vein is the main venous drainage of the glans penis, corpus spongiosum, and distal two-thirds of the corpora cavernosa. Usually, a single vein, but sometimes more than one deep dorsal vein, runs upward behind the symphysis pubis to join the periprostatic venous plexus.
3. Emissary veins from the infrapubic penis drain the proximal corpora cavernosa and join to form cavernous and crural veins. These veins join the periurethral veins from the urethral bulb to form the internal pudendal veins.

Lymphatics

Lymphatics of the prepuce and penile shaft converge dorsally, and then drain into both right- and left-sided superficial inguinal lymph nodes via channels alongside superficial external pudendal vessels. Lymphatics of the glans and penile urethra pass deep to Buck's fascia and drain into both superficial and deep inguinal nodes.

Innervation

The penis is supplied by both somatic and autonomic nerves. The somatic dorsal nerves provide sensory innervation (as well as provide some degree of autonomic function) for the penile skin and glans, and approximately follow the course of the dorsal penile arteries, eventually becoming the pudendal nerve (after joining with other nerves) and entering the spinal cord via S2–S4 nerve roots. Sympathetic autonomic fibers derive from the hypogastric plexus and join parasympathetic autonomic fibers from S2–S4 in the pelvic plexus. Cavernous nerves represent the penile branches of the pelvic plexus that ramify once they have pierced the corporal bodies, and thus contain both sympathetic and parasympathetic fibers.

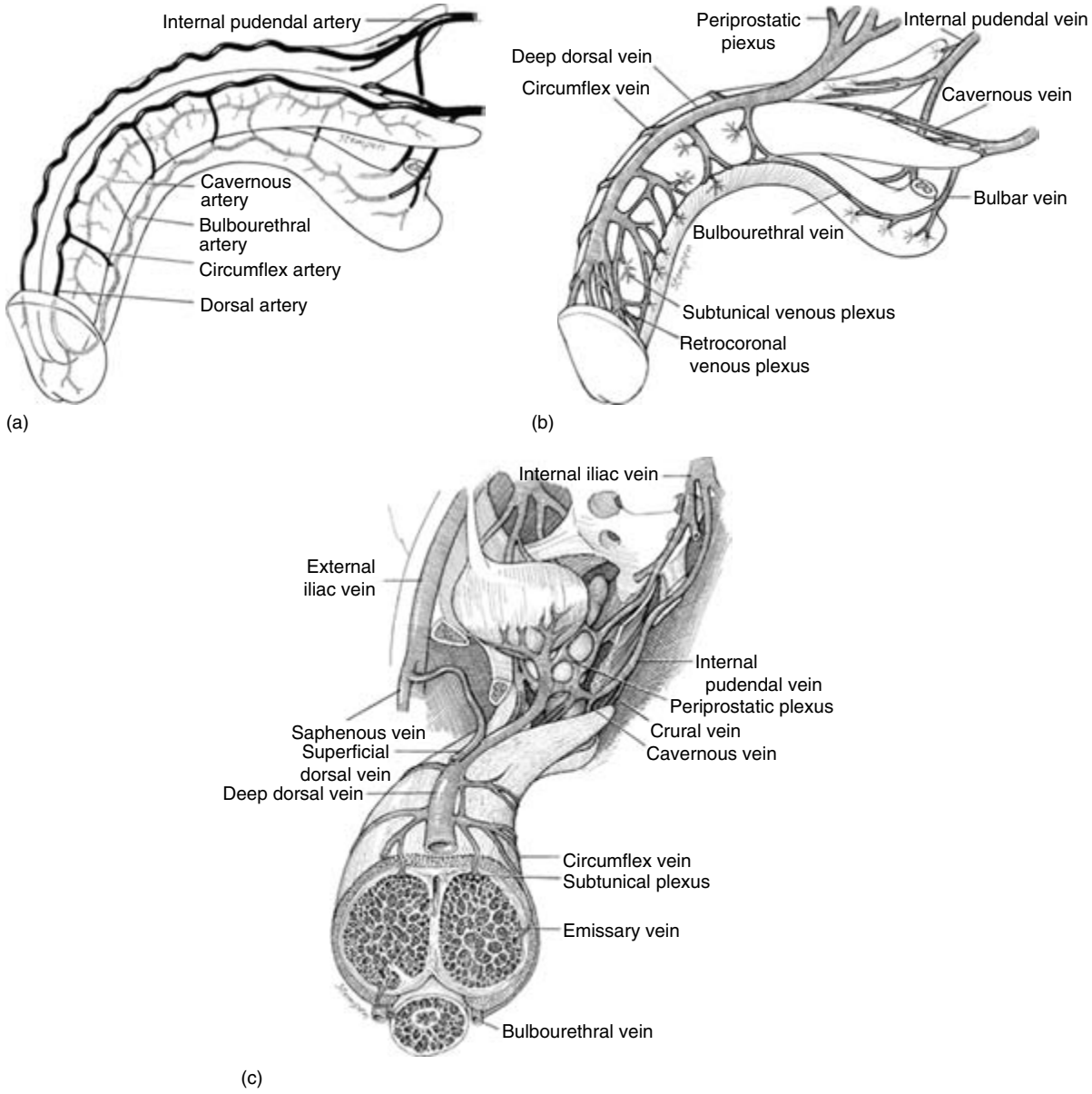

Figure 4.2 Arterial and venous anatomy of the penis. (a) penile arterial supply; (b) penile venous drainage; (c) cross-sectional penile and related pelvic venous drainage. With permission from Mulcahy JJ, ed. Male Sexual Function, 2nd edn. New Jersey: Humana, 2006.[7]

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5 Microscopic anatomy of erectile function

Anthony J Bella, William O Brant, and Tom F Lue

Introduction

Penile erection is dependent upon successful integration of gross and microscopic aspects of neurovascular function, culminating in the hemodynamic changes of tumescence. Recent progress in the understanding of physiologic mechanisms responsible for erectile function has been accompanied by the identification and characterization of key penile ultrastructural components that are able to respond to various stimuli or provide a physical framework for increased blood flow to the corpora cavernosa and veno-occlusive trapping that restricts outflow. In this chapter, the microscopic anatomy of the tunical fibroelastic skeleton of the penis, corpora cavernosa (supportive and smooth muscle components), and penile innervation and blood supply are reviewed in the context of the erectile process.

Tunica albuginea

The primary function of the tunica albuginea is to afford rigidity, flexibility, and tissue strength to the penis.[1] It is a bilayered covering of the corpora cavernosa with multiple sublayers (Figure 5.1). The inner-layer bundles of the corpora cavernosa are circular, and serve to support and contain the cavernous tissue. Furthermore, intracavernosal pillars radiate from the inner layer into the corpora, acting as struts to augment the penile septum and provide support to the erectile tissues. The outer longitudinally oriented layer is composed of connective tissue bundles that extend from the glans penis to the proximal crura, inserting on the inferior pubic rami.[2]

The tunica itself is composed of elastic fibers that form an irregular, latticed network on which the collagen fibers rest (Figure 5.2). This ultrastructural arrangement provides strength and allows the tissue to return to its baseline configuration after the corporal expansion during erection. Key to this function is the composition and distribution of component fibers; the tunica albuginea is primarily composed of type I, but also of type III, fibrillar collagen in organized arrays, throughout which are interspersed elastin fibers.[3] Both fiber types are essential for normal function: the steel-like tensile strength of collagen is unyielding and resists uncontrolled deformity at high pressure, while elastin content allows for tunical expansion because these fibers are able to stretch to approximately 150% of 'resting' length.[4] Elastin content is also a key determinant of stretched penile length.

The presence or absence of both tunical layers, the thickness of the tunica itself and of the intracavernous pillars varies throughout the course of the penis, as does the histological composition, reflecting the relationship between anatomical 'design' and function. The strength and thickness of this layer correlates with location, with the thinnest portion noted to be between the 5 o'clock and 7 o'clock positions.[5] This coincides with the absence of the outer longitudinal layer at the ventral groove over the urethra; extrusion of penile prosthesis is most common at this location.[6] As the crura diverge proximally, circular fibers provide sole support. A higher elastin-to-collagen ratio, as well as the absence of the outer layer and struts, for the tunica overlying the corpus spongiosum ensures a low-pressure structure during erection.[7]

The average thickness of the tunica is also seen to relate to the stress forces applied to this structure prior to penetration (i.e. during rigid erection). The 0.8 ± 0.1mm thickness between the 6 o'clock and 7 o'clock positions has associated forces of $1.6 \pm 0.2 \times 10^7$ Newtons (N)/m^2, there is 1.2 ± 0.2 mm thickness at the 9 o'clock position, with $3.0 \pm 0.3 \times 10^7$ N/m^2, and 2.2 ± 0.4 mm thickness at the 11 o'clock position, with $4.5 \pm 0.5 \times 10^7$ N/m^2 (mirror-image measures are nearly identical).[5]

In addition to providing a supportive framework to the paired corpora, the tunica albuginea is essential to venous trapping, and pathophysiological changes such as those seen with Peyronie's disease may compromise this function and lead to venous leak. The emissary veins, as described in Chapter 4, travel between the inner and outer layers of the tunica for short distances, and often pierce the outer bundles in an oblique manner (Figure 5.3).[8] The outer longitudinal layer serves as a backboard, resulting in compression of the emissary veins during penile engorgement and limiting the amount of penile blood that is able to drain away from the corpora (Figures 5.4 and 5.5). The end-result is maintenance of an erect penis. Inadequate venous occlusion may result in erectile dysfunction (ED) via the following mechanisms:[2]

- degenerative tunical changes secondary to Peyronie's disease, aging, or diabetes, or secondary to traumatic injury impairing subtunical and emissary vein compression;
- alteration in the fibroelastic components of the cavernous smooth muscle, trabeculae, or endothelium;

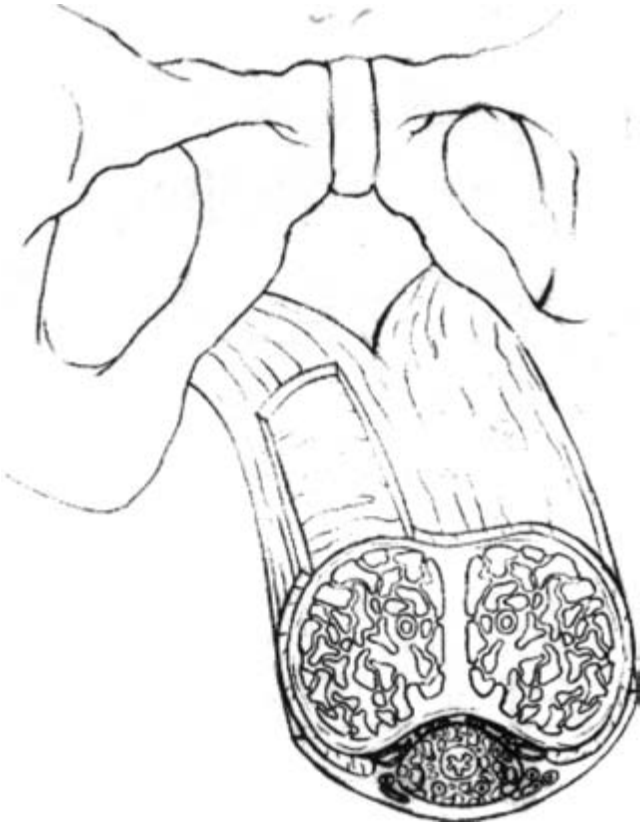


Figure 5.1 Structure of the tunica albuginea.

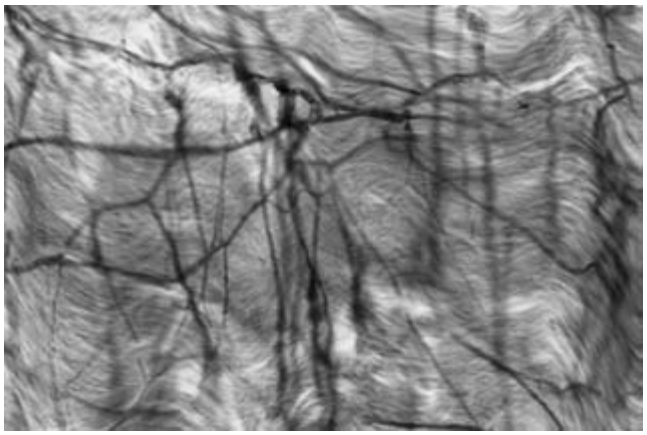


Figure 5.2 Human tunica albuginea, demonstrating interwoven elastic fibers and fine collagen fibers. Reproduced with permission from reference 2.

- inadequate cavernous smooth muscle relaxation;
- acquired venous shunts; or
- congenital anomalous large venous channels.[1]

Inherent differences for the arterial system ensure that occlusion by the tunica albuginea does not occur during tumescence; the cavernous artery and branches of the dorsal artery traverse the outer layer in a more direct (perpendicular) manner and are instead surrounded by a periarterial fibrous sheath, limiting occlusive ability.[3]

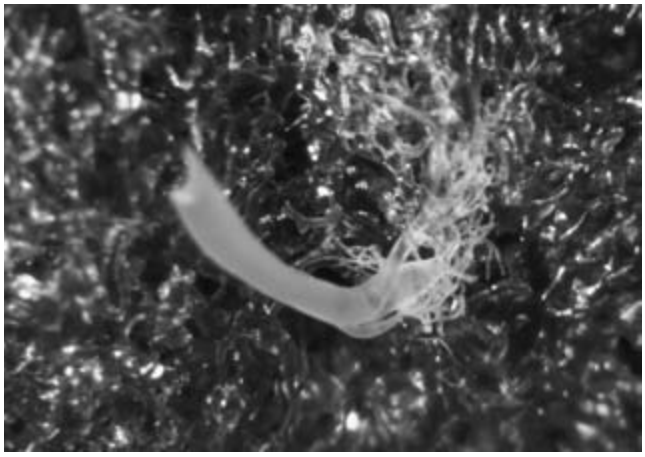


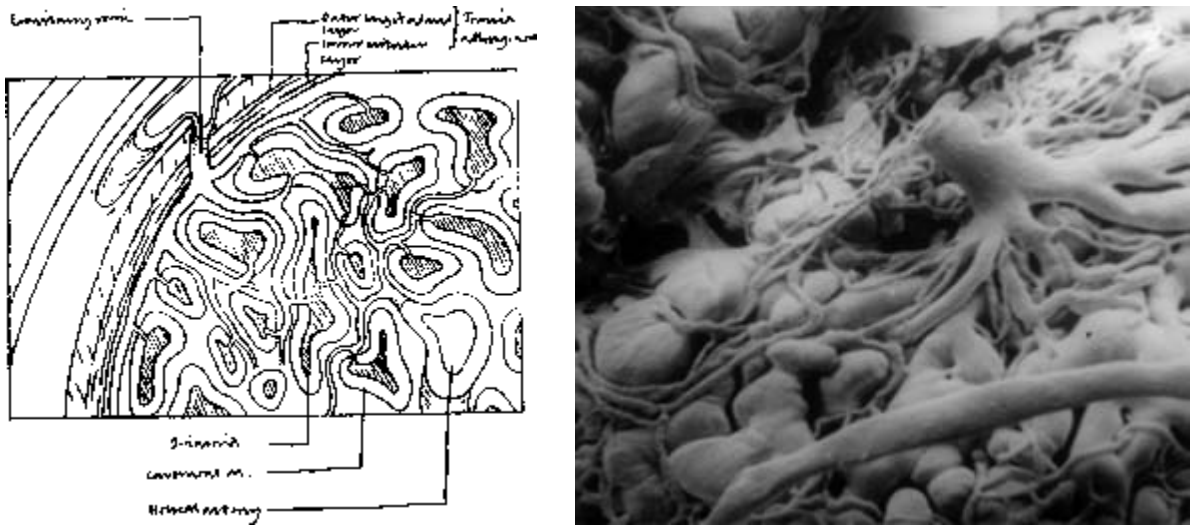
Figure 5.3 Emissary vein with subtunical venous plexus (human penile cast). The cast was made by injecting blue material into the corpus cavernosum and yellow material into the deep dorsal vein. Skin and tunica albuginea were digested away. Reproduced with permission from reference 2.

Corpora cavernosa ultrastructure, the corpus spongiosum and the glans penis

The spongy corpora cavernosa are paired cylinders contained within the supportive envelope of the tunica albuginea; located on the dorsal aspect of the penis, the proximal ends (crura) originate at the undersurface of the puboischial rami as two separate structures and merge under the pubic arch, continuing as a unit to the glans. Support for the corpora is provided by a fibrous skeleton that includes the tunica albuginea, the intracavernous pillars, the intracavernous fibrous network, and the periarterial and perineural fibrous sheath.[2] The midline corporal septum is incomplete, allowing blood to flow from one side to the other.

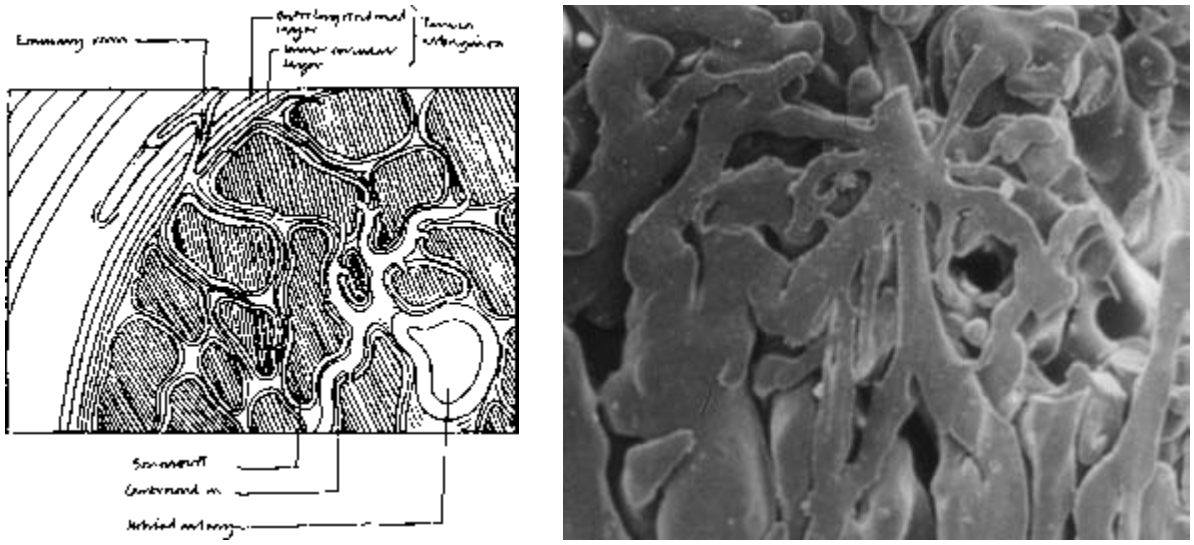
As with the tunica, cavernosal design reflects a functional need for rigidity, strength, and flexibility. It has been suggested that the intracavernous fibrous framework adds strength to the tunica albuginea. Within the tunica are the interconnected sinusoids separated by smooth muscle trabeculae and surrounded by collagen (predominantly types I and IV), elastin, fibroblasts, and loose areolar tissue.[9,10] Smooth muscle predominates, accounting for 45% of corporal volume.[11] Alterations of the cytoskeleton either for tissue type components or for relative quantities may be responsible for changes in penile morphology in flaccid and erect states. For example, loss of compliance of the penile sinusoids has been observed as a by-product of aging, and is associated with increased deposition of collagen; hypercholesterolemia-induced dysregulation of collagen may also cause loss of compliance.[12]

Terminal branches of the cavernous nerves and helicine arteries are intimately associated with corporal smooth muscle; sinusoids are larger in the center and become progressively smaller towards the periphery.[2] Blood slowly diffuses from the central to the peripheral sinusoids in the flaccid state, and the blood gas levels are similar to those of venous blood. During



(a) (b)

Figure 5.4 (a) Microscopic changes during penile erection. In the flaccid state, the arteries, arterioles and sinusoids are contracted. The inter-sinusoidal and subtunical venular plexuses are open, allowing free flow to the emissary veins. (b) Scanning electron micrograph of canine subtunical venous plexus cast in flaccid state. Part (b) reproduced with permission from reference 2.



(a) (b)

Figure 5.5 (a) In the erect state, the muscles of the sinusoidal wall and the arterioles relax, allowing maximal flow to the compliant sinusoidal spaces. Most of the venules are compressed between the expanding sinusoids. The larger intermediary venules are sandwiched and flattened by distended sinusoids and the tunica albuginea; this effectively reduces the venous flow to a minimum. (b) Scanning electron micrograph of canine subtunical venous plexus cast in erect state. Part (b) reproduced with permission from reference 2.

erection, the oxygen tension approximates that of arterial blood due to the rapid entry of arterial blood to the central and peripheral sinusoids.[13]

Corporal geometry is a key characteristic that allows erections to occur.[14] Midline septal fibers stretch tautly between the dorsal and ventral corporal aspects, creating a functional 'I-beam', resulting in anteroposterior rigidity.[7] Relative indispensability of the paired lateral columns adds to stability during erection, while intrasinusoidal pressures within the corpora distend the tunica albuginea to its maximal capacity.[2] The tunica itself resists out-of-column deformities.

The structure of the corpus spongiosum is similar to that of the corpora except that sinusoids are larger and the outer layer of the tunica is absent. Intraspongiosal pressures reach only one-half to one-third of those of the cavernosa, owing to the less constraining tunical layer, resulting in lesser venous occlusion.[12] The glans itself has no tunical covering, but is able to engorge, owing to the presence of continued arterial inflow and venous outflow during erection (a functional arteriovenous fistula).[2] Partial compression of the deep dorsal and circumflex veins between Buck's fascia and the engorged corpora cavernosa also contribute to glanular tumescence. During the rigid erection phase, spongiosal and penile veins are externally compressed by the ischiocavernosus and bulbocavernosus muscles, further increasing engorgement and pressure in the glans and spongiosum.

Cavernous smooth muscle

In the flaccid state, cavernous (or corporal) smooth muscle is tonically contracted with a partial pressure of oxygen measuring approximately 35 mmHg.[13] Blood flow to the penis is approximately 5 ml per minute.[15] With sexual stimulation and the release of neurotransmitters from the cavernous nerve terminals (see Chapter 11) smooth muscle relaxation occurs, and the end-result is an erect penis. Modulation of the cavernous smooth muscle tone is a complex process regulated by a myriad of intracellular events and extracellular signals, and therefore it is not surprising that the ultrastructure reflects these physiologic functions.

Cavernous smooth muscle cells are composed of thin, intermediate, and thick filaments, which are primarily composed of, respectively, actin, desmin or vimentin, and myosin.[3] In humans, two types of electrical activity have been reported for the corpus cavernosum: spontaneous and activity-induced.[16] Further, DiSanto and associates have reported overall composition to be in between that of aortic (tonic) and bladder smooth muscle (phasic).[17]

Smooth muscle contraction and relaxation is primarily regulated by sarcoplasma free calcium. Each of the filament types has a specific role, but the primary mechanism is the interaction between actin and myosin. Contractile tone is conferred by cross-bridges linking regulatory myosin light chain globular heads and actin; tone is maintained with minimal expenditure of energy.[18] Relaxation occurs as cytosolic calcium is lowered.

Smooth muscle fibers damaged by vasculogenic or neurogenic causes of impotence demonstrate similar ultrastructural changes, suggesting a variety of pathological mechanisms with common end-points.[19] Patients undergoing implantation of a penile prosthesis for ED of varying etiologies have been shown to have a decreased number of smooth muscle cells and sinusoidal endothelial changes.[2] The decreased oxygen tension of arteriogenic ED may diminish trabecular smooth muscle content, leading to venous leakage. Hypercholesterolemic rabbits demonstrate early atherosclerotic changes and significant smooth muscle degeneration with loss of cell-to-cell contact.[20] Diabetes may compromise contractility, reduce cavernous smooth muscle content, thicken the basal lamina, increase collagen, and cause the loss of endothelial cells.[2] Cavernous nerve injury at the time of radical prostatectomy may also decrease levels of cavernous smooth muscle while increasing collagen content, compromising the erectile process.[21]

Functional neuroanatomy

Penile innervation is both autonomic (sympathetic and parasympathetic) and somatic (sensory and motor). The cavernous nerves are the primary influence on the neurovascular events during erection and detumesence; they originate from neurons in the spinal cord and peripheral ganglia, and they consist of sympathetic and parasympathetic fibers (Figure 5.6). Somatic nerves fulfill sensory roles and contract the bulbocavernosus and ischiocavernosus musculature.

Parasympathetic fibers originate from the second, third, and fourth sacral vertebral segments (S2, S3, and S4) of the spinal cord; S3 is the primary source of erectogenic fibers.[22] The cavernous nerves project from the pelvic plexus, leaving the pelvis between the transverse perineal muscles and membraneous urethra. Cadaveric dissection has identified medial and lateral branches, which accompany the urethra and pierce the urogenital diaphragm 4 mm and 7 mm laterally to the sphincter, respectively, as well as multiple communications between the cavernous and dorsal nerves.[23] Since cavernous nerve damage during extirpative surgeries for prostate, bladder, and rectal cancer commonly causes neurogenic ED, it is essential to understand their anatomic course. Preservation and minimal disruption of these nerves is paramount, because they represent the final pathway for vasodilatory and vasoconstrictive input to the cavernous smooth muscle; cavernous nerve injury may also occur secondary to pelvic fracture, with ED the end-result of direct nerve trauma, vascular insufficiency, or a combination of both.[3] The cavernous nerve itself divides into a lesser branch (supplying the corpus spongiosum erectile tissue and penile urethra) and a major branch (enabling penile erection). The major branch courses along the prostatovesicular artery and veins as part of the neurovascular bundle of the prostate.[23,24] Key surgical landmarks are as follows.[23,24]

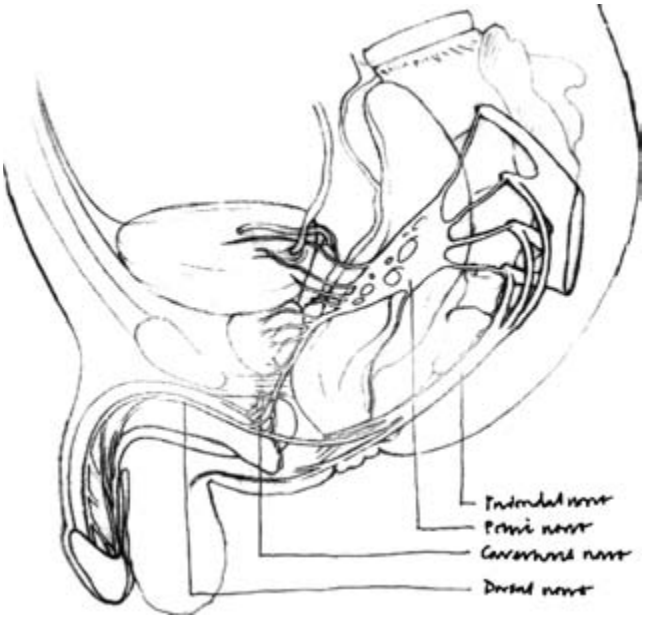


Figure 5.6 Somatic and autonomic innervation of the penis.

- After passing the tip of the seminal vesicle, the cavernous nerve continues along the posterolateral aspect of the prostate at the five o'clock and seven o'clock positions within the endopelvic fascia.
- At the level of the prostatic apex and membranous urethra, the nerves are located at the three o'clock and nine o'clock positions.
- Distally, some fibers penetrate the tunica albuginea of the corpus spongiosum while the remaining fibers proceed more anteriorly at the eleven o'clock and one o'clock positions. These enter the penile crura along with terminal branches of the pudendal artery and exiting cavernous veins.

Sympathetic preganglionic cavernous nerve fibers are primarily responsible for detumescence; these fibers arise from preganglionic neurons in intermediolateral gray matter from the eleventh thoracic (T11) to the second lumbar (L2) spinal cord segments. Variability in cavernous nerve composition (i.e. in the ratio of parasympathetic to sympathetic fibers), as well as in sympathetic fiber origin (from as high as the ninth thoracic cord segment to as low as the fourth lumbar cord segment), has been described.[7,25] These preganglionic fibers most commonly arise from the tenth thoracic to the second lumbar segments, passing to the paravertebral sympathetic chain ganglia where synaptic connections with ganglion cells are formed. Postganglionic fibers originating in the sacral and caudal lumbar ganglia proceed to the urogenital tract via the cavernous nerves as well as via the pelvic and pudendal nerves. A second pathway for sympathetic preganglionic fibers occurs without lumbar synaptic contacts; fibers leave the chain ganglia and pass along the lumbar splanchnic nerves to prevertebral ganglia in the superior hypogastric plexus (overlying the great vessels at the third lumbar to first sacral vertebrae).[3] The superior hypogastric plexus (or presacral nerve) divides into the left and right hypogastric nerves, descending to the inferior hypogastric (or pelvic) plexus. In addition to their role in the erectile process, sympathetic fibers from T11–L2 are also responsible for contraction of internal accessory organs (prostate smooth muscle, seminal vesicle, and bulbourethral gland), ducts (ejaculatory ducts, vasa deferentia, ductus epididymis, ductuli efferentes), closure of the internal urethral sphincter, and ejaculatory emission.[2,3,7]

Sensory (somatic) function of the glans is unique, in that 80–90% of afferent glans terminals are unmyelinated C or myelinated A-δ fiber-free nerve endings.[26] Sensory pathways also originate at receptors found within the penile skin, urethra and corpus cavernosum, with nerve fibers from these receptors converging to form bundles of the dorsal nerve of the penis. The dorsal nerve joins other nerves to become the internal pudendal nerve, entering the spinal cord at the dorsal roots of S2–S4 to terminate in the central gray region of the lumbosacral segment.[2] Spinothalamic and spinoreticular pathways to the thalamus and sensory cortex convey messages of pain, temperature, and touch via the dorsal and pudendal nerves. Afferent input from the skin and glans is also the mechanism responsible for reflexogenic erections. It is important to note that the dorsal nerve of the penis is not purely somatic, but also contains nerve bundles demonstrating nitric oxide synthase, which is indicative of autonomic function, therefore providing evidence for a dual role (erectile and ejaculatory function).[27]

The center of somatomotor penile innervation is Onuf's nucleus in S2–S4. The motor pathway to the penis traverses the sacral nerves to the pudendal nerve, innervating the bulbocavernosus muscle (rhythmic contraction of ejaculation) and ischiocavernosus muscle (contraction results in the rigid erection phase) via the perineal branch. The pudendal nerve leaves the pelvis via the greater sciatic foramen on the medial aspect of the internal pudendal artery; it continues as the dorsal nerve of the penis along the dorsal artery, terminating at the glans.[28]

Intercellular communication

Histological studies of the cavernosal tissues have demonstrated that autonomic innervation consists of widely spaced nerve fibers. However, the process of penile erection and detumescence requires a co-ordinating mechanism among the cavernous smooth muscle fibers that allows synchronized relaxation and contraction; electromyography confirms that activity in the cavernous tissue of patients with normal erectile function is synchronous.[29,30]

Transport channels termed 'gap junctions' are present in the membranes of adjacent cavernous smooth muscle cells, allowing exchange of ions such as calcium and second messenger molecules.[31] Electron microscopy demonstrates prominent gap junctions, which are formed by a hemichannel hexamer of connexin proteins, creating pore-like aqueous intercellular channels.[2,3] The major component of gap junctions is connexin-43, a membrane-sparing protein of less than 0.25 μm that has been identified between smooth muscle cells of human corpus cavernosum and that facilitates the transmission of electrical or chemical signals.[32] Cell-to-cell myocyte communication does not occur via individualized innervation, rather via gap junction links that allow synchronized smooth muscle tone. These connections have been shown to modulate nitric-oxide-induced cavernous smooth muscle relaxation, as well as alpha-1-adrenergic- and enthothelin-1-induced contractility. Although their pathophysiological impact is not fully elucidated, connexin-43 expression in cavernous tissues excised from men with organic erectile dysfunction demonstrates significant heterogeneity.[3] For example, in men with severe arterial disease, a loss or reduction of membrane contact has been demonstrated as the presence of collagen fibers between cellular membranes alters the co-ordinated smooth muscle response to erectile stimulus.[33]

Arterial microanatomy of the penis

The majority of the arterial supply to the erectile tissue is via the cavernosal artery, which itself is a branch of the internal pudendal artery (the terminal branch of the hypogastric artery) (Figure 5.7). The cavernosal artery extends through the cavernosal bodies after entering at the inferomedial aspect of the hilum of the penis where the crura merge, piercing the tunica. At the base of the penis the cavernosal arteries are close to the septum, whereas distally they are centrally located in each cavernosal body. Two types of branches occur: outer capillaries, which provide nutrition during flaccidity, supplying the nerve fibers and smooth muscle; and multiple helicine branches, which supply the erectile tissue, opening directly into the cavernous spaces without entering capillaries and then emptying into postcavernous venules (Figure 5.8). The helicine arteries appear tortuous and contracted when the penis is flaccid, becoming straight and larger in caliber during erection. The corkscrew-like shape ensures that flow is not compromised, allowing for elongation and dilatation. These arteries are surrounded by multiple layers of smooth muscle, which remains contracted during the non-erect state (allowing only small quantities of blood into the lacunar spaces).[2,3,7]

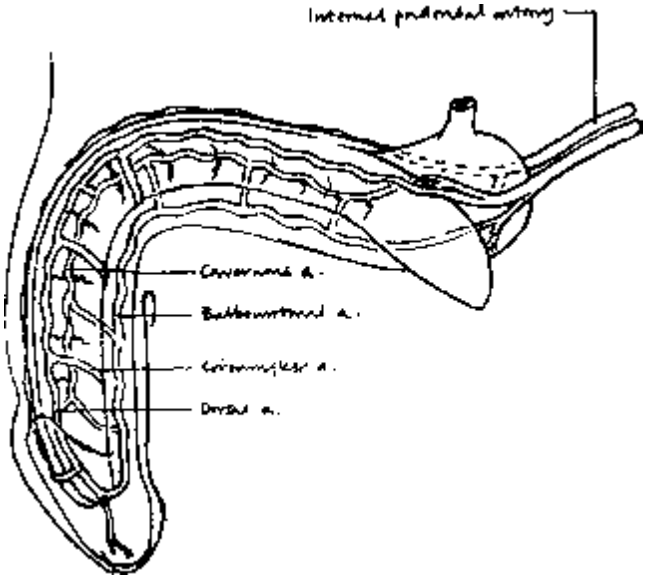


Figure 5.7 Arterial supply of the penis.

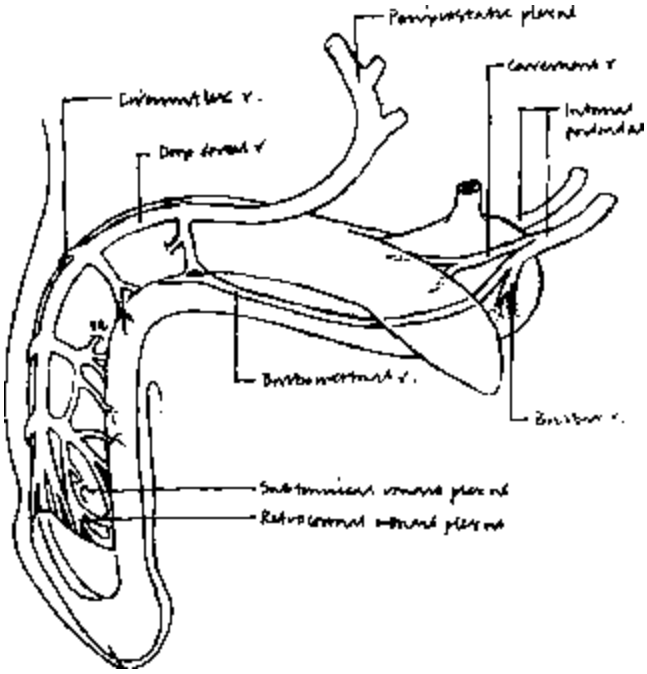


Figure 5.8 Venous drainage of the penis.

It is not uncommon for the erectile tissue to be primarily supplied by accessory arteries, such as the accessory pudendal artery. In fact, the dominant blood supply to the corpora may arise from the external iliac, obturator, vesical or femoral arteries, or even derive exclusively from a single (unilateral) cavernous or accessory pudendal artery.[34] Careful preservation during radical prostatectomy is suggested for the accessory pudendal vessels, as this maneuver has been shown to protect, and hasten the recovery of, sexual function.[35]

In addition to the cavernosal artery, the common penile branch of the internal pudendal artery branches in the anterior perineum into the dorsal artery of the penis and the bulbourethral artery. These vessels form a vascular ring near the glans; the paired dorsal arteries course within the neurovascular bundles at the eleven o'clock and one o'clock positions, lateral to the dorsal vein and medial to the dorsal nerves. The dorsal arteries supply the more superficial components of the penis; they supply the spongiosum distally via circumflex branches; they provide frenular branches; and they may contribute to the blood supply of the erectile bodies.[2] They are also responsible for glans engorgement during erection. The bulbourethral artery continues as the urethral artery after its bulbar offshoot, coursing along the ventral surface of the corpus spongiosum beneath the tunica albuginea. Of note, given the blood supply to the glans, it can be completely separated from the corpora cavernosa during surgery without compromising vascularization.

Decreased perfusion pressure and arterial flow to sinusoidal spaces may occur, owing to atherosclerotic or traumatic arterial occlusive disease of the hypogastric–cavernous–helicine arterial tree; clinically, arterial disease may manifest itself as an increased time to maximal erection or as decreased rigidity. As the number of vascular risk factors increases (e.g. hypertension, hyperlipidemia, diabetes, and cigarette smoking), the occurrence of atherosclerotic lesions of the internal pudendal, common penile, and cavernous arteries increases significantly.[36] On the other hand, a focal stenosis of the common penile or caverous artery is most often seen in young patients who have sustained blunt perineal or pelvic trauma.[37] Thus, both generalized and focal arterial disease may manifest itself as erectile dysfunction.

Conclusion

The microanatomy of erectile function reflects the physiological changes necessary for the human penis to attain an erect state. Erection is dependent upon intact innervation and arterial supply, as well as on a normal cavernous smooth muscle response to stimuli and an efficient veno-occlusive trapping mechanism. During erection, the relaxation of smooth muscle in the cavernous trabeculae and arterial walls facilitates the complex cascade responsible for penile rigidity:[12]

1. Increased penile blood flow caused by dilation of arterioles and arteries.
2. Expansion of sinusoids and resultant trapping of blood.
3. Compression of subtunical venous plexuses between the tunica albuginea and peripheral sinusoids, reducing venous outflow.
4. Tunica albuginea expansion, further decreasing venous outflow as emissary veins are occluded between inner circular and outer longitudinal layers.
5. Intracavernous pressure increase to approximately 100 mmHg (full erection phase).
6. Ischiocavernous muscle contraction, which further increases intracavernous pressures to several hundred mmHg (rigid erection phase).

Detumescence occurs as gradual smooth muscle contraction against a closed venous system causes a transient increase in

intracavernous pressure, followed by a slow pressure decrease as venous channels open with a resumption of basal arterial flow, and, finally, a rapid pressure decrease with fully restored capacity for venous outflow.

Whether isolated to a single element of penile microscopic anatomy or occurring on more than one tissue level, pathologic structural changes may compromise the physiologic processes that lead to penile erection, and so result in erectile dysfunction.

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6 Vascular physiology of erectile function

Noel N Kim

Introduction

The previous chapters on penile anatomy emphasize the importance of the vasculature in mediating erectile function. The penile corpora cavernosa are highly specialized vascular structures that are uniquely suited to their function of becoming engorged during sexual arousal. In addition, the network of resistance arterioles that carry blood to the corpora cavernosa plays an equally important role in determining the state of penile engorgement. In the non-aroused, flaccid state, the arterial and trabecular smooth muscle remain constricted, and the hemodynamic environment of the corpora cavernosa is similar to the venous circulation in terms of pressure, flow, and oxygen tension. There is low resistance to the drainage of blood from the cavernosal bodies, and this contributes to the maintenance of penile flaccidity.

The onset and maintenance of penile tumescence is initiated by central psychogenic or peripheral reflexogenic sensory stimuli (or both), as described in greater detail in the following chapters. Both central and peripheral pathways stimulate sacral parasympathetic efferent nerve fibers, which ultimately cause the relaxation of the vascular smooth muscle in the resistance arterial bed and the trabeculae of the corpora cavernosa. These events result in a higher rate of blood flow into the penis, and greatly increase the compliance of the cavernosal bodies, enabling expansion and accommodation of the increased blood volume within the cavernosal lacunae. The increased blood flow also potentiates local vasodilation through endothelial shear stress-induced responses. During this early filling phase, the hemodynamic environment within the erectile tissues transitions into an arterial system with respect to blood flow and oxygen tension. However, blood pressure remains low.

The rapid volume expansion of the erectile tissue leads to engagement of the veno-occlusive mechanism, reducing the outflow of blood. The restriction of blood drainage is accomplished by elongation and compression of the subtunical venules that are located between the corpora cavernosa and the tunica albuginea. Veno-occlusion enables the trapping of blood within the cavernosal sinusoids and causes the intracavernosal pressure to rise to systemic arterial levels. As the pressure gradient between the systemic arterial circulation and the intracavernosal vascular compartment is dissipated, blood flow decreases. Altogether, these events act in concert to achieve and maintain full tumescence and rigidity.

Thus, changes in smooth muscle tone are crucial for regulating erectile function. In that regard, continuing research to elucidate the myriad of mechanisms that regulates vascular smooth muscle cell (VSMC) contractility is essential to understanding erectile physiology. The basic paradigm of smooth muscle, endothelium, and nerve interactions to influence vascular reactivity is universally acknowledged, but warrants more detailed consideration within the context of genital tissues. This chapter describes the basic mechanisms that regulate VSMC contractility, including additional consideration of non-contractile responses in VSMCs. However, discussion of specific neurotransmitters, receptor pharmacology, and regulation of extracellular matrix by smooth muscle have been omitted, since these are addressed elsewhere in this book. While much of the information specific to genital tissue vascular physiology is derived from studies on penile corpus cavernosum, findings from cardiovascular research will also be presented to gain further insight into VSMC function.

Endothelium: an active regulator of vascular function

The endothelium consists of a monolayer of cells that forms a continuous surface, lining the vascular compartment throughout the body. The total mass of the endothelium has been estimated to be 500 g in the average adult human, the majority of which is contained in the pulmonary vasculature.[1] Much like skin, the endothelium may be considered a single organ with multiple functions and differential responses that are dependent upon both the systemic and local environments. Among other functions, a healthy endothelium serves to provide an anti-thrombotic, anti-inflammatory, and anti-atherogenic surface while also regulating vascular tone and permeability. The importance of endothelial regulation can be better appreciated by considering pathological states that have in common dysfunctional endothelium. Endothelium-dependent relaxation of blood vessels has been shown to be compromised in animal models of atherosclerosis, hypertension, diabetes, aging, smoking, and renal failure.[1–4] Thus, diseased or damaged endothelium has been proposed to be a major contributor to vascular insufficiency of genital tissues.

The endothelium produces many vasoactive compounds that can influence the contractile, trophic, or synthetic function

of vascular smooth muscle cells. Factors that cause relaxation include nitric oxide (NO), carbon monoxide, endothelium-derived hyperpolarizing factor, prostacyclin and endothelin (through ET_B receptors). Factors that cause contraction include endoperoxides, thromboxane A_2, superoxide anions, and endothelin (through ET_A receptors). One of the more novel mechanisms of regulating endothelial signaling involves changes in the number of caveolae on the surface of endothelial cells. Caveolae are invaginated microdomains of plasma membrane that are rich in endothelial NO synthase and contain the family of transmembrane structural proteins known as caveolins, as well as cholesterol, sphingolipids, and glycosyl phosphatidyl inositol-linked proteins. In addition, caveolae contain numerous other signaling proteins, such as receptors with seven-transmembrane domains, G proteins, adenylyl cyclase, phospholipase C, protein kinase C, calcium pumps, and calcium channels. Thus, these specialized signaling regions have been termed transductosomes.[5]

Multiple functions of vascular smooth muscle

As a major constituent and primary effector of the vascular structures in the genitals, the VSMC is highly adaptable and multi-functional. The two primary functions of VSMCs are contraction and synthesis or maintenance of extracellular matrix. In cell culture experiments, VSMCs have been characterized as having either 'contractile' or 'synthetic' functional phenotypes. However, these two categories are considered to be extremes that are manifested under *in vitro* conditions, and it is likely that a range of intermediary phenotypes exist in any given tissue *in vivo*. Increasingly, protein and gene expression studies are illustrating the ability of VSMCs to alter their cellular phenotypes in response to changes in their environment.[6,7] In addition, studies by developmental biologists indicate that VSMCs in different vascular beds may arise from varying cellular lineages (multiple sources of progenitor cells) and can be recruited from different locations in the developing embryo.[8] Furthermore, comparative studies have led investigators to speculate that lineage-specific differences in VSMC growth and transcriptional responses may persist beyond the early developmental period and into the adult organism.[8] It remains unclear as to what extent the observed heterogeneity of VSMCs is due to adaptation in altered cellular environments as opposed to differences in lineage. The apparent mosaic nature of smooth muscle throughout the body may account for some of the diversity in responses found in different vascular tissues in health and disease. Nevertheless, most VSMCs in peripheral blood vessels are derived from the mesoderm and exhibit a set of common characteristics.

Co-ordinated regulation of vascular smooth muscle cells

Most VSMCs in blood vessels and in cavernosal tissues are not adjacent to, or in direct contact with, an endothelial cell or nerve terminus. However, the thickness of any arteriole or trabecular bundle is limited to several cell layers. Given this arrangement, intercellular communication, for the purpose of regulating smooth muscle tone in a co-ordinated fashion, can be accomplished by two general mechanisms:

- extracellular diffusion of vasoactive and trophic factors released by endothelium, nerves and smooth muscle (paracrine and autocrine regulation); and
- intracellular diffusion of second messengers from stimulated cells into adjacent cells by means of gap junctions.

These mechanisms are not mutually exclusive and it is likely that they act in complementary fashion to propagate regulatory signals.

Extracellular diffusion of regulatory substances requires sufficient concentrations to be secreted near a population of effector cells. The magnitude of the response is determined by the number of cells directly stimulated by the secreted substance. In contrast, intracellular propagation of signals across multiple cells through gap junctions does not require each responding cell to be activated by the initial stimulus. A single cell may be stimulated by a secreted substance and generate second messengers that can diffuse into neighboring cells. In this mechanism, the magnitude of response is directly proportional to the number of cells activated by the spread of intracellular messengers, rather than the number of cells directly stimulated by the secreted substance.

The structure and function of gap junctions in the vasculature have been studied for the past several decades. VSMCs and endothelial cells are known to form functional syncytia by virtue of junctional plaques in their plasma membranes.[9,10] These plaques contain hundreds to thousands of gap junction complexes. The diameters of plaques between VSMCs range from 0.2 μm to 0.5 μm, whereas those between endothelial cells have been observed to be up to twice as large.[9] The area of each junctional plaque may be important in determining the rate of signal propagation. Each gap junction channel is formed by the docking of two hemi-channels, each hemi-channel being contributed by an opposing cell. Hemi-channels are hexameric structures formed from connexins, a large family of proteins derived from multiple genes.[11] VSMCs have been shown to express connexin (Cx) 40 and Cx43, whereas endothelial cells express Cx37 in addition to Cx40 and Cx43.[9] Cx proteins apparently have relatively short half-lives with estimated cycling times of 1–5 hours.[10] This suggests that junctional plaques are highly dynamic structures that may have the ability to attenuate or potentiate smooth muscle responses.

While the role of most connexins has not been studied in genital tissues, the expression of Cx43 has been confirmed in smooth muscle and endothelial cells derived from human penile corpus cavernosum.[9,10] Furthermore, functional and pharmacological studies suggest that they play an important role in signal propagation.[12] In studies using non-genital tissues, junctional plaques between endothelial and smooth muscle cells have been observed.[13,14] However, the presence of these 'myoendothelial' gap junctions has not been studied in genital tissues and their significance remains unclear. Thus, gap junctions enable smooth muscle and endothelial cells to form a continuous network of functional units. These cellular networks can rapidly co-ordinate the response to various