Impotence in the Age of Viagra

by Arnold Melman

Just as the birth-control pill ushered in the sexual revolution for many women, Viagra has brought about its own revolution for men. Since the introduction of the drug last year, millions of men have sought and received prescriptions of Viagra for the treatment of impotence, which doctors commonly refer to as erectile dysfunction. The rush for this medication and physicians' willingness to dispense it mark a sea change in how people view the condition, which decades ago was considered to be mainly of psychogenic origin—in other words, "it's all in your head."

This change has significant impact for the approximately 10 percent of the male population who will at some point in their lives face the complete inability to achieve or maintain an erection. This condition, which becomes more prevalent with age, has the effect of making sexual intercourse difficult, if not impossible. Although proved medical interventions have been available for more than 20 years, recent advances in the understanding of the processes that lead to an erection have spurred new treatments and promise even more targeted therapies in the future.

Before the advent of modern therapies, erectile dysfunction was often treated through psychoanalysis, when treated at all. Now many cases can be diagnosed as having organic causes, including nerve damage, hormonal imbalances and vascular diseases. The shift in diagnoses from psychogenic to organic has moved the primary responsibility for treating patients from psychiatrists to urologists. A second shift has recently taken place, spurred by the introduction of Viagra: family and general practitioners and internists now treat, with a simple prescription, most cases of erectile dysfunction in this country. A third change may take place in the future: with the aging of our population, geriatricians may become most responsible for treating the condition.

Although our understanding of the penis's erectile mechanism allows us to treat the organic causes of dysfunction in many ways, Viagra has become a catch-all cure. The famous blue pill is now the treatment of choice in approximately 95 percent of erectile dysfunction cases. This development raises some concerns: in many cases, other treatments aside from Viagra may be safer and just as effective. But on the positive side, Viagra has brought impotence out of society's closet and changed the way men and their doctors confront the condition.

Penile Anatomy

To understand the causes of erectile dysfunction, one must first know something about the anatomy of the penis. The organ's functions, of course, are to enable urine to exit the body and, when rigid, to help introduce sperm into the vaginal canal. An erection, however, is not absolutely necessary for impregnation of a female partner, because orgasm and ejaculation can occur in a semirigid state. The penis contains three well-vascularized cylinders of spongy tissue: the two corpora cavernosa and the corpus spongiosum [*see illustration on page 64*]. The latter has in its center the urethral channel, a tubular structure lined with specialized flattened cells through which urine passes. The three cylinders act as draining pools for the penis's blood supply, producing an erection when they are engorged. Smooth muscle and nerve beds line the entire phallus.

Blood flows toward the penis from the two pudendal arter-

A new understanding of the mechanism that causes erections has led to a wide range of options for treating impotence

ies, which emerge from the pelvis and then separately fork into two smaller branches, the dorsal and cavernous arteries, which run into the penis. Because the pudendal artery passes through the region between the anus and the base of the scrotum before reaching the penis, it is particularly vulnerable to injuries such as pelvic fracture or trauma from falling onto a post or bicycle bar [see "Spokes Man for a Hard Problem," on page 60]. The two branches of the pudendal artery branch off into smaller arteries once inside the penis, decreasing to a diameter of only 0.4 millimeter when the penis is flaccid. These relatively narrow blood vessels are susceptible to blockage from various arterial-narrowing conditions such as hypertension and atherosclerosis. The high incidence in our society of cardiovascular disease, which is exacerbated by diabetes and smoking, makes diminished blood flow to the penis the most common cause of organic erectile dysfunction.

Three primary types of cells live in the tissue of the penile corpora cavernosa: endothelial cells, smooth muscle cells and neurons. Endothelial cells line blood vessels and the sinusoids—the spaces within the corpora cavernosa—and secrete substances that aid in the relaxation and contraction of adjacent smooth muscle cells.

The penis has two states, flaccid and erect. The difference between the two depends on the filling of the penile chambers with blood up to the level of pressure in the major arteries of the body. For humans, this level is an average systolic blood pressure of 120 millimeters of mercury. If not sexually active, normal men are flaccid about 23 hours of the day, with approximately one aggregate hour of erection occurring during a part of rapid eye movement (REM) sleep. Men average four or five REM erections a night, each lasting about 15 minutes. Although the cause and function of these erections are not known, they are associated with dreaming. The frequency of REM erections usually diminishes with age. The number and duration of daytime erections for sexually active men varies greatly from person to person.

When flaccid, the penis's corporal sinuses have a blood pressure of only a few millimeters of mercury and blood flow of only five milliliters per minute (five milliliters is equivalent to one teaspoon). Whereas this is relatively low compared with other organs, such as the kidney—which receives about 500 milliliters per minute—it is sufficient to supply oxygen and nutrients to the penile tissue. The amount of blood entering the penis is regulated by the tone of the smooth muscle cells that line the three spongy corpora. When these muscle cells contract, blood flows freely in and out of the penis. When the cells relax, however, they press against the small veins that drain blood from the corpora. This pressure compresses the vessels like a closing valve; blood pools in the spongy tissues, and an erection occurs. But certain diseases and medications, as well as aging and anxiety—with its concomitant elevation of stress hormones in the blood—can prevent the smooth muscle cells from relaxing, thus keeping the valve partially or completely open. The corporal sinusoids then cannot fill with blood.

The Science of Stimulation

Most men do not walk around with a constant erection; this is because of the brain's inhibitory control over the erectile mechanism. (When that control is removed suddenly, as in the case of a hanging, a spontaneous erection sometimes occurs.) A stimulus is needed to begin the process. This sexual signal can be visual, tactile, auditory, gustatory or olfacto-

TREATMENTS FOR IMPOTENCE include **(clockwise from top)** ***a vacuum pump; a flexible penile implant; Viagra pills; a MUSE applicator, which inserts prostaglandin into the urethra; an inflatable penile implant; and Caverject, an injection of prostaglandin*** **(at center).**

SAM OGDEN

ry, or it may arise during dream-associated sleep. Conscious or unconscious neurological signals originating in the cerebral cortex and limbic system are sent to the hypothalamus and relayed down the spinal cord into the sympathetic and parasympathetic neurons of the penis. The nerve endings then release neurotransmitters that relax the smooth muscle cells lining the corporal bodies and the arteries supplying blood to the penis. More blood enters than exits, and the penis becomes rigid. The entire sequence of events, from stimulation to erection, can take place in seconds.

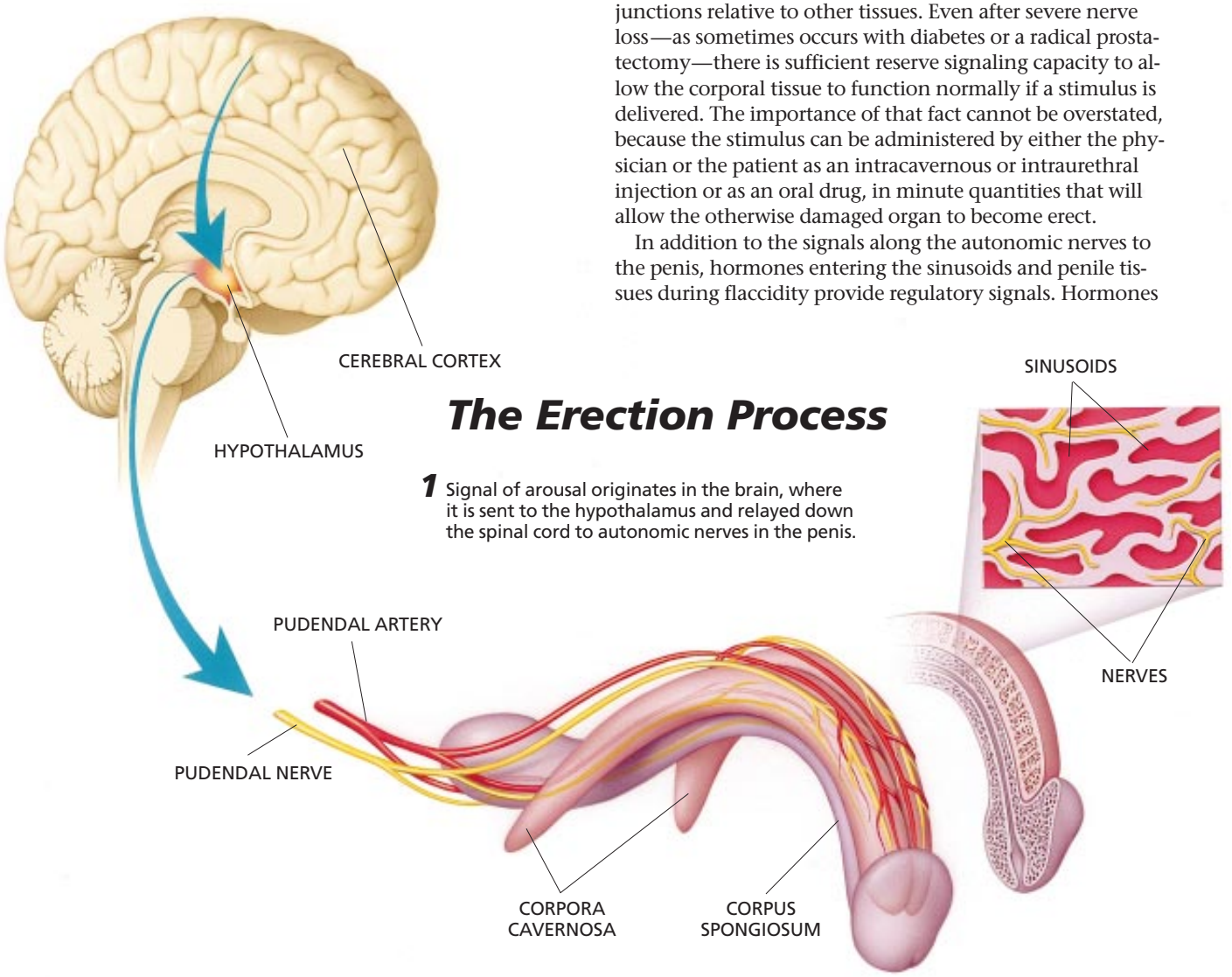
Many types of nerves and molecules participate in the signal transmission that culminates in an erection. The primary pathway is through autonomic nerve fibers that release molecules of nitric oxide near the smooth muscle cells of the penis. The nitric oxide diffuses through the cell membranes and begins a chemical cascade that culminates in the relaxation of the cells [*see illustration on opposite page*]. The secondary pathway is through cholinergic nerves, which release the neurotransmitter acetylcholine. This chemical stimulates endothelial cells to produce nitric oxide, which then seeps into the adjacent smooth muscle cells. But the most abundant nerves in the penis are actually adrenergic fibers, which provide brakes to the erection process in the absence of stimulation.

Regulation of the erection process depends on the concentrations of certain ions within the smooth muscle cells, and those concentrations can be affected by other neurotransmitters. For example, the neurotransmitter norepinephrine increases the amount of calcium ions (Ca^{++}) in the cells, prompting them to contract. Men who are anxious, cold or afraid sometimes secrete large quantities of norepinephrine, which causes transient contraction of the penile smooth muscle; the penis shrinks in length and cannot become erect. Potassium ions (K^{+}) also play an important role in regulating the contraction and relaxation of smooth muscle cells. When potassium ions leak out of a cell, the resulting electrical gradient prevents calcium ions from getting in, thus leading to the relaxation of the smooth muscle.

Specific therapies can target parts of this network of messages that enable an erection. Studies done in my lab, the Laboratory of Molecular and Integrative Urology at the Albert Einstein College of Medicine, have shown that the events in the penile corpora are coordinated via thousands of gap junctions—intercellular passages that allow ions and molecules to move from cell to cell. The coordination occurs in a precise order, developing into a synchronous wave of smooth muscle relaxation along the length and across the diameter of the penis, thus producing an erection.

Computer models developed by members of my laboratory team have shown that the penis has a great excess of gap junctions relative to other tissues. Even after severe nerve loss—as sometimes occurs with diabetes or a radical prostatectomy—there is sufficient reserve signaling capacity to allow the corporal tissue to function normally if a stimulus is delivered. The importance of that fact cannot be overstated, because the stimulus can be administered by either the physician or the patient as an intracavernous or intraurethral injection or as an oral drug, in minute quantities that will allow the otherwise damaged organ to become erect.

In addition to the signals along the autonomic nerves to the penis, hormones entering the sinusoids and penile tissues during flaccidity provide regulatory signals. Hormones

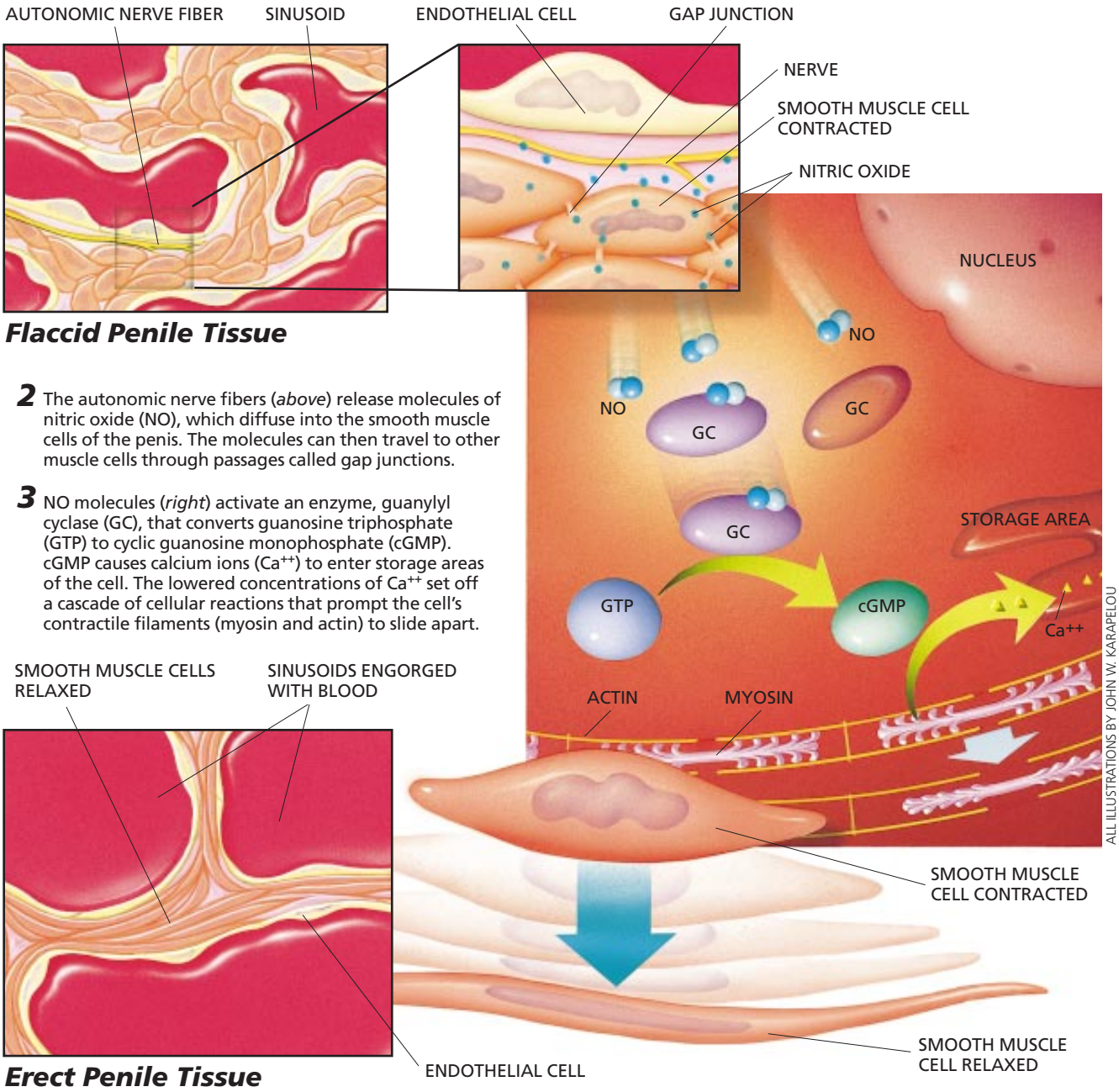


such as noradrenaline secreted from the adrenal glands and testosterone from the testes help to regulate the tone of the corporal smooth muscles and the secretory capacity of certain nerve fibers.

Causes of Dysfunction

Anything that interferes with the nerve pathway can cause erectile dysfunction. Trauma such as head and spinal cord injuries, stroke, Parkinson's disease, and diseases with systemic effects such as multiple sclerosis and diabetes can diminish nerve function and lead to impotence. Aging can be contributory, because it is often accompanied by a decrease in penile nerve endings and blood flow and by an increase in smooth muscle cell tone (making achieving an erection more difficult). Certain medications and alcoholism can also cause impotence. Vascular conditions such as hardening of the arteries can damage vessels supplying blood flow to the penis. Furthermore, anything impacting the primitive hypothalamic regions responsible for libido has the potential to cause erectile dysfunction. These factors include aging, depression, anxiety, chronic illness and medications that affect the central nervous system.

Finally, our new understanding of the erection process does not rule out the presence of secondary psychological problems emerging as a result of erectile dysfunction (which are often incorrectly blamed for the condition). In addition, certain psychological conditions, such as anxiety disorders,



Flaccid Penile Tissue

2 The autonomic nerve fibers (*above*) release molecules of nitric oxide (NO), which diffuse into the smooth muscle cells of the penis. The molecules can then travel to other muscle cells through passages called gap junctions.

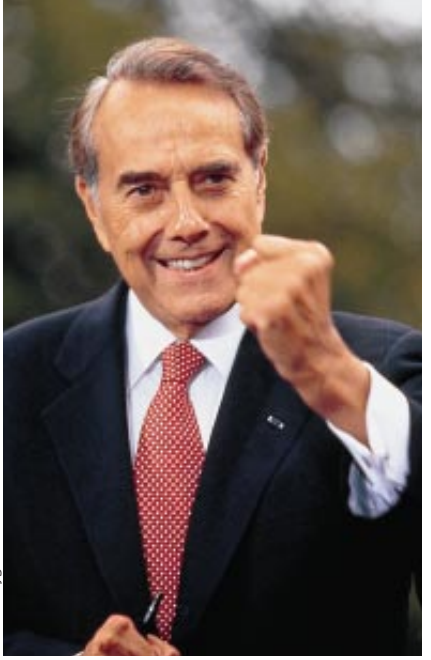
3 NO molecules (*right*) activate an enzyme, guanylyl cyclase (GC), that converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP causes calcium ions (Ca^{++}) to enter storage areas of the cell. The lowered concentrations of Ca^{++} set off a cascade of cellular reactions that prompt the cell's contractile filaments (myosin and actin) to slide apart.

Erect Penile Tissue

4 The smooth muscle cells relax (*above, right*), pressing against the small veins that drain blood from the penis. Blood collects in the sinusoids (*above*), the spaces between the smooth muscle cells, and the penis becomes erect.

can be the primary cause of impotence.

The earliest effective treatment for organic impotence was the penile implant, successfully performed for the first time in 1947 using a single rigid plastic strut surgically inserted into the penis. Previous surgical efforts using a piece of rib or cartilage had failed because of rapid breakdown and absorption of the implant by the body. Although the plastic strut allowed some men to resume coitus, it was the introduction of medical-grade silicone in the 1960s that ushered in a truly practical surgical solution. The single flexible silicone rod was quickly followed by the introduction of more anatomically correct semirigid rods that bend like pipe cleaners, allowing manual positioning of the penis into an erection. Soon afterward, a three-component inflatable device was designed. The components include a bulb placed inside the scrotum, an inflatable cylinder positioned inside the penis and a saline sack inserted into the abdomen. Pumping the bulb causes fluid to fill the cylinder, bringing about rigidity. A release valve in the bulb allows a return to the flaccid state. Today three companies in the U.S. manufacture a variety of semirigid and inflatable prosthetic devices.



B. KRAFT *Sygma*

***BOB DOLE,** former presidential candidate, participated in the trials for Viagra and has appeared in ads for Pfizer, the drug's manufacturer.*

The average age of a patient choosing a prosthetic is 50. Implants seldom wear out, even after decades of use; each implant carries a manufacturer's lifetime guarantee. Implants are safe and almost 100 percent effective. In addition, the approach offers a particular advantage not present in any other impotence treatment currently on the market: it allows coitus without prior planning. That fact greatly increases the overall satisfaction of the men and their partners who choose this option.

Another mechanical treatment is a vacuum pump, a temporary, nonsurgical approach that works on the same principle as milking machines placed over a cow's udder. Pumping air out of an airtight chamber covering the penis creates a vacuum, which draws blood into the penile sinusoids. A tourniquet is placed at the base of the penis to trap the blood in the phallus after removal of the vacuum chamber. Though safe, the instrument produces varying degrees of penile rigidity for each man and during each episode of use.

Penile Injections

The next major treatment advance was hit on by serendipity: in 1979 French vascular surgeon Ronald Virag accidentally injected papaverine rather than saline into a patient's penis during a diagnostic procedure. To his (and probably the patient's) surprise, the man became erect. Virag quickly recognized the utility of papaverine, a drug used to induce smooth muscle relaxation. After confirming the reproducibility of triggering an erection, which occurred minutes after intracorporal injection of the drug, Virag announced his findings. This discovery highlighted for the first time that smooth muscle relaxation was the key erectile mechanism and set the direction for the next generation of basic research. Of particular interest is that papaverine acts very far down in the chemical cascade needed for erection by increasing the concentration of cyclic adenosine monophosphate (cAMP), a chemical that helps to block the entry of calcium ions into the cell, which in turn results in smooth muscle relaxation. Activity at this point in the erectile process negates the need for sexual excitement in achieving erection. This discovery made available an inexpensive, safe, repeatable treatment that was effective in a very high percentage of men with diverse origins of impotence.

Other injectable agents soon followed, each affecting the erectile mechanism at different points in the signaling process. The drug phentolamine induces erections by blocking norepinephrine. Prostaglandin induces cAMP production, which then causes cell relaxation in the same way as papaverine. Because these drugs act at different points in the erection process, they can act to optimize one another's effects. Researchers have taken advantage of this, and now combinations of the drugs are widely used as an intracavernous injectable mixture.

Although these injectable drugs are effective in about 80 percent of patients, they require some advance planning, as there is about a 10-minute waiting period before erection. In addition, side effects, which are seen in a very small percentage of users, can include corporal scarring and penile pain. The most significant disincentive for their use, however, appears to be the psychological barrier to self-injection.

The inclusion of injectable treatments in the recommendations of a 1992 National Institutes of Health conference on impotence helped to legitimize the treatment of erectile dysfunction in the eyes of the government. Subsequent approval by the Food and Drug Administration of Caverject (an intracavernous injection of prostaglandin) and MUSE (a prostaglandin intraurethral pellet) brought about Medicare reimbursement for some nonsurgical treatments of erectile dysfunction.

Popping a Pill

In the tradition of previous erectile-dysfunction therapy discoveries, the erection-inducing effect of sildenafil—more commonly known by its brand name, Viagra—was discovered inadvertently. While performing clinical studies of sildenafil as a treatment for heart failure, researchers noticed that a statistically significant number of men were getting erections after taking the drug. Knowing a good thing when they saw it, the researchers began a separate clinical program to evaluate the drug as an impotence treatment. The heart treatment protocol was eventually dropped because of a high rate of fatal arrhythmias. But as a treatment for impotence, Viagra became the fastest-selling new drug on record, registering worldwide sales of some $700 million in its first nine months on the market.

Viagra works by inhibiting the degradation of cyclic guanosine monophosphate (cGMP), which is the last molecule in the chemical cascade that causes an erection. Viagra blocks

the activity of one type of phosphodiesterase, an intracellular enzyme found in vascular smooth muscle. This enzyme normally breaks down cGMP, but when Viagra inhibits the enzyme, the cGMP remains active, and the signal for smooth muscle relaxation is left in the "on" position. Viagra is effective in inducing erection in about 70 percent of men, as long as they have healthy penile blood flow, intact nerves and sufficient capacity to produce nitric oxide, a precursor to cGMP production. Because the drug is dependent on nitric oxide release, which is a result of nerve signals to the penis, sexual stimulation must occur for an effect to be seen.

Viagra acts not only on penile tissue but also throughout the body, potentially causing dose-related side effects such as facial flushing, headaches, gastrointestinal distress and a blue tinge to vision. The drug should be taken on an empty stomach and without alcohol. Some advance planning is needed because the drug does not take effect until up to an hour after pill ingestion. The major drawback with the medication may be the possibility of death: the FDA reported approximately 130 U.S. deaths potentially related to the use of Viagra in the first eight months that the drug was on the market. Although it can be argued that this represents a very small percentage of the men who have taken the drug, there are almost no reports of death with other therapies for penile dysfunction.

Viagra has affected more than just the treatment of impotence: it has also changed the way the condition is diagnosed. Before the introduction of the drug, a specialist would often seek to evaluate the number, duration and hardness of a patient's nocturnal erections with a Rigiscan, a device that includes a microcomputer strapped to the leg and contracting bands placed over the penis. Now, in most cases, the efficacy of Viagra is used to determine the cause of the condition. Questionnaires are also used to evaluate the drug's efficacy, although they provide only subjective data from the patients.

Other Approaches

Some treatments are designed to correct an imbalance that may exist in male sex hormones, which can also cause erectile dysfunction. Cases of significantly low levels of testosterone, often resulting from a congenital abnormality or from trauma or vascular injury to the testes, can be corrected with monthly intramuscular injections of the hormone or daily application of transdermal skin patches. Hyperprolactinemia, an overproduction of the hormone prolactin caused by an anterior pituitary tumor, can be treated with the drug bromocriptine or by surgical removal of the pituitary gland (pituitary hormones must be supplemented after surgery).

The use of topical agents for various types of erectile dysfunction, though not very effective in the past, are undergoing clinical trials. These vasodilating creams do not seem to show much promise, however, because the drugs probably need to enter general circulation to achieve a practical effect.

Pfizer, the pharmaceutical company that makes Viagra, is exploring various new ways of administering the drug, such as nasal and wafer delivery systems that may allow for more rapid absorption, thus reducing the waiting time for an erection. Meanwhile other researchers are testing different oral medications. A drug called apomorphine, which stimulates the hypothalamus to induce erection, is being tested in the form of a tablet that dissolves in the mouth—an attempt to minimize its main side effects of nausea and vomiting. Phentolamine, currently used as a stand-alone and combination injectable drug, is also being tested in an oral form.

Gene therapy represents a new area of research, one for which the penis is particularly well suited. Because the penis is external and easily accessible, a tourniquet can be readily applied (for up to 10 minutes) to prevent any injected genes from entering the rest of the body. Moreover, vascular smooth muscle cells, the probable targets for many gene therapies, have a low turnover rate, increasing the chances for the effects of the therapy to last for weeks or months. Gene therapy can be used in different ways, including the insertion of genes into penile cells to produce proteins that are lacking because of missing or defective genes. Injected DNA could also generate proteins that would make the penis more sensitive to compensate for an organic disorder.

Two gene therapy approaches are currently being tested. Jacob Rajfer of the University of California at Los Angeles Medical Center is attempting to introduce a precursor gene into the penis to boost nitric oxide production when the gene is activated by a chemical stimulant or irritant. My own lab is investigating the efficacy of inserting a gene subunit that would allow potassium ions to move freely out of the cells of the corpora cavernosa. This change would increase the relaxation of the smooth muscle cells and make the penis extremely sensitive to stimulation. In studies on rats, the inserted DNA remained active for at least four months. The penises of diabetic and aged rats receiving the gene responded to stimuli in the same manner as the organs of young or healthy rats did. There have been no adverse effects on the hundreds of rats tested. The potential for a safe, sustained therapy in humans that would allow spontaneous erections is truly encouraging and will be brought to clinical testing in the near future. SA

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Further Reading

NITRIC OXIDE: A PHYSIOLOGIC MEDIATOR OF PENILE ERECTION. A. L. Burnett et al. in *Science,* Vol. 257, pages 401–403; July 17, 1992.

A REVIEW OF ERECTILE DYSFUNCTION: NEW INSIGHTS AND MORE QUESTIONS. S. E. Lerner et al. in *Journal of Urology,* Vol. 149, No. 5, Part 2, pages 1246–1255; May 1993.

Abstracts of articles in the *International Journal of Impotence Research* are available at http://www.stockton-press.co.uk/ijir/ on the World Wide Web.

Information on the European Society for Impotence Research is available at http://www.esir.com on the World Wide Web.