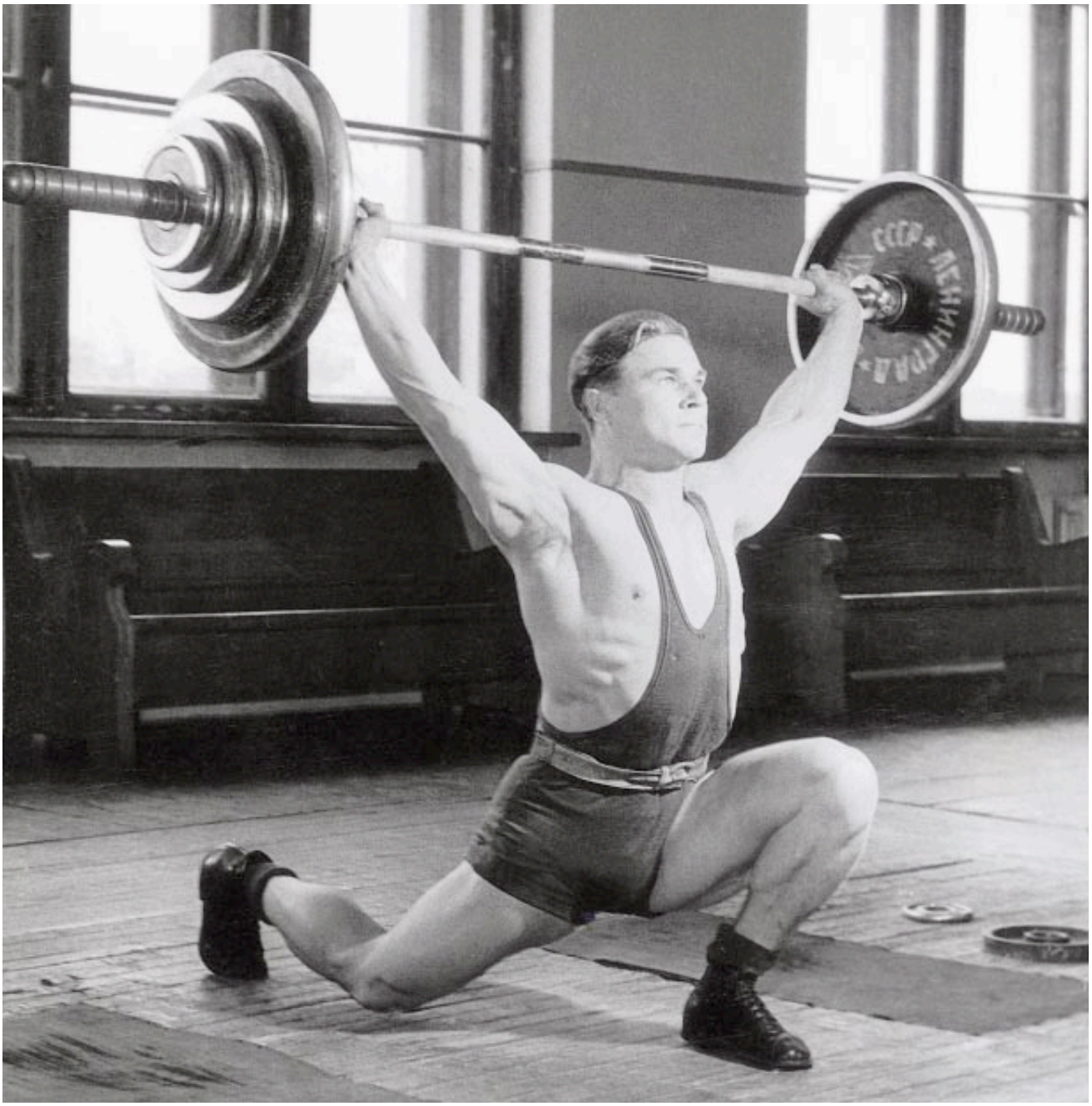
The History of Synthetic Testosterone

Testosterone has long been banned in sports as a performance-enhancing drug. This use may soon be accepted in medicine alongside other legitimate hormonal therapies

by John M. Hoberman and Charles E. Yesalis



V. NOSKOV AND N. MAXIMOV *courtesy of Terry Todd*

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On June 1, 1889, Charles Édouard Brown-Séquard, a prominent French physiologist, announced at the Société de Biologie in Paris that he had devised a rejuvenating therapy for the body and mind. The 72-year-old professor reported that he had drastically reversed his own decline by injecting himself with a liquid extract derived from the testicles of dogs and guinea pigs. These injections, he told his audience, had increased his physical strength and intellectual energy, relieved his constipation and even lengthened the arc of his urine.

Almost all experts, including some of Brown-Séquard's contemporaries, have agreed that these positive effects were induced by the power of suggestion, despite Brown-Séquard's claims to the contrary. Yet he was correct in proposing that the functions of the testicles might be enhanced or restored by replacing the substances they produce. His achievement was thus to make the idea of the "internal secretion," initially proposed by another well-known French physiologist, Claude Bernard, in 1855, the basis of an organotherapeutic "replacement" technique. Brown-Séquard's insight that internal secretions could act as physiological regulators (named hormones in 1905) makes him one of the founders of modern endocrinology. So began an era of increasingly sophisticated hormonal treatments that led to the synthesis in 1935 of testosterone, the primary male hormone produced by the testicles.

Since then, testosterone and its primary derivatives, the anabolic-androgenic steroids, have led a curious double life. Since the 1940s countless elite athletes and bodybuilders have taken these drugs to increase muscle mass and to intensify training regimens. For the past 25 years, this practice has been officially proscribed yet maintained by a $1-billion international black market. That testosterone products have served many therapeutic roles in legitimate clinical medicine for an even longer period is less well known. Fifty years ago, in fact, it appeared as though testosterone might become a common therapy for aging males, but for various reasons it did not gain this "legitimate" mass-market status. Perhaps most important, physicians were concerned that these drugs often caused virilizing side effects when administered to women, including a huskier voice and hirsutism.

Today, however, there is compelling evidence that these spheres of "legitimate" and "illegitimate" testosterone use are fusing. Further research into the risks and the medical value of anabolic-androgenic steroids is under way. Indeed, scientists are now investigating the severity of such reported temporary short-term side effects as increased aggression, impaired liver function and reproductive problems. And some physicians are currently administering testosterone treatments to growing numbers of aging men to enhance their physical strength, libido and sense of well-being. Our purpose here is to describe the largely forgotten history of male hormone therapy that has culminated in the prospect of testosterone treatments for millions of people.

SOVIET MIDDLEWEIGHT Vasily Stepanov is shown practicing in 1955. Many Soviet weightlifters began taking testosterone products to build strength before their American competitors did. At the 1954 World Championships the physician for the Soviet team told John Ziegler, his American counterpart, about the efficacy of these drugs. Ziegler then tested them on himself and several athletes in the U.S.

Organotherapy

Brown-Séquard provided samples of his *liquide testiculaire* free of charge to physicians willing to test them. The offer generated a wave of international experiments aimed at curing a very broad range of disorders, including tuberculosis, cancer, diabetes, paralysis, gangrene, anemia, arteriosclerosis, influenza, Addison's disease, hysteria and migraine. This new science of animal extracts had its roots in a primitive belief that came to be known as *similia similibus,* or treating an organ with itself. Over many centuries since ancient times, physicians had prescribed the ingestion of human or animal heart tissue to produce courage, brain matter to cure idiocy and an unappetizing array of other body parts and secretions—including bile, blood, bone, feces, feathers, horns, intestine, placenta and teeth—to ameliorate sundry ailments.

Sexual organs and their secretions held a prominent place in this bizarre therapeutic gallery. The ancient Egyptians accorded medicinal powers to the testicles, and the Roman scholar Pliny the Elder reports that the oil-soaked penis of a donkey or the honey-covered penis of a hyena served as sexual fetishes. The *Āyurveda* of Suśruta (circa 1000 B.C.) recommended the ingestion of testis tissue as a treatment for impotence. Johannes Mesuë the Elder (A.D. 777–857) prescribed a kind of testicular extract as an aphrodisiac. The *Pharmacopoea Wirtenbergica,* a compendium of remedies published in 1754 in Germany, mentions horse testicles and the phalluses of marine animals. These therapeutic exotica are significant because they dramatize the impossibility, for ancients and moderns alike, of separating sexual myth from sexual biology.

Two of the researchers inspired by Brown-Séquard's work were the Austrian physiologist Oskar Zoth and his compatriot Fritz Pregl, a physician who eventually turned to analytic chemistry and received a Nobel Prize in 1923. When sports physiology was in its infancy, these men investigated whether testicular extracts could increase muscle strength and possibly improve athletic performance. They injected themselves with a liquid extract of bull's testicles and then measured the strength of their middle fingers. A Mosso ergograph recorded the "fatigue curve" of each series of exercises.

Zoth's 1896 paper concluded that the "orchitic" extract had improved both muscular strength and the condition of the "neuromuscular apparatus." Most scientists now would say these were placebo effects, a possibility these experimenters considered and rejected. Yet the final sentence of this paper—"The training of athletes offers an opportunity for further research in this area and for a practical assessment of our experimental results"—can lay claim to a certain historical significance as the first proposal to inject athletes with a hormonal substance.

The growing popularity of male extracts prompted other scientists to search for their active ingredient. In 1891 the Russian chemist Alexander von Poehl singled out spermine phosphate crystals, first observed in human semen by the microscopist Anton van Leeuwenhoek in 1677 and again by European scientists in the 1860s and 1870s. Poehl claimed correctly that spermine occurs in both male and female tissues, and he concluded that it increased alkalinity in the bloodstream, thereby raising the blood's capacity to transport oxygen.

This was an interesting observation insofar as hemoglobin does pick up oxygen in a slightly alkaline environment

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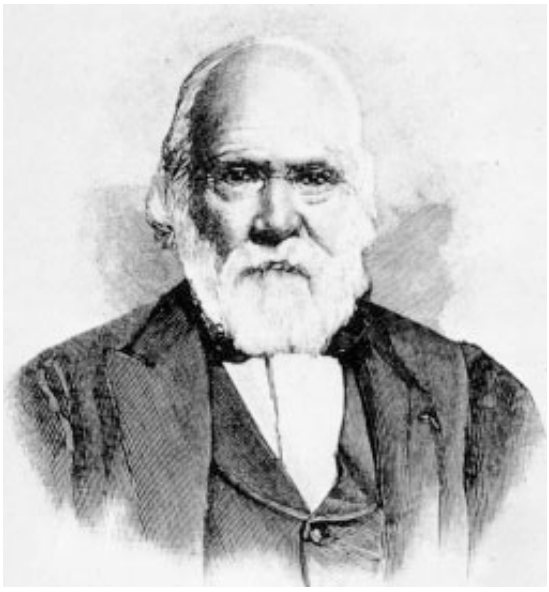

MUSÉE D'HISTOIRE DE LA MÉDICINE, PARIS

CHARLES ÉDUOARD BROWN-SÉQUARD, a 19th-century French physiologist, claimed to have reversed his own aging process by injecting himself with testicular extracts. The injections could not have rejuvenated him, as he declared, but for his insight he is considered a founder of modern endocrinology.

and releases it when the pH is slightly acidic. But he was incorrect in that no chemical mediates the binding of oxygen to hemoglobin. Still, Poehl believed he had improved on Brown-Séquard's work, for if spermine did accelerate oxygen transport, then it could claim status as a "dynamogenic" substance, having unlimited potential to enhance the vitality of the human organism. As it turned out, spermine's function remained unknown until 1992, when Ahsan U. Khan of Harvard Medical School and his colleagues proposed that it helps to protect DNA against the harmful effects of molecular oxygen.

Testicle Transplants

Between the flowering of spermine theory before World War I and the synthesis of testosterone two decades later, another sex gland therapy debuted in the medical literature and made wealthy men of a few practitioners. The transplantation of animal and human testicular material into patients suffering from damaged or dysfunctional sex glands appears to have begun in 1912, when two doctors in Philadelphia transplanted a human testicle into a patient with "apparent technical success," as a later experimenter reported. A year later Victor D. Lespinasse of Chicago removed a testicle from an anesthetized donor, fashioned three transverse slices and inserted them into a sexually dysfunctional patient who had lost both of his own testicles. Four days later "the patient had a strong erection accompanied by marked sexual desire. He insisted on leaving the hospital to satisfy this desire." Two years later the patient's sexual capacity was still intact, and Lespinasse described the operation as an "absolutely perfect" clinical intervention.

The most intrepid of these surgeons was Leo L. Stanley, resident physician of San Quentin prison in California. Stanley presided over a large and stable population of testicle donors and eager recipients. In 1918 he began transplanting testicles removed from recently executed prisoners into inmates of various ages, a number of whom reported the recovery of sexual potency. In 1920 "the scarcity of human material," Stanley wrote, prompted him to substitute ram, goat, deer and boar testes, which appeared to work equally well. He performed hundreds of operations, and favorable word-of-mouth testimony brought in many patients seeking treatment for an array of disorders: senility, asthma, epilepsy, diabetes, impotence, tuberculosis, paranoia, gangrene and more. Having found no ill effects, he concluded that "animal testicular substance injected into the human body does exert decided effects," including "relieving pain of obscure origin and promotion of bodily well-being."

Early organotherapy of this kind existed on the boundary separating legitimate medicine from quackery. Stanley's work, for example, was respectable enough to appear in the journal *Endocrinology*. Like Brown-Séquard, he complained about the " 'lost manhood' charlatans" and "medical buccaneers" who navigated "this poorly charted sea of research" in a half-blind state and sometimes pursued financial gain rather than medical progress. Yet Stanley himself performed operations without hesitation and was persuaded by much ambiguous evidence. And the controversial "monkey gland" transplants performed by Serge Voronoff during the 1920s earned this Russian-French surgeon a considerable fortune.

In an appreciative retrospective monograph, the medical historian David Hamilton argues for Voronoff's sincerity at a time when endocrinology was a new field and medical ethics committees were few and far between. Although medical journals sounded regular warnings against "marvel mongering," "haphazard, pluriglandular dosing" and "extravagant therapeutic excursions," they expressed some cautious optimism as well. Given the limited knowledge and therapeutic temptations of this era, these treatments are better described as cutting-edge medicine than as fraud.

The Isolation of Testosterone

Before Stanley and his fellow surgeons started performing transplant operations, other scientists had begun searching for a specific substance having androgenic properties. In 1911 A. Pézard discovered that the comb of a male capon grew in direct proportion to the amount of animal testicular extracts he injected into the bird. Over the next two decades researchers used this and similar animal tests to determine the androgenic effects of various substances isolated from large quantities of animal testicles or human urine. Their quest entered its final stage in 1931, when Adolf Butenandt managed to derive 15 milligrams of androsterone, a nontesticular male hormone, from 15,000 liters of policemen's urine. Within the next few years, several workers confirmed that the testes contained a more powerful androgenic factor than did urine—testosterone.

Three research teams, subsidized by competing pharmaceutical companies, raced to isolate the hormone and publish their results. On May 27, 1935, Kàroly Gyula David and Ernst Laqueur and their colleagues, funded by the Organon company in Oss, the Netherlands (where Laqueur had long been the scientific adviser), submitted a now classic paper entitled "On Crystalline Male Hormone from Testicles (Testosterone)." On August 24 a German journal received from Butenandt and G. Hanisch, backed by Schering Corporation in Berlin, a paper describing "a method for preparing testosterone from cholesterol." And on August 31 the editors of *Helvetica Chimica Acta* received "On the Artificial Preparation of the Testicular Hormone Testosterone (Androsten-3-one-17-ol)" from Leopold Ružička and A. Wettstein, announcing a patent application in the name of Ciba. Butenandt and Ružička eventually shared the 1939 Nobel Prize for Chemistry for this discovery.

The struggle for the synthetic testosterone market had begun. By 1937 clinical trials in humans were already under way, employing injections of testosterone propionate, a slow-release derivative of testosterone, as well as oral doses of methyl testosterone, which

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is broken down in the body more slowly than is testosterone. These experiments were initially as haphazard and unregulated as the more primitive methods involving testicular extracts or transplants. In its early phase, however, synthetic testosterone therapy was reserved primarily for treating men with hypogonadism, allowing them to develop fully or maintain secondary sexual characteristics, and for those suffering from a poorly defined "male climacteric" that included impotence.

Testosterone, Women and Sports

Early synthetic testosterone products were also applied to a variety of female complaints, such as menorrhagia, painful breast conditions, dysmenorrhea and estrogen-driven breast cancers, on the grounds that testosterone neutralized estrogen. For about a century, physicians have recognized that altering the hormonal balance in certain women can cause their metastatic breast tumors to regress. Today it is accepted that about a third of all women with breast cancer have "hormone-dependent" tumors; androgen therapy serves as a second- or third-choice treatment for postmenopausal women with advanced breast cancers. In contrast, the androgen treatments of the 1940s were administered to women of various ages at a time when the mechanism of their antitumor effect was even less well understood than it is now. A clinically valid observation from this period, however, was that androgens could relieve pain, increase appetite and weight and promote a sense of well-being even if they failed to arrest tumor growth.

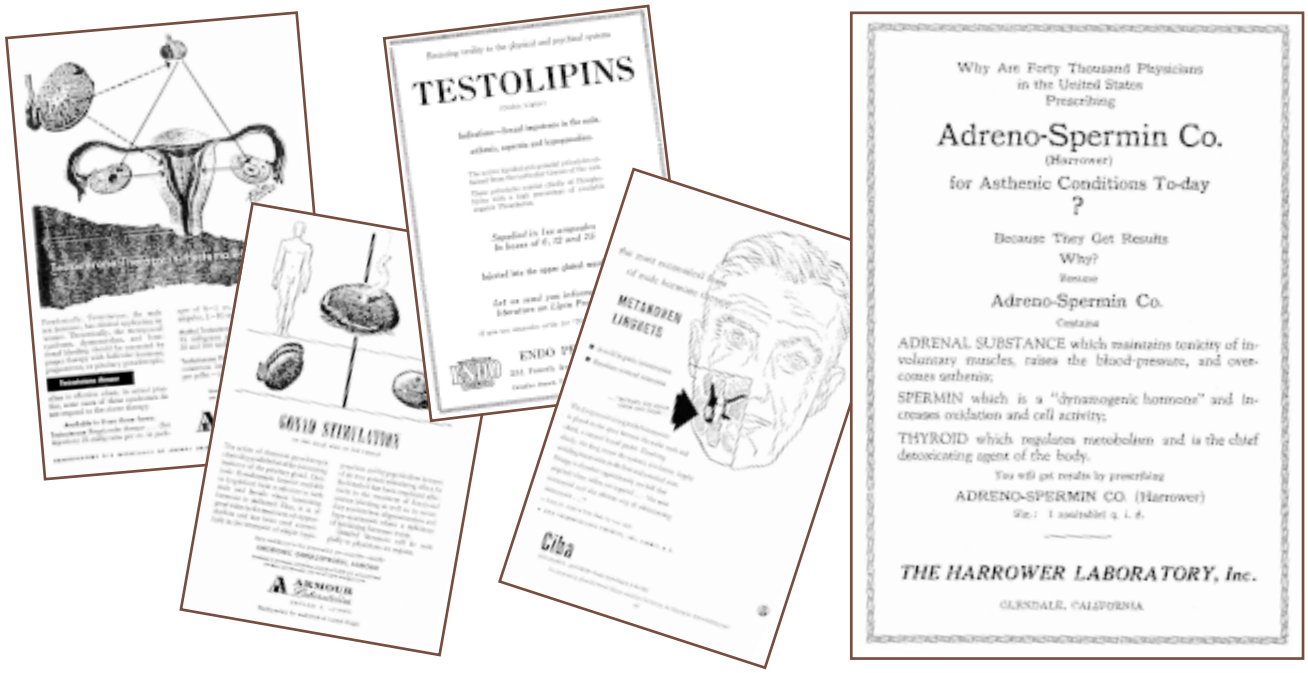
A consequence of treating women with testosterone was the discovery that androgens could renew or intensify female libido in most patients. One investigator reported in 1939 that the daily application of a testosterone ointment had enlarged the clitoris of a married woman who was then able to achieve orgasm. More commonly, subfascial pellets and injections were used to achieve similar effects, and the massive doses given to some breast cancer patients rarely failed to intensify their sex drive.

The use of testosterone to enhance female sexual response did not, however, become standard therapy. Currently it appears that only a small number of physicians in the U.S., and a greater proportion in Britain and Australia, use androgens for this purpose. As mentioned, testosterone therapy did not catch on in part because of certain side effects. Then, as now, some patients experienced reawakened sexual urges as emotionally disruptive and unwelcome. The most important impediment to a general testosterone therapy, though, was that clinicians wanted an anabolic steroid that would not virilize their female patients, giving them a deeper, husky voice, hair on the face and body, and an enlarged clitoris. Although not all physicians were alarmed by these symptoms, different assessments of them, including whether they might be irreversible, led to heated exchanges in professional journals.

The idea that testosterone could counteract the effects of estrogen led to its use as a therapy for male homosexuals (a goal the transplant surgeons had embraced in the early 1920s). "It is clearly evident that the estrogenic values are higher among the homosexuals," wrote one research team in *Endocrinology* in 1940, concluding that "the constitutional homosexual has different sex hormone chemistry [from] the normal male." In 1944 another group described "a series of clinical trials of organotherapy" involving 11 "overt homosexuals who applied for treatment for various reasons." In one Orwellian turn of phrase, they revealed that four subjects had "accepted organotherapy by compulsion"—a court order in one case and parental injunctions in the other three.

The organotherapy, which was uncontrolled by a placebo group, was a failure. Indeed, given that five subjects complained of increases in their sexual drive, the researchers conceded the likelihood that "the administration of androgen to the active (or aggressive) homosexual would rather regularly intensify his sex drive" instead of reducing it. Yet even this obstacle did not entirely extinguish their *furor therapeuticus.* "The results in appropriate cases," they wrote, "are too good to permit undue pessimism as to the value of this treatment."

Also during the 1940s, scientists dis-



ADVERTISEMENTS for male hormone products have appeared in American medical journals for many years. The earliest one shown (*far right*), which ran in the *Journal of the National Medical Association* in 1924, boasts that "Adreno-Spermin Co." is "dynamogenic," a term that Brown-Séquard associated with the animal testicular extracts he himself prepared.

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covered that testosterone could facilitate the growth of muscle tissue. Charles D. Kochakian, a pioneer in synthetic hormone research, reported as early as 1935 that androgens stimulated the protein anabolic processes, offering the possibility that androgen therapy might restore protein tissue and stimulate growth in patients suffering from a spectrum of disorders. The clinical literature of the early 1940s often discussed the correlation between androgens and heightened muscularity, including speculations about the use of these drugs to boost athletic performance. One group of researchers decided in 1941 "to investigate whether the endurance in man for muscular work could be increased by testosterone" and obtained positive results. In 1944 another scientist wondered whether "the reduction of working capacity with age might proceed differently if the sex-hormone concentration could be artificially maintained at a higher level."

The writer Paul de Kruif popularized many of these findings in *The Male Hormone,* published in 1945. This widely read book may have helped promote testosterone use among athletes. According to anecdotal reports, West Coast bodybuilders began experimenting with testosterone preparations in the late 1940s and early 1950s. News of the efficacy of these drugs apparently spread during the early 1960s to other strength-intensive sports, from the throwing events of track and field to football.

Over the past 30 years anabolic steroid use has entered other Olympic sports, including hockey, swimming, cycling, skiing, volleyball, wrestling, handball, bobsledding and soccer. Steroid use is well documented among male athletes in college and high school. Of the estimated one million steroid abusers in the U.S., many take these drugs for noncompetitive bodybuilding. Drug-testing programs, designed to suppress steroid use in sports, have been seriously flawed since they were first implemented in the 1970s. These procedures often lack the sensitivity needed to catch drug users, and many elite athletes and corrupt sports officials have learned to avoid detection.

Clinical Uses of Testosterone

Some of the clinical uses of testosterone products date from the earliest period of androgen therapy. The most frequent and accepted application of anabolic steroids has been as a replacement therapy for men with hypogonadism. They have also been administered to treat impotence in patients with normal and below normal serum testosterone levels. Testosterone esters are frequently employed to stimulate growth and to initiate puberty in boys experiencing a significant developmental delay. Since the 1940s androgens have been used to treat wasting conditions associated with chronic debilitating illnesses (such as those suffered by victims of Nazi concentration camps) and trauma (including battle injuries), burns, surgery and radiation therapy.

Because anabolic steroids increase red blood cell production (erythropoiesis), they were the first-choice therapy for a variety of anemias before bone marrow transplantations and synthetic erythropoietin treatments became common. And from the late 1930s to the mid-1980s psychiatrists prescribed anabolic steroids for the treatment of depression, melancholia and involutional psychoses. Testosterone esters are now routinely used as an adjunct to human growth hormone (hGH) therapy for children who are hGH deficient. Most recently some physicians have begun testing anabolic steroids as a treatment for the weakness and muscle wasting that occurs during the progression of HIV infection and AIDS. Clinical case studies are promising and indicate that these patients experience an improved sense of well-being and an increase in strength, lean mass and appetite.

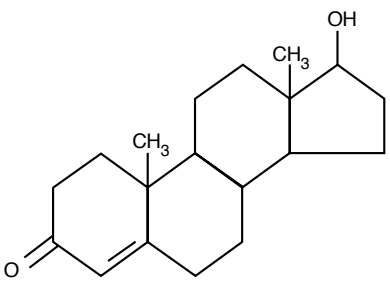
In addition, since the late 1970s testosterone esters have been evaluated as a possible method to regulate male fertility via the endocrine feedback loop. The hypothalamus reacts to high levels of testosterone in the blood by reducing the release of yet another hormone, luteinizing hormone–releasing hormone, which via the pituitary gland affects not only the body's production of testosterone but also of sperm. In 1990 the World Health Organization reported results from a 10-center, global trial that established the efficacy of anabolic steroids as a male contraceptive that produces minimal short-term physical side effects. It is interesting to note that the doses prescribed for these subjects exceeded those taken by the banned Olympic sprinter Ben Johnson. This comparison suggests that legitimizing anabolic steroids as male contraceptives would weaken the medical argument against their routine use by athletes.

During the late 1980s, researchers again began evaluating the effects of testosterone on "successful" aging, motivated in part by a graying society and favorable preliminary results of hGH supplementation in healthy older men. During the early 1990s, several scientists conducted pilot studies of the effects of testosterone supplementation in men over 54 years old who had either low or normal testosterone levels. The results were generally positive, including a gain in lean body mass and strength, a possible decline in bone resorption (with the potential to reverse or improve frailty), an increase in reported sexual desire and activity, and better spatial cognition and word memory.

Because most physicians intuitively accept the efficacy of hormonal replace-

Anabolic-Androgenic Steroids

The anabolic-androgenic steroids are all synthetic derivatives of testosterone (*molecular structure below*), the natural male hormone produced primarily by the testes. Women also produce testosterone, but in lower amounts than do men. The hormone is responsible for the androgenic, or masculinizing, and anabolic, or tissue-building, effects noted during male adolescence and adulthood. The main androgenic effects in males include the growth of the reproductive tract and the development of secondary sexual characteristics. In the pubertal male the latter is charted by increases in the length and diameter of the penis, development of the prostate and scrotum, and the appearance of the pubic, axillary and facial hair.



The anabolic effects are those that take place in the somatic and nonreproductive tract tissue, including thickening of the vocal cords, an acceleration of linear growth appearing before bony epiphyseal closure, enlargement of the larynx and development of libido and sexual potentia. An increase in muscle bulk and strength as well as a decrease in body fat also occurs.

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RONALD C. MODRA *Sports Illustrated*

BEN JOHNSON was stripped of his gold medal in the 1988 Olympics in Seoul, South Korea, after drug tests revealed that he had taken anabolic steroids to enhance his performance. The doses this Canadian sprinter took, however, were allegedly lower than what the World Health Organization subsequently found to be safe to administer as a male contraceptive. The comparison draws into question the medical arguments against steroid use in sports.

ment therapy in women, they may readily adopt a comparable hormone therapy for men. Implicit cultural acceptance of mass male hormone therapy seems evident in the fact that over the past several years the lay press has broadcast and printed numerous reports on the potential benefits of both testosterone and estrogen therapy for the aging population. The Hormonal Healthcare Center in London administers testosterone injections to hundreds of men irrespective of age, and a gynecologist at Chelsea and Westminster Hospital in London currently prescribes testosterone pellets for about 25 percent of his postmenopausal patients. This trend is likely to continue, meaning that mass testosterone therapy could become standard medical practice within a decade.

This prediction is based on the fact that popular expectations and commercial motives can help define new medical "disorders." In 1992, for example, the National Institutes of Health requested proposals for research on whether testosterone therapy can prevent physical ailments and depression in older males, thereby raising the question of whether the aging process itself is about to be officially recognized as a treatable deficiency disease. John B. McKinlay, director of the New England Research Institute in Watertown, Mass., and a specialist on aging, has offered the following prognosis: "I don't believe in the male midlife crisis. But even though in my perspective there is no epidemiological, physiological or clinical evidence for such a syndrome, I think by the year 2000 the syndrome will exist. There is a very strong interest in treating aging men for profit, just as there is for menopausal women."

Commercial interest in response to the public's demand for androgens could cause physicians to overlook possible deleterious side effects and overestimate their clinical value. For example, in the January 1994 issue of the *Journal of Urology,* McKinlay and his colleagues stated that there was no correlation between any form of testosterone and impotence, a "major health concern" affecting a potential market of 18 million men for whom testosterone has long been prescribed on a much smaller scale. But failing to confirm the value of testosterone for one disorder is unlikely to deter its use to strengthen aging bodies or restore a waning interest in sex. Indeed, aging is increasingly being viewed as a medical problem, and this shift is leading to the recognition of a "male menopause" as treatable as its female counterpart. The official status of such a syndrome will signify new societal definitions of physiological normality and further legitimize ambitions to boost the human organism to higher levels of mental and physical performance.

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