The Pursuit of Perfection

THE PROMISE AND PERILS
OF MEDICAL ENHANCEMENT

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Indeed, the very diversity of opinion means that enhancement will have both proponents and detractors. One school will condemn it, another will celebrate it. Since there is so much allure for consumers and so much financial gain for physicians, there is little doubt that surgical enhancement, like medical enhancement, will go forward without significant attention to risks.

SIX

Borrowed Manhood

DISCOVERING THE SECRETS OF THE MALE BODY, like the fascination with the female body, occupied a prominent place on the research agenda for the new disciplines of physiology and endocrinology. Just as investigators in the first decades of the twentieth century shifted the female principle from the uterus to the ovaries, so they moved the male principle from the sperm released by the testes to the hormone released by the testes, that is, testosterone. The identification and eventual isolation and synthesis of testosterone altered clinical practice, providing a remedy for admittedly rare cases of delayed sexual development. From the very start, however, physicians had grander ambitions. Testosterone promised to preserve and restore manhood, reinvigorate physical and intellectual capacities, ward off old age, and reverse senescence. As with estrogen, physicians dispensed the hormone without distinguishing between cure and enhancement or concerning themselves with its potential risks.

These similarities notwithstanding, crucial differences distinguished the medicine practiced on men from the medicine practiced on women. Physicians' attitudes toward the male body and men's attitudes toward their own bodies differed from women's in crucial ways. The medical gaze never focused quite as intently or narrowly on male-specific organs and men were not so receptive to a message of Masculine Forever. Hormone replacement therapy, with testosterone as the counterpart to estrogen, did not become a standard male regimen. Why it might have assumed such a position, and why ultimately it did not,

illuminate a fascinating chapter in both the history of gender and the history of enhancement.

I

Well before the nineteenth century, both folklore and medicine had explored the sources of maleness, seeking ways to promote strength, vitality, and potency. Ancient physicians administered potions of ground-up animal testes to men, in the belief that the testes, as the anatomical seat of masculinity, contained substances that promoted or restored vigor. Variations on this practice continued over the centuries, with the popularity of such brews and nostrums reflecting an intense demand for the products and a hope in their efficacy. After all, as every farmer knew, the testes affected energy and muscularity; to castrate a rooster produced a capon—fatter, softer, and less active. To castrate an aggressive farm animal (a horse, dog, or bull) rendered him more docile and manageable. Indeed, popular lore recognized that men castrated—whether by accident or on purpose (to maintain, for example, the high pitch of their singing voice or to render them suitable to guard the harem)—lost their manly characteristics. They gained weight, tired more easily, and were less assertive. The logic, then, was obvious: if a loss of testicular function rendered men weak, surely a gain in testicular function would render them strong.

Underlying these associations was the idea that the visible product of the testes, sperm and seminal fluid, represented the male principle. Of course, this product was essential to reproduction but it was also linked, wrongly, to other male attributes. It was commonly believed that the production of sperm was necessary for the development of male secondary sexual characteristics, including muscle mass and genital growth—otherwise why would castration inhibit their development? By the same token, the production of sperm was tied to sexual performance. Castration ostensibly made men impotent, which was precisely why some criminal codes invoked it as a penalty for sexual offenders.

These propositions encouraged the idea that because sperm was the source of male prowess, it, therefore, should not be squandered.

Through the nineteenth century, an entrenched medical as well as cultural concept of "spermatic economy" warned men to limit the frequency of their discharges. Excessive sexual intercourse or, worse yet, frequent masturbation deprived the male body of its vital substance and rendered the abuser weak, sickly, or even mad. This notion of an essential and finite male fluid sustained a vision of maleness as static and fixed. Semen assured masculinity, but the body's reservoir of the substance could not be expanded. It had to be hoarded because it could not be replaced.

The knowledge that the testes produced something more than sperm and seminal fluid, that this additional substance, discharged into the bloodstream, was critical to sustaining manhood, and that the attributes of maleness might be more plastic than fixed, came very slowly. Although unappreciated for at least fifty years, the 1848 experiments of the German physician and zoologist Arnold Berthold showed the way. Like later physiologists who had no qualms about vivisection or seemingly unnatural research, Berthold surgically removed the testes from six young male fowl. He left two alone, and as expected, they grew into capons. With two others, he removed and then reattached one of their testes to their intestinal tissue (which was rich in blood). Both of them grew into typical cocks, growing combs, crowing, fighting with rivals, and, in his words, showing "the customary attention to the hens." With the last two, Berthold removed one testis from each, exchanged them, and replanted them in the intestinal tissue. Both of these fowls became cocks. From these clever, even daring, experiments, Berthold correctly concluded that the testes released a substance into the bloodstream that produced and maintained male characteristics.[1] Although his work went unnoticed, he had, in fact, demonstrated the biological power of an internal secretion from a ductless gland.

Some forty years later, the research, if it may called that, of Charles Édouard Brown-Séquard did revolutionize the field. Brown-Séquard had impeccable credentials in French medical-scientific circles derived from his mapping of the sensory pathways of the spinal cord and identifying some of the causes of epilepsy. Not until very late in his career, in 1889 when he was seventy-two years old, did he publish his first paper in the emerging field of endocrinology. And what a paper it was.

To his colleagues' amazement, Brown-Séquard reported that he had been injecting himself with testicular extracts. For several years he had been suffering from muscular weakness, growing fatigue, sleeplessness, and constipation; to find relief, he had taken a solution composed of testicular blood, testicular extracts, and seminal fluids from dogs and guinea pigs. The results over a three-week period were spectacular. He was now able to work long hours in his laboratory and then write a demanding paper. His muscle strength, as measured on a dynamometer, increased dramatically, his urinary jet stream was 25 percent longer, and his chronic constipation had disappeared.

Although now treated in the history of medicine as something of a buffoon, Brown-Séquard actually brought an impressive logic to his self-experiment. The intervention, as he explained, was based on what were at the time considered unimpeachable facts. First, men castrated before adulthood were "characterized by their general debility and their lack of intellectual and physical activity." Second, masturbation and other forms of sexual excesses produced debility. Third, young men who refrained from sexual activity and conserved their seminal fluid had exceptional physical and mental strength. Putting these observations together, Brown-Séquard reasoned that "in the seminal fluid, as secreted by the testicles, a substance or several substances exist which, entering the blood by resorption, have a most essential use in giving strength to the nervous system and other parts." Thus, weakness, as in his case the weakness of old age, might reflect the "gradual diminishing action of the spermatic glands," and were this deficiency corrected, physical and mental capacities would increase. But how was one to revive the spermatic glands? Brown-Séquard offered a formula: a solution of blood from the testicular veins of animals mixed with semen and the juice extracted from the crushed testicles of dogs and pigs.

Although such strange concoctions were hardly novel, Brown-Séquard's formula inspired laboratory research and clinical applications. If the professor of experimental medicine at the Collège de France advocated such an approach and supported it with objective data (on muscle strength and urinary streams), it might well prove effective. Moreover, Brown-Séquard was breaking new ground (or, more accurately, reviving Berthold's neglected observation) in identifying the testes as a gland that discharged an internal fluid. He did not yet have the facts or language quite right; he continued to call the second substance "sperm." But he was joining what had been old men's tales with the young field of endocrinology.[2]

A number of physicians rushed to administer the substances to their patients, and some reported remarkable success. One Parisian physician injected spermatic fluid into "three old men," aged fifty-four, fifty-six, and sixty-eight, and claimed rejuvenating effects. In the United States, William Hammond, a former surgeon general, reported that the preparation reduced pain, restored potency, and improved cardiac functioning in his patients. Encouraged by these findings, Brown-Séquard became more confident that his own physical improvement had a physiological, not psychological, cause, and soon he was publishing new formulas. Cut bull testicles into four or five slices, mix with one liter of glycerine, store for twenty-four hours turning frequently, wash in boiling water, pass the liquid through a paper filter, and then sterilize at 104 degrees.[3]

Physiologists, for their part, began to investigate the biology of male sexual characteristics. They castrated fowls, rabbits, frogs, and pigs to study the aftereffects. Some of them repeated Berthold's work, confirming that the testicles discharged substances into the bloodstream that maintained secondary male characteristics. Others, noting that removal of testes led to an elongation of bone and body structure, began to explore the role of the testes in regulating growth and metabolism. The most original work focused on the physiology of the testes, seeking to pinpoint precisely which tissues secreted which substance. The key findings came from the highly imaginative animal research conducted by two French investigators, Pol Bouin and Paul Ancel. They hypothesized that the testes were made up of two distinct types of tissues that fulfilled two different functions. One type produced sperm, and the other a male substance secreted directly into the blood. The sperm-producing tissue was responsible for fertility (the primary male characteristic); the other was responsible for generating and maintaining secondary male sexual characteristics. To test the theory, Bouin and Ancel tied off the sperm ducts on experimental animals, rendering them sterile, and found that physical size, strength, and mating instincts were

unchanged. They went further, removing one testis and excising the sperm-producing tissue in the other; they then examined the altered testis and found that the remaining tissue, the so-called interstitial tissue, or Leydig cells, had doubled in size, and was capable of maintaining the animal's secondary sex characteristics. They concluded, accurately, that fertility and masculinity owed nothing to each other. Sterility and maleness were perfectly compatible. One could be fully a man but incapable of reproduction.[4]

Other investigators were no less ingenious in confirming and extending these findings. Two English researchers, S. G. Shattock and C. G. Seligmann, experimenting on sheep and fowl, blocked the tubes that carried sperm from testicle to penis, and observed that the now sterile animals retained masculine characteristics. Clearly, the testes were producing and secreting some other substance into the bloodstream that sustained male characteristics and they, along with Bouin and Ancel, located the source of production in the testes' interstitial tissue.[5] In fact, these findings confirmed the common observation that men with two undescended testicles could not produce sperm but had typical male secondary characteristics.[6]

Thus, by 1910, the science of male physiology had successfully distinguished sperm from this other "male principle." But the two substances did not generate the same excitement among researchers. The male fluid, not the spermatic fluid, captured almost all the attention. Part of the reason was the challenge and intrinsic difficulty of isolating this newly identified fluid, which was discharged internally, not externally. Even more important, (male) investigators were far more interested in masculinity than fertility. They defined the male not so much by his ability to reproduce but by his manliness. Secondary characteristics trumped primary ones.

Why this should have been so reflects a profound scientific and cultural differentiation of male and female identities. Reproduction belonged to women, and for most of the twentieth century the study of infertility or, for that matter, contraception belonged to the gynecologist. The preeminent male attributes involved physical activity, performance, and virility, to which fertility was irrelevant. These distinctions to mind, it became the task of the biological sciences to understand the

Pacific & Atlantic

FIG. 54. The long and short of it!

The circus is in town. The greatest feature is the "World's tallest and shortest man." This chapter explains why such freaks exist

FIG. 55. The child at the left is a cretin; at the right is shown the same child after one year of thyroid treatment. What changes do you see?[1]

Examples of "circus freaks" and "cretinism" in a 1928 high school health textbook, used to spark students' interest in endocrinology.

(Reprinted from N. B. Foster, "Diseases of the Thyroid Gland," Nelson Loose-Leaf Living Medicine, *Vol. III, Thomas Nelson and Sons.)*

Gertrude Atherton *(front row, extreme left)*
with Samuel Goldwyn and his other "eminent authors."

Gertrude Atherton consulting with
her own "gland doctor" after
Black Oxen made them famous.
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By 1944 facial rejuvenation was an accepted
surgical procedure and was carried out in hospitals.
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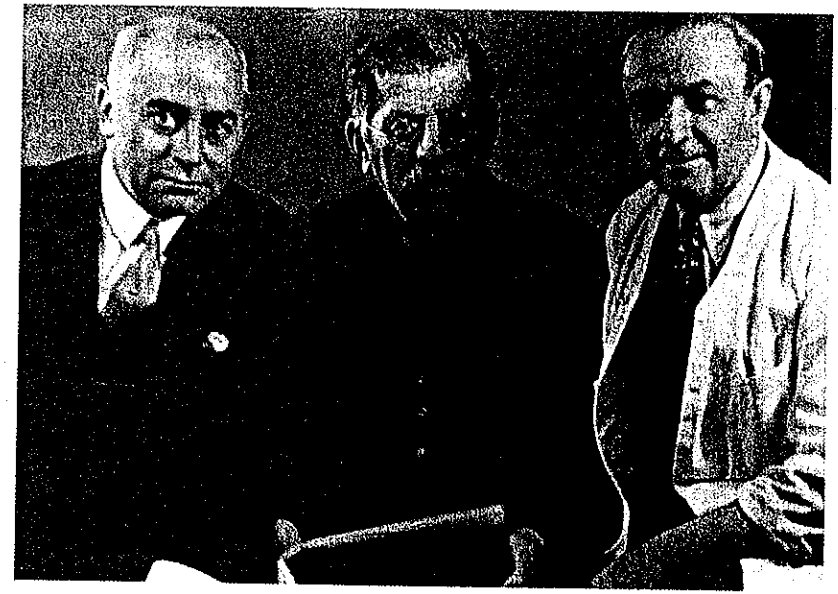

Drs. Harry Benjamin, Magnus Hirschfeld, and Max Thorak,
each committed to using medical skills to transform or rejuvenate the body.
(Courtesy of The Kinsey Institute for Research in Sex, Gender, and Reproduction)

H. G. Wells, the prolific and prescient British author of science fiction.
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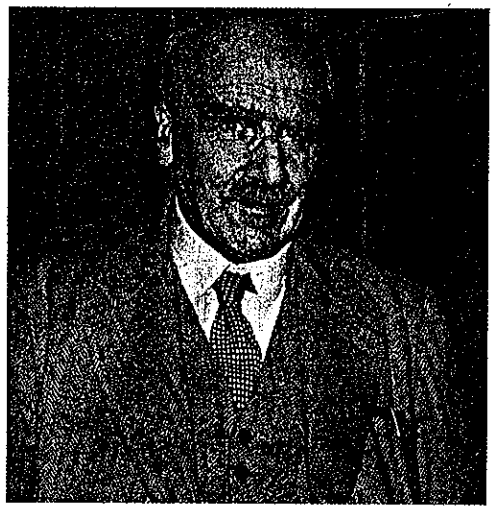

J.B.S. Haldane, one of England's most prominent and versatile scientists and the author of *Daedalus, or Science and the Future.*
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Claude Bernard, a pioneer in endocrinology and in the ethics of human experimentation.
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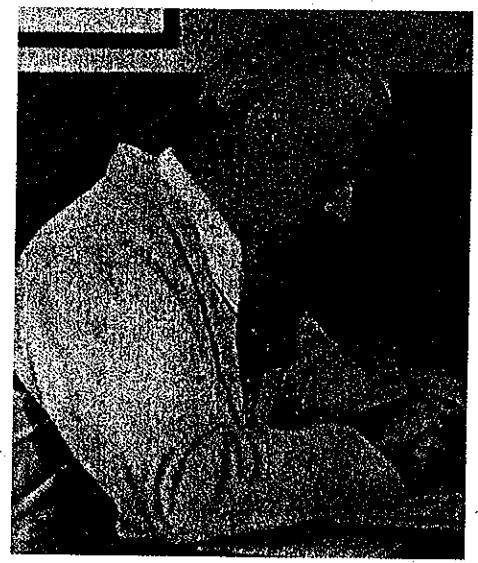
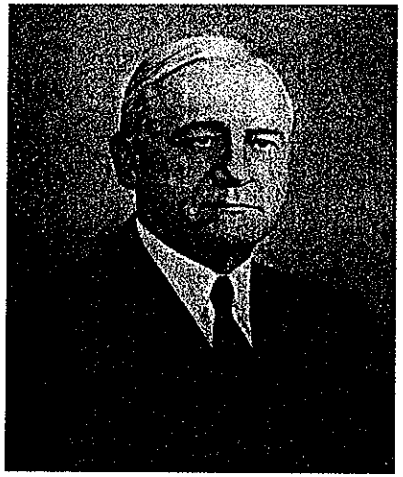
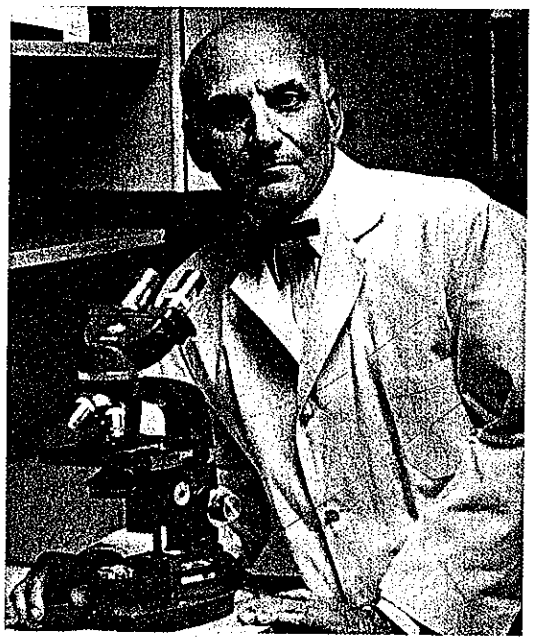


Eugen Steinach, who performed vasectomies on elderly men in an effort to increase their supply of testosterone.
(Reprinted from George F. Corner, Rejuvenation, *New York, Thomas Seltzer, 1923.)*



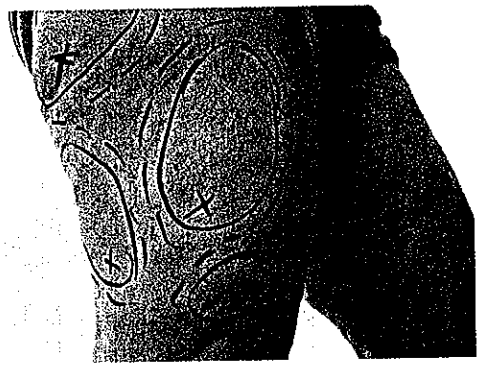
Emil Novak, professor of gynecology at Johns Hopkins and author of one of the most widely used gynecology textbooks.
(Reprinted with permission from MedChi, *the Maryland State Medical Society.)*

Paul de Kruif, who helped popularize not only microbe hunters but also testosterone hunters.
(Courtesy of the Curtis Publishing Company.)

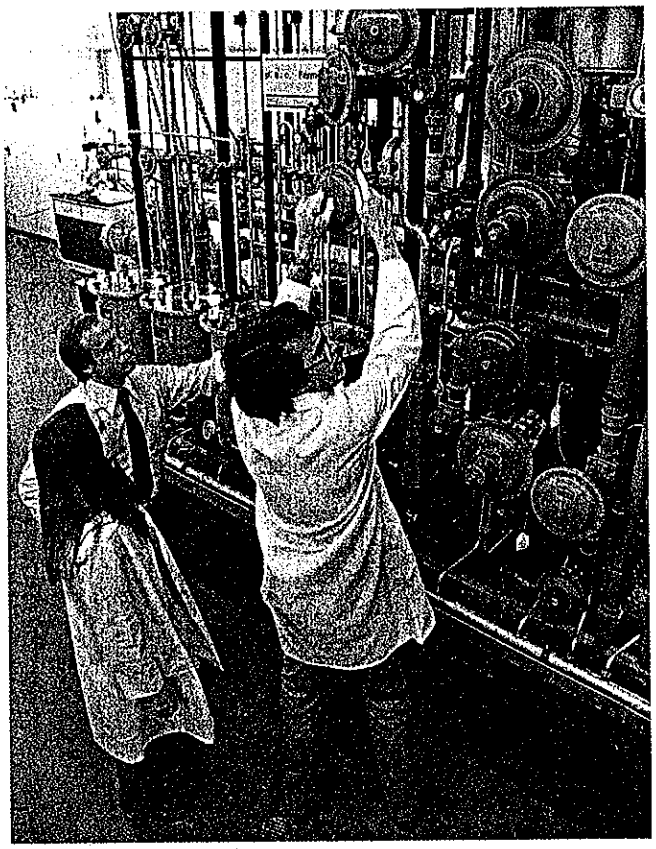


William Masters, one of the first and most influential proponents of hormonal therapy for postmenopausal women.
(Courtesy of Becker Medical Library, Washington University School of Medicine)

An early advertisement for estrogen by Parke, Davis & Company, 1937.
(Courtesy of Pfizer Consumer Healthcare, Pfizer, Inc.)



Preparing a woman for liposuction.
(Copyright © Bettmann/CORBIS)



The president of Genentech with company researchers, just before Genentech began producing human growth hormone.
(Copyright © Roger Ressmeyer/CORBIS)

hormonal base of masculine capacities and the task of medicine to bring or restore capacities to young men of arrested development or old men of superannuated development.

II

No sooner was sperm tissue differentiated from interstitial tissue than an odd assortment of clinicians attempted to translate this finding into medical practice. One of the first was Eugen Steinach, who, like Brown-Séquard, was well trained in experimental physiology and well positioned within the profession. (Here, as elsewhere, credentials gave an unearned credibility to interventions—a dynamic that is still ongoing.) Born in 1861 in the Austrian Alps to a family steeped in medicine—both his father and grandfather were doctors—Steinach followed in their footsteps, taking his medical degree in 1886 from the University of Vienna. He then moved to the University of Prague and for the next twenty years conducted significant research on blood vessels and body muscles. With his reputation achieved (he became a full professor in 1907), he returned to Vienna and devoted his attention to hormones, particularly male hormones. His first investigations reviewed well-traveled territory. He demonstrated that when castrated rodents received a transplanted testicle, they reacquired their male characteristics; when they received a transplanted ovary, they assumed female characteristics. Along with Bouin and Ancel, he also located the source of male hormone in interstitial tissue.[7]

Had Steinach stopped there he would have secured a minor place in physiology textbooks. His fame, or his notoriety, came from what he did next. Steinach believed he had discovered the simplest and most effective clinical method for elevating the level of male hormone. Rather than follow Brown-Séquard's method of injecting the substance, he advocated the practice of vasoligation, not for the purpose of sterilization (what we now call vasectomy) but to increase male hormone production. "By a minor and absolutely harmless operation," he announced, "it is possible to activate, i.e., to stimulate to renewed vigorous endocrine activity, the patient's gonads."[8]

Steinach's logic was that by sealing off the vas deferens, the small tube through which sperm travel to the male organ, the amount of spermatic tissue would decline and, therefore, the amount of interstitial tissue would increase. It was as if the testes had an internal scale balancing the two functions; were the sperm side lowered, the hormone side would be elevated. The higher level of the male hormone would then "reactivate the entire endocrine system and organism."[9] By his own estimate, aging men would experience many benefits, the most important of which would be the prevention and cure of senility.

Steinach, like so many others, equated the symptoms of aging with the symptoms of castration. Forty- and fifty-year-old men first exhibited "presenile" symptoms, that is, "decreased libido and sexual potency." They next entered a senile state, experiencing fatigue, failing memory, indifference, and even depression. As physical debilitation and emotional and intellectual lethargy persisted, old men came to resemble old women, just as little boys and girls resembled each other. "The old man," wrote Steinach, "reveal[s] only traces of his former masculine aggressiveness and the old woman but feeble remnants of her former modest timidity and yielding gentleness."[10] Because every step in this degenerative process pointed to the effects of a decline in sex hormones, aging represented not a natural or inevitable state but a relatively easily diagnosed and curable illness.[11] Increase hormone levels and blood pressure and blood circulation would improve, as would strength, energy, and mental concentration, which Steinach believed was particularly important for the "intellectual class."[12] More, hormone therapy would remedy arteriosclerosis, adult-onset diabetes, depression, and prostate enlargement.[13]

Although these improvements came from a procedure that rendered the subject sterile, at least were it applied to both testicles, no one paid particular attention to this side effect. It seemed irrelevant insofar as the aged male was concerned, and almost irrelevant to the degree that younger men were more concerned about virility than fertility. And no one gave much thought to other possible risks. The idea that the decline in testosterone levels might protect the older male from diseases such as cancer had little currency. To the contrary. Physicians—it is difficult to know precisely how many—brought Steinach's findings right into the clinic. No matter that male hormone deficiency could not yet be accurately measured and no data confirmed that vasoligation actually raised levels of the male principle or of the other hormones. No matter that aging was not necessarily a disease or that interventions might well be enhancements. Doctors were facing unhappy patients, old men complaining of a reduced sex drive, impaired mental performance, fatigue, and malaise. Rather than just standing there, the doctors were doing something.

In the United States, no one more aggressively touted and employed Steinach's technique than Harry Benjamin. Remembered today as one of the first physicians to bring endocrinology to the treatment of transsexuals and persons undergoing sex-change operations—James/Jan Morris was one of his patients—Benjamin, who lived to be 101, was drawn to endocrinology because of its purported ability to treat aging. (He was, as we have noted, the very doctor who treated and inspired Gertrude Atherton.) Trained in Germany, he moved to the United States in 1913 at the age of twenty-eight and set up practice in New York City. In light of his German background and interest in hormones, he was among the first Americans to read Steinach's writings. Aware of the "boundless enthusiasm and exaggerated hopes" raised by the procedure and sensitive to the ethical question of whether Steinach was "interfering with the laws of Nature, and endangering our morals by producing roués," Benjamin traveled to Vienna in 1921 to meet him and review his cases. He came away totally convinced of the efficacy of the procedure—its outcomes were "striking and remarkable." In lectures and articles, mostly for medical audiences, he promoted the intervention, calling it not rejuvenation but the "surgical retardation of senility." "Vasoligature," he explained to New York colleagues, "causes atrophy of the spermatogenetic apparatus of the testes." Then, just as Steinach contended, the interstitial tissue expands, produces more of the male hormone, energizes the endocrine system and, in this way, prevents and postpones the symptoms of old age.[14]

Benjamin claimed that he had ample evidence to support the proposition. "I am satisfied to say," he declared, "that a regeneration and restoration of the vitality of younger years is actually possible for the aging organism." His first articles cited successful outcomes in Europe

but soon he was presenting his own findings, reporting a success rate of more than 70 percent with seventy-five patients. Among them, he was delighted to note, "the intelligent class predominates by far," represented by doctors, authors, college professors, lawyers, musicians, and no fewer than twenty-three businessmen. Complaining that so many physicians adopted "an overcritical attitude towards everything new," he urged them instead "to follow some intuition in the practice of medicine in order to make headway."[15]

Presenile and senile patients, Benjamin emphasized, all shared the same symptoms, but they were generally overlooked by doctors precisely because they were so common.[16] To document the point, he published a series of case studies that included: "Physician, aged seventy-one. General decline. Frequent spells of dizziness. Loss of weight." "Salesman, aged fifty-five. Lack of pep and ambition. . . . Was frequently sleepy during the day. . . . Had to 'whip himself' to his work. Distinct decline in sexual ability." "Mechanic, aged forty-five. Drowsy and tired always." "Music teacher, aged sixty-nine. Felt distinct general and sexual decline. Wanted to restore his physical and mental strength." According to Benjamin, the Steinach procedure benefited all of them, producing weight gain, improved physical strength, increased sexual vigor, smoother skin, fewer wrinkles, reduced blood pressure, and, for the seventy-one-year-old physician, the ability to "study for longer periods with more satisfactory results." Benjamin insisted that side effects were nonexistent. The only possible risk was that the rejuvenated men would overexert themselves and suffer a stroke or cardiac failure. "The old man, who has regained some of his former vitality, is easily tempted to abuse his newly gained abilities and should most earnestly be warned not to change his mode of living for quite some time. He should enjoy his benefit moderately in work as well as in pleasure, and if he will heed this warning no harm can befall him."[17]

III

The benefits of elevating the levels of the male hormone seemed so substantial that physicians experimented with still other methods, including

transplanting testes. Since testicular implants seemed to work so well with animals, they might be equally effective in humans. The first attempts involved desperate circumstances. In 1913, Victor Lespinasse, professor of surgery at the University of Chicago, reported a case of a thirty-three-year-old man who had lost both his testicles (one by accident, the other through botched hernia surgery) and was complaining of an inability to have sexual relations. Lespinasse decided to give him a testicle transplant, citing "the experimental work . . . done by Berthold." To his surprise, a testicle was "easily obtained"; although he gave no details, it probably involved a sale. The surgery went well, the testicle was implanted in the scrotum, and "the fourth day after the operation, the patient had a strong erection accompanied by a marked sexual desire." In fact, the patient "insisted on leaving the hospital to satisfy this desire."[18]

The largest series of testicular transplants occurred in California's San Quentin Prison under the direction of its chief physician, L. L. Stanley. Inspired by Brown-Séquard, he began in 1918 "engrafting human testicles from recently executed prisoners to senile recipients." After 1920, he switched to using animal testicles. Having performed 21 transplants with human testicles and over 300 with animal testicles, Stanley boasted of his excellent outcomes. San Quentin inmates were apparently lining up to get the procedure, and were subsequently reporting "a feeling of buoyancy, a joy of living, an increased energy . . . and mental activity."[19] Stanley went on to inject another 500 inmates with a substance made from animal testicles, and again reported positive results. The procedure alleviated such different complaints as nervousness, senility, sexual lassitude, and impotence, as well as acne, asthma, and rheumatism.[20]

Testicular transplantation also attracted publicity-hungry practitioners. Probably the most flamboyant was the Russian-born and French-educated Serge Voronoff. Following the path of Nobel Prize winner Alexis Carrel, Voronoff was drawn to experiments with organ transplants. When he was in his early fifties, he joined the faculty at the Collège de France, the institution of Bernard and Brown-Séquard, and combined his interest in transplantation with endocrinology. In 1919, Voronoff began transplanting monkey testicles into patients who com-

plained of debility or loss of sexual drive. He announced his always favorable results in press interviews, not medical journals, and also wrote several popular books on the subject. The procedure, he declared, promoted not only physical and mental prowess but also had the potential to create a superior breed of human beings. Were bright young children grafted with testicles, they would grow up as a "new super-race of men of genius."[21]

The logic underlying testicular transplants and his own personal connections to Steinach and Voronoff encouraged Max Thorek, a surgeon at the American Hospital in Chicago, to establish "a little experimental station on the roof." A native of Hungary, Thorek was attracted, in his words, to the idea of "tampering with nature." After visiting the clinics of Steinach and Voronoff, he returned to Chicago to champion "therapeutic gonadal implantation" as a cure for "well-defined pathologic states."[22] The most important one was the male climacteric, manifested in "nervous, emotional, and vasomotor phenomena . . . analogous to menopause symptoms."[23] Between 1919 and 1923, Thorek performed 97 testicular transplants; most of the testes came from apes and monkeys but some were from human cadavers. His results were good but by his own account inconsistent. The majority of his transplant patients (69) suffered from senility; after the procedure, 44 of them apparently returned to normal or were markedly improved, 25 were slightly improved or failures. Thorek also experimented with transplanting testicles into patients with mental illness, and about half of these patients, he believed, showed improvement.[24]

Thorek's readiness to tamper with nature led him to other interventions as well. He was among the first surgeons to do breast reduction and abdominal excisions (in the days before liposuction) to get rid of fat. His 1942 text on plastic surgery (one of the first to appear) justified these still very novel procedures. "In the business and social world," Thorek explained, "the individual afflicted with abnormal states of the breasts or abdominal wall is seriously handicapped," experiencing grave physical and psychological consequences no less serious than "congenital or acquired defects in other portions of the body. The need for scientific reconstructive surgery to remedy these handicaps is therefore evident." Like the endocrinologists, Thorek was convinced that raising

the quotient of patient happiness was a legitimate medical task. "If surgery can restore happiness and enjoyment of life to an individual who has lost them, that is as strong a justification for its use as restoration to health."[25] The plastic surgeon who wrote the foreword to his text was even more intent on raising the quotient of happiness. The surgeon must remedy "the fixed fate" that nature has dispensed. "If the child can be given shapely ears he should have them for his own happiness; and who is to deny him that happiness if he can attain it?" If pendulous breasts restrict a woman's economic opportunities and "destroy her happiness, it is an obvious evasion of professional responsibility" not to treat her.[26]

Pharmacy joined surgery in the effort to realize the benefits of male hormones. Physicians prescribed an array of testicular extracts, including Henry Harrower's Gonad tablet. Not very imaginatively named, it contained 0.25 gram of adrenal, 0.50 gram of thyroid, 1 gram of pituitary, and 1.5 grams of prostate and Leydig cell extracts, and was to be taken three to eight times a day. Other preparations kept their precise formulas secret, but described them generally as mixtures of animal glands. The California Endocrine Foundation Laboratories, for example, sold Concentrated Orchitic Solution, which was one part tissue from the "small, hard testicular gland of the healthy young, live Goat, Ram, or Monkey," dissolved in a solution of alcohol and water. Testacoids, produced by Reed & Carnick, who also marketed Ovacoiods, contained testicular as well as prostate hormones.

How much standing did male hormone therapy have in its initial appearance? It all depended on who you asked. The intervention had just the right combination of major accomplishments, ambiguous findings, and outright fraud to animate all sides. Proponents cited the scientific credentials of the innovators and emphasized the logic of the procedure. If old men resembled castrates, then surely a hormone deficiency was the primary cause of aging, and a hormone supplementation was an apt remedy. Indeed, with medicine seeming to be on the cusp of an endless frontier, it was hardly far-fetched to imagine that it could reinvigorate the elderly. Others were distinctly uncomfortable with associating physical and mental prowess with a sexual gland and at least one physician cautioned that "testosterone must not be injected indis-

criminately into every knave who aspires to emulate the sex behavior of the cock."[27] And still others wanted better data on whether hormonal deficiencies were real and whether hormonal supplementation actually worked. But these questions prompted still others: How much evidence of efficacy was evidence enough? Should a treatment's success with animals encourage physicians to try it on their patients? Or, put more broadly, when were laboratory findings properly translated into clinical practice, and who decided when to go forward?

These issues sparked an especially acrimonious debate between two camps, university-trained investigators and their specialist colleagues on the one side, and general physicians on the other. At stake, in the first instance, was the proper use and misuse of the new hormonal substances. When was it appropriate to be prescribing male hormones or other endocrine derivatives to patients? Under what conditions should the substances be given and with what degree of caution? Inseparable from these practical questions was the more general issue: Who set the standards for medical practice? Was it the clinician who drew upon his day-to-day experience or the university medical center researcher and specialist who drew on laboratory findings and clinical trials? How much credence should be given to the physician's report of the one patient who succeeded on a particular regimen, and how much to data scrupulously collected? In effect, decisions about treatment became enmeshed with debates over professional privileges and standing. Thus, the ordinary physician who prescribed hormones to his patients was either properly exercising the discretion of the general practitioner or not giving due deference to professional medical and scientific authorities.

The controversy permeated medical meetings, conferences, and journals. The most vigorous defense of the prerogatives of the general practitioner appeared in the pages of *The Endocrine Survey*. The journal was published by Dr. Henry Harrower, the founder of the California-based Harrower Laboratory Inc., which manufactured and sold (to physicians and druggists, but not to the public) the Gonad tablet. Harrower, who had spent two years in Europe studying hormones, had been among the founders of the first American medical society devoted to endocrinology and the first managing editor of its official

publication, *Endocrinology*. But because of disagreements over hormonal therapies, Harrower broke with the society and began publishing *The Endocrine Survey*.

The case made in this journal for trusting to the ordinary practitioner rested on the value of "empiricism" within medicine, that is, the wisdom that physicians acquired in the day-to-day treatment of their patients. "Laboratory workers," complained *The Endocrine Survey*, "have extended their sphere of influence and have claimed the right to investigate and to develop methods of treatment that are taboo for the mere practitioner until permission has graciously been given."[28] If a therapy "has not been sanctioned in the laboratory," it is dismissed as empirical.[29] But "to disparage a new method of treatment on the plea that authorities have not sanctioned it is childish."[30] Ordinary practitioners were right to trust to their clinical experience and "employ a method of treatment that is not fully and definitively established"; in this way, patients would be benefited and knowledge about the intervention's strengths and weaknesses advanced.[31] After all, Jenner's vaccinations and Pasteur's vaccines were empirically established. Moreover, if physicians had waited until all the animal studies on the efficacy of thyroid extract against cretinism had been completed, they would not, even now, be prescribing this highly effective treatment.[32] "The only way to find out certain things is to—find them out."[33] Caution was its own vice. "If we wait in all doubtful cases . . . no new methods of fighting disease will ever be produced."[34]

Although the empirical school did not disparage all clinical trials, it objected strenuously to a system in which "treatment becomes simply a matter of laws, and the 'healing art' gives way to a healing science."[35] The ordinary clinician knew things that the clinical investigator did not, including the physical and psychological differences among patients. "No two persons react in exactly the same way . . . to the same disease of the same severity."[36] Never discount the "immense amount of information stored away in the head of . . . the mere doctor." So too, never discount what can be learned from a physician's report of a single patient who "suddenly benefits from a certain mode of treatment."[37] Bedside wisdom, the anecdote of a patient cured, was every bit as reliable as knowledge acquired through formal investigations.

The empiricists also attacked medical specialists who "limit themselves so absolutely to their own specialties as to forget that no patient is merely a subject for the knife or exclusively a pair of sick eyes." Specialists forget that "invariably the entire organism is sympathetically interfered with in its functioning." Hence, a "visit to the specialist may possibly result in improved vision . . . but as long as the general condition of the patient is not given attention, his health will not be restored."[38] By contrast, the wise clinician recognized the value of studying the patient "from every possible angle. . . . The doctor cannot afford, and does not have the right to aim at, only one organ in his therapeutic procedures." Specialists might complain about the general practitioner's resort to a variety of drugs, but prescribing only a single preparation was to treat patients "more or less as experiment animals." To the empiricist camp, laboratory physiologists were even less reliable guides to proper clinical treatments. Investigators sought knowledge for knowledge's sake, not for the relief of patients. They were "men who have never treated a sick person and whose knowledge is confined entirely to artificial conditions created in the laboratory."[39] By contrast, "the aim of the practitioner of medicine is scientific . . . but only in so far as the results . . . enable him to improve his means and methods of relieving his patients of their illness."[40] With great pride, *The Endocrine Survey* quoted Alexis Carrel's dictum that the task of the practicing physician is "very much more difficult than that of the physiologist who can select his problem . . . and solve it by . . . experiments." The good physician was aided by science, but then "he has to guess. The great clinician must possess the intuitive power of the man of genius."[41] In all, "the proper study of mankind (the sick portion of mankind) is not the guinea-pig or the rabbit or the white rat. It is man—sick man or woman or child."[42]

If the manifest purpose of *The Endocrine Survey* was to elevate general physicians above specialists and researchers, the latent function was to sell drugs. A publication underwritten by a drug company had an obvious self-interest in encouraging physicians to dispense the new substances and to prescribe based on a single patient's success. Thus the journal proclaimed: "We never cease witnessing new surprises concerning the remarkable and good effects that can be obtained from judicious combinations of endocrine substances. The actual experiences of many

thousands of general practitioners have established this fact, and no university professor, no experimenter or research worker has the right to question these results."[43]

But question the results is exactly what researchers did, sometimes in anger, frequently with condescension. No practice distressed university investigators and specialists more than efforts by individual practitioners and drug houses to publicize and promote the uses of the male hormone. To Herbert Evans, the investigator who first demonstrated the link between the pituitary hormone and physical growth, endocrinology "suffered obstetric deformity in its very birth," because the midwives were the likes of Brown-Séquard and Steinach.[44] The American Medical Association's Council on Pharmacy and Chemistry complained bitterly about the "unwarranted and unsupported claims" that the companies issued for the male hormones; the preparations were "a menace" to sound medical practice. As another pioneering endocrinologist, Hans Lisser, insisted, a "drought descended upon the field," indeed, on the entire profession.[45] Hormonal therapies were "suspiciously sweet," noted the editors of the *Journal of the American Medical Association*. "How much longer will our profession continue to merit such criticism? Just so long as our profession continues to give serious criticism to pseudoscientific rubbish promulgated by the exploiters of organic extracts."[46]

Moreover, exaggerating the merits of hormone therapy undermined the use of therapeutic agents of "proven value." George Murray, who had demonstrated the efficacy of thyroid extracts in curing cretinism, decried how "little satisfactory evidence" supported the injection or ingestion of testicular substances. "To those of us who have devoted attention to endocrinology for many years, the recent exploitation of organotherapy for all kinds of diseases is deplorable, as it is apt to discredit a valuable means of treatment when properly employed."[47] The excesses also subverted sound research. As another *JAMA* editorial exclaimed, the ignorant physician "hinders medical progress by substituting simple faith and enthusiasm for the careful, critical study that is sorely needed."[48]

Despite their heated rhetoric, the defenders of research and specialization were actually in something of a bind. For one, they could not always agree among themselves on which therapies were truly effective.

For all the opprobrium heaped on Brown-Séquard and his successors, some physicians from reputable institutions, publishing in the major journals, believed that Leydig cells might proliferate after vasoligation, that ingested hormonal substances might galvanize the individual's endocrine system, and that testicular transplants might stimulate the patient's own glands to increase their output. Moreover, investigators had to be careful that in throwing out the snake oil, they did not inadvertently kill the snake—that is, endocrinology as a specialty had to survive the blind enthusiasm of general practitioners. Cast enough doubt on efficacy of hormone preparations and the ethics of their promoters, and the whole field might appear worthless.

Sensitive to such considerations, a number of specialists tried to stake out a middle ground. Lewellys Barker, a prominent endocrinologist at Johns Hopkins, was convinced that what passed for current therapy was unproven and haphazard. But he also appreciated how difficult it was for a general practitioner to resist patients' enthusiasm for a remedy that they had recently read or heard about, even if the supporting evidence was flimsy. Barker tried to set out good practice guidelines that would be acceptable to all sides, but his effort demonstrated how difficult, if not futile, it was to reach a compromise position.

Barker urged physicians to be more discriminating in their clinical decisions, to follow the "*principles,* or *laws,* that we believe to be well established, or that seem likely to become so." Physicians should attempt "to make complete diagnostic studies before they plan their therapy," and use "scientific imagination in devising better methods of application." In this way, they will be "doing their best to secure all that is obtainable for their patients, to help their colleagues in the profession by extending knowledge and improving technique, and to protect their fellows as well as themselves from any deserved opprobrium."[49] But even general practitioners who heeded such advice still had enormous discretion. They could freely dispense preparations that were "likely" to become, but had not yet become, "established:" They were free to rely upon "scientific imagination," not just hard data, in making decisions. They were to think of themselves as part doctor and part researcher, which only opened the door wider to potential misuses.[50]

The physician-in-chief at Boston's prestigious Peter Bent Brigham Hospital, Henry Christian, was trapped in the same bind. Writing in 1924, he confessed how easy it was to become either "over-enthusiastic" or excessively skeptical about endocrinology. "Somewhere between these two lies the happy mean." It was tempting to conclude that "this or that gland of internal secretion is hyperfunctioning or hypofunctioning or dysfunctioning when there is some superficial resemblance . . . to changes noted in animals when some gland of internal secretion has been in some way disturbed." But physicians needed specific evidence of a link between the pathological changes and a hormone deficiency and compelling evidence of the efficacy of a particular preparation. Most interventions, albeit not all, failed these two tests. Certainly in the case of male hormones, "past use justifies no confidence in any efficiency for testicular extract." At the moment, Christian argued, "the abuse of endocrinology is out-weighing the use among our practitioners." Nevertheless, the promise of marvelous discoveries—insulin was his case in point—made it imperative that "experiments should continue and new preparations be tested out. . . . Could the active principles of more of the glands be prepared in such form that they could be introduced into the body without losing their activity, we would have new therapeutic agents of very great value. . . . Because of so many failures, were we to become skeptical of any new claims and stop testing them, progress would inevitably end."[51]

IV

With the male as with the female principle, the laboratory breakthrough in isolating and synthesizing the hormone came over the decade 1925 to 1935. If anything, the dubious nature of the existing preparations made the search for the active substance more intense. Products like those distributed by the Harrower Laboratories did not drive out good research. Gresham's law did not operate in science.

If physiology first undertook the challenge of identifying the male hormone, biochemistry completed it. The field has its own special history. Between 1900 and 1920, it separated itself from general chemistry (which paid little attention to biological substances), medical chem-

istry (which concerned itself with toxins), and physiological chemistry (which was exclusively devoted to animals). By 1920, the leading medical schools all had departments of biochemistry, and within them, one of the highest priorities went to isolating and synthesizing the active agents in hormones.[52]

Although confronting formidable technical challenges, investigators made steady progress. In 1927, a biochemistry graduate student at the University of Chicago, Lemuel McGee, working under the direction of Fred Koch, managed to extract from freshly ground testicles of bulls a substance that when given to capons spurred the growth of male combs. Bringing an entirely new level of precision to hormone research, Koch together with his colleagues devised "test measures for detecting the presence or absence of the male hormone" by calculating its effects (in centimeters) on cocks' combs and photographing the different stages of growth.[53]

The tools of biochemistry and exacting standards made it apparent that none of the drug company male compounds had efficacy. "I am unaware," declared Koch in 1930, "of any active hormone preparation on the market." Biochemical analysis also put to rest any claims for efficacy of Brown-Séquard's recipes or Steinach's procedure. Brown-Séquard's preparations had been dissolved in water but it turned out that the active agent of the male hormone dissolved only in fat. So too, Leydig cells did not increase their production of the male hormone if sperm cells were eliminated. Nor was testicular transplantation any more useful. "We have as yet," concluded one biochemist, "no evidence that the introduction of foreign testis tissue has any effect." In all, reviewing forty years of preparations and methods, the conclusion was inescapable: "The clinical application of the testis hormone is highly questionable. . . . The idea of increasing the life span and usefulness has unfortunately crept into the general concept of the function of male hormone without any apparent basis of fact."[54]

But no sooner was the verdict issued than it was outdated. In 1929, several investigators discovered that male urine contained the male hormone. In 1931, Adolf Butenandt, on the faculty of the University of Göttingen and cooperating with the Schering pharmaceutical company, purified and identified minute amounts of the substance, naming it

androsterone. (For this feat, he was co-winner of the 1939 Nobel Prize in chemistry.)[55] Then, in 1934, Leopold Ruzicka, a biochemist whose earlier work had involved synthesizing the chemicals essential to odors (which was of great value to the perfume industry), purified the hormone from cholesterol (and shared the 1938 Nobel Prize with Butenandt). Finally, in 1935, Ernst Laqueur and his colleagues at the University of Amsterdam, with the help of a Dutch pharmaceutical company, Organon, purified an even more powerful version of the hormone from bull testes and called it testosterone.[56]

V

The newfound ability to produce the male hormone in the laboratory, albeit not without considerable expense and difficulty, sparked an even more zealous effort to establish its clinical uses. Between 1936 and 1939, over two hundred articles on the use of testosterone appeared. Earlier negative findings now became irrelevant because testosterone, particularly when chemists reformulated it as testosterone propionate (which was some four times more powerful than the original), was a highly active agent. But active to what end? Would the compound be able to correct for sexual underdevelopment? Would it finally become possible to realize the ambitions of Brown-Séquard and his followers, and reverse the disabilities of old age?

The most unambiguous answer was that testosterone could restore masculinity to young men deprived of it because of a birth defect, accident, or illness. Like insulin, it could effectively compensate for a marked deficiency or total absence of the naturally produced hormone. One of the first and often repeated accounts of a successful intervention came in 1937 from James Hamilton, a physiologist at the Albany Medical College. Justifying his report of a case of one because testosterone was new on the market, Hamilton told of a twenty-seven-year-old male medical student who was engaged to be married. He complained of hot flashes, fatigue, sexual incapacity, and "social stigmata due to feminine aspect and high voice." In appearance, the student resembled a "pre-pubertal castrate," with wide hips, an absence of body hair, and

underdeveloped genitals. In presentation, he was "intelligent, industrious, trustworthy, prone to anxiety, and feeling somewhat inferior because of his condition." Hamilton gave injections of testosterone, and within three days, he was reporting erections; within two weeks, his genitals grew larger, the hot flashes disappeared, his energy level increased, and he seemed "more self-assured and in higher spirits." Then, without informing him, Hamilton substituted a placebo for the testosterone, and the earlier symptoms returned. When Hamilton resumed the testosterone treatment, his symptoms disappeared. Confident that the changes were physiological and not psychological, Hamilton concluded that testosterone was an effective treatment for sexual underdevelopment.[57]

Over the next several years, physicians frequently reported success in such cases. "With the synthesis of testosterone," observed one researcher, "there ended one of the most amazing chapters in the history of biomedical research." And *amazing* was the term commonly invoked. Clinicians recounted how one patient underwent an "amazing change in his personality." Another patient became "jubilant."[58] The drug was equally effective with men who had been castrated. As soon as he could obtain testosterone (from the Schering drug company), Walter Kearns, a urologist and biochemist at Marquette University, contacted some of his former patients, "broken men," he called them, "nervous, apprehensive, depressed, unable to concentrate, devoid of libido." He gave them testosterone, which "produced a change . . . as definite and pleasing as anything in my experience." Five milligrams injected twice a week "increased strength and endurance, a desire to expand their work, the appearance of libido, erections, ejaculations, ability to copulate and an increase in growth of the beard.[59]

Case reports were often published with accompanying photographs, arranged as "before" and "after."[60] Some of them were body shots, demonstrating that once feminine shapes had given way to a more lean and muscular appearance. The hallmark of the photographs were close-ups of the genitals. The accompanying text gave the precise measurements of change, one centimeter before, four centimeters after. Whatever concern physicians might have had for patient privacy—many faces were blocked out but a sizable minority were not—the overarching need was to present incontrovertible evidence of physiological change after treatment. Having suffered through the days of Brown-Séquard and Steinach, investigators were insistent on demonstrating efficacy, and they did so by following the tradition of showing combs growing on cocks. Testosterone had restored manhood and confirmation was to be found in the pictures of enlarged genitals.[61]

The treatment did have limits. Investigators understood that testosterone could not restore fertility; in fact, it reduced the production of sperm. They realized, too, that it could not cure impotence or erectile dysfunction, except where it exerted a placebo effect. They also reported (incorrectly, as it turned out) that testosterone administered to individuals with normal levels of the hormone exerted no effects. And they believed, again wrongly, that testosterone had no side effects. "No undesirable actions have been observed in any cases treated with testosterone," noted the endocrinologist Henry Turner. This finding was particularly important because it meant that physicians could give patients a trial of the drug even without knowing whether they were or were not actually deficient in the hormone. The patient would start on testosterone and, if benefits followed, then apparently a deficiency existed and the treatment would be continued. If it did not bring benefits, it could be stopped, apparently with no adverse consequences.[62]

These successes acknowledged, the open question was whether testosterone was effective as an anti-aging compound. Inevitably, the successful treatment of young boys and men who lacked adequate levels of testosterone led to attempts to treat older men who might also have an analogous condition.[63] Since testosterone corrected a pathological state might it correct an undesirable state? Could testosterone not only cure but enhance?

No one was more certain of its ability to do that than Paul de Kruif. Famous for his book *Microbe Hunters* (1926), which probably inspired more students to pursue science and medicine than any other single volume, de Kruif in 1945 published something of a sequel, this one devoted to the hormone hunters. One hormone in particular, testosterone, was the focus of the book and supplied its title: *The Male Hormone.* The previous year de Kruif had written a brief article for *Reader's Digest* entitled "Can Man's Prime Be Prolonged?" His new book gave the answer:

an unqualified yes. The section headings outlined the argument: Growing Old Isn't Natural. The Rescue of Broken Men. Testosterone the Builder. A New Lease on Life.[64]

The physician whom de Kruif credited for inspiring his account was Herman Bundesen, president of the Chicago Board of Health. According to de Kruif, Bundesen was extraordinarily active at the age of sixty-two, mounting public health campaigns to eradicate one or another disease, writing papers, and generally pursuing life to its fullest. Although de Kruif was coy about it, there was little doubt that Bundesen was using testosterone, and proud of it. "The chemists suspect that growing old simply isn't natural," de Kruif quoted him as saying. "They're suspecting that growing old the way we do now is really only another disease." Where to find the cure? Bundesen knew the answer: "Don't sell these new organic chemists short."[65]

The case for testosterone seemed to de Kruif, as to others before him, irresistible. Once again, logic trumped the need for data. "If testosterone brought back muscular strength, mental keenness, joy in life to broken men without testicles, bringing them back to normal, wasn't it likely that this same testosterone did play a role in keeping up the muscle and brain power of normal men?" And since testicular activity apparently waned with age, "what was so cockeyed about supposing that injections of testosterone might replace what the aging testicles were no longer so active in producing?"[66] Because testosterone "could transform feeble and fuzzy-witted eunuchoid humans into alert and hard-working males," surely it could do the same for the elderly.[67] The reasoning seemed so self-evident that de Kruif attributed physicians' reluctance to dispense testosterone to personal and professional timidity. They were frightened to unleash "this new sexual T.N.T.," too worried about "what kind of spectacle would human oldsters make of themselves, with their banked sexual fires flaring again, with them prancing about under testosterone's hot influence?"[68] De Kruif himself had no such concerns and, at the age of fifty-four, was ready to trust himself to endocrinology in general and testosterone in particular. "Now I see a gleam of hope of science to help me extend the prime of my life. . . . So, no different than a good diabetic child who knows that insulin every day makes the difference between living and dying, I'll be faithful and remember to take my twenty or thirty milligrams a day of testosterone. . . . It's borrowed manhood. It's borrowed time. But, just the same, it's what makes bulls bulls."[69]

However chatty de Kruif's style or simplistic his argument, testosterone as an anti-aging compound had some support in the medical literature. For example, Allan Kenyon and colleagues from the University of Chicago School of Medicine, with funding from the National Research Council, demonstrated in 1942 that testosterone "exerts metabolic influences which are compatible with the formation of new nongenital tissue." Moreover, the new tissue was deposited in the muscle, thereby likely increasing body mass and strength in the elderly. In other words, Brown-Séquard was right in theory but not in practice. His "guiding idea that the testes might play some decisive role in somatic senescence has never been entirely lost sight of."[70]

Although the publicity given to de Kruif's claims irritated a number of investigators, their own work actually confirmed some of his propositions. Carl Heller and Gordon Myers, publishing in *JAMA*, complained that "physicians are deluged with requests for treatment by hopeful readers." But their findings supported the efficacy of testosterone in a subcategory of elderly men. Heller and Myers devised a test for measuring testosterone levels (using a combination of urine analysis and testicular biopsy) to help determine whether male climacteric or male menopause was a valid diagnostic entity, a normal part of aging or a true pathologic condition. They then tested a group of 38 men, all of whom complained of the symptoms of male menopause, including fatigue, irritability, and hot flashes; 32 of the men also reported impotence. The group was divided in two, those identified by the new test as having normal testicular functioning (15 of the 38) and those having abnormal functioning (23 of the 38). Heller and Myers administered testosterone to 9 men from the normal group and 20 from the abnormal, and found markedly different results. With abnormals, "definite improvement in the symptomatology was noted by the end of the second week in all of the 20 cases treated." With the normals, "none of the 9 patients demonstrated any improvement whatsoever," including sexual potence (although what was causing them to have such symptoms remained unclear). Heller and Myers concluded that male meno-

pause did exist, that it was uncommon and it was eminently treatable. Recognizing that most practicing physicians would not be able to perform their complicated and invasive test, they recommended that clinicians give all their elderly male patients who complained of fatigue or impotency testosterone for two weeks. If they did not improve, the testosterone should be discontinued. If they did improve, it should be continued indefinitely.[71]

But others were far less comfortable with de Kruif's prescriptions, strenuously objecting to the idea of a male menopause and highly skeptical about the outcome data. A *JAMA* editorial on the "Climacteric in Aging Men" inveighed against both the concept and the practice of male hormone therapy. Comparing male to female menopause was inappropriate because men did not undergo sudden or abrupt changes. Moreover, investigators had not been able to confirm the accuracy of the Heller-Myers test, thereby leaving unresolved the question of whether a true hormonal deficiency existed among older men. Still, it remained uncertain whether opposition to testosterone use reflected insufficient data or medical conservatism. Other *JAMA* editorials, for example, noted that testosterone could "exert a tonic and stimulating effect" on patients regardless of their testicular levels.[72] And critics persisted in arguing that the hormone "may influence quite harmfully the physiologic and psychologic condition of previously well adjusted elderly men." It might encourage sexual behavior that would be "distracting and ill adapted to the needs of both husband and wife." There was also a concern about medicine sanctioning tonics and restoratives. A profession that was finally becoming scientific should not prescribe a putative "elixir of youth."[73]

The AMA's Council on Pharmacy and Chemistry was critical of the new testosterone compounds, although it, too, mixed scientific with social judgments. Since the marketed brands showed promise "in only a few conditions," the council would not include them in its roster of approved remedies.[74] It found that some drugs, such as those produced by Ciba, were inert, undercutting Ciba's claim that they cured impotence, senility, obesity, or the "climacteric of man." Other products were more effective in specific conditions. Treating eunuchs with testosterone produced "excellent results," although the council worried that

since the therapy had to be continued indefinitely, "the economic factors are formidable." The drug also helped sexually underdeveloped young boys, but the council worried that it might lead to "masturbation and other undesirable behavior." It found no evidence of effectiveness in treating sterility and impotence and, most important, in treating "senility." Despite drug companies' eagerness to persuade physicians that "in the ampule of testosterone propionate lies the Foundation of Youth," reports of "attempted rejuvenation are not at all promising." The council was most comfortable with the stance adopted by James Hamilton, who feared the consequences of possible behavioral changes. "The patient experiences a sense of well-being on receiving testosterone. Moreover, euphoria is not uncommon and should be guarded against by strict insurance that the patient gets rest and does not overexert. Stimulation of an older man with androgens may cause him to feel younger and to attempt to lead the life of a younger man. The situation is to some extent like that of pouring new wine into old bottles."[75]

VI

The drug houses had no doubts about the efficacy of testosterone, determined to sell their versions of new wine. Schering was one of several companies to produce a lengthy and detailed "clinical guide" for physicians on male sex hormone therapy. Modeled on a medical text, it was organized by disease (sexual underdevelopment, impotence), replete with references to medical journals (227 footnotes), included exact recommended dosages, and tried throughout to encourage testosterone's use. The guide opened with a brief history of the hormone, starting with Berthold and Brown-Séquard, going on to Laqueur, Ruzicka, and Butenandt, and then brought the story to the present, when "primary male sex hormone is available for therapeutic use, its potency exactly known and invariable." Meticulous clinical research, "to which Schering has constantly contributed," now demonstrated testosterone's true efficacy. The company's preparations "represent the most advanced forms of male hormone therapy. . . . They are potent, chemically stable, and clinically dependable."[76]

Testosterone, the Schering claim went, acted not only on the genital tract but on "virtually every tissue." The Schering guide first attempted to establish the hormone's efficacy by documenting the successful treatment of sexual underdevelopment; "this condition offers a clear-cut instance of deficiency disease treated by wholly satisfactory replacement therapy." But sexual underdevelopment was too rare to constitute a substantial market. To make a profit, Schering had to convince doctors to prescribe the hormone as a general buffing tonic. Accordingly, it made the sweeping but dubious claim that "the male hormone increases resistance of the central nervous system against fatigue," and the equally unproven assertion that it relieves "nervousness, irritability, insomnia, increasing fatigue, apprehension, and restores effective mental ability not only in concentration but in the fulfilling of social and economic responsibility." Indeed, the company shrewdly linked these disparate symptoms to the new diagnosis—male climacteric—and promoted its product—male hormone—to remedy it. The guide explained that the male climacteric "syndrome," also known as "functional hypogonadism" (to give it more medical cachet), developed in middle-aged men, paralleling the appearance of menopause in women. Its symptoms represented "a "slackening of the life force . . . and, most conspicuously, a weakening or loss of sexual potency."

Schering had an antidote to this harrowing condition. Its testosterone product accomplished the "more or less complete rehabilitation of the patient," reversing all the symptoms, including impotence. Whatever failures marked the drug in the past were now irrelevant, for Schering's preparation was assuredly effective. It worked directly both on the tissues of the genital tract (restoring erections) and on the entirety of the constitution. The patient performed better because "the patient feels better." In fact, if the physician was uncertain whether his patient actually was suffering from testosterone efficiency, he should begin treatment with the hormone and see if it did any good.

Schering also claimed testosterone was effective against the benign enlargement of the prostate. It conceded that the mechanism by which it accomplished this shrinkage was unknown—perhaps the hormone improved muscle tone or reduced inflamation—but what mattered was that it relieved the symptoms of frequent urination and weak urinary

flow, all the while heightening an overall sense of well-being. Testosterone was just what the doctor needed when seeing his older patients—and what the company needed to enlarge its profits.

What about side effects? Schering acknowledged the possibility of edema, particularly swelling in the ankles, and noted that a "sensitive" patient might experience stomach distress, but then the physician had only to reduce the dose or give sodium bicarbonate. In general, the preparation was "absorbed as a physiological substance and is not capable of any side-effects whatsoever in the adult male." The one major caveat was really more of a promotion for the drug than a caution: elderly patients taking testosterone might indulge in "undue activity," obviously of a sexual kind, which would strain their cardiovascular systems. What did the guide omit? Not a word appeared about testosterone's possible cancer-causing properties, the likelihood of reduced sperm count, or the threat of fluid retention to cardiac functioning.[77]

To increase sales, drug companies placed advertisements in medical journals that were even less subtle in their effort to promote physician enthusiasm. Ciba, Schering, and others regularly ran full-page advertisements in journals such as *Endocrinology*. The advertisements, like the guides, blurred any distinction between prescribing the hormones to combat a disease and to optimize well-being. The preparations apparently gave physicians near-magical powers. "Schering's potent endocrine preparations enable physicians to influence almost every phase of man's existence from the ovum through the span of life."

Many of the testosterone advertisements were heavy in text, listing all the symptoms and conditions that it might treat. Schering's presentation of Oreton promised it would provide "striking amelioration of the emotional and mental state." The drug was also appropriate for "Aging Men"—"Oreton has shown a definite tonic action in bringing about a sense of increased well being and renewed vigor." It also cured impotence (which in both younger and older men "frequently responds well to Oreton"). In all, Oreton would be "a highly effective means of 'finding' the man who is 'lost in his forties.' " It relieved the male climacteric that was "subtly" manifested in an "impairment of mental and physical energies," and worked equally well in cases of "profound emotional upsets, weakness, fatigue, and depression."[78]

Ciba, for its part, preferred to rely on eye-catching images. One advertisement for Perandren, its testosterone drug, devoted the top part of the page to a photograph of a grim-looking man wearing jacket and tie. The banner was in boldface type: "Psychic Trauma." The text itself explained that "the 6th decade often sees a conflict raging between the yet active mentality and the waning sexual forces." Perandren would effectively promote the sexual force. Another Ciba advertisement included a photograph of a very dejected man, dressed in tuxedo and black tie, staring vacantly into space. The banner: "The Fifth Age of Man." The text: "The male decline . . . is a period of sexual, particularly prostatic insufficiency . . . well recognized both by physical and mental aberrations. The rational therapeutic attack is . . . Perandren." Ciba's least subtle image was a drawing of a figure identified as Richard the Lion-Hearted, on a horse, helmeted and armored, thrusting his lengthy sword upward. The text, attributed to one Aretaeus the Cappadocian, compared a man who was "well braced in limbs, hairy, well voiced, spirited, strong to think and act" with another who was "shriveled" and "effeminate." Times had changed, the text explained. "Then there was no treatment. Now, there is Perandren." The shriveled could become erect.

VII

What place, then, did testosterone occupy within medicine at the outbreak of World War II? Despite some holdouts and critiques, the consensus, as evidenced by medical textbooks and journal overviews, shared a distinct bias toward its use. Among the most widely read and consulted texts was Cecil's, the work of Russell Cecil, professor of clinical medicine at Cornell medical school. His 1930 edition, which had appeared before testosterone had been synthesized, briefly addressed "Diseases of the Sex Glands," particularly sexual underdevelopment and aging. The "Treatment" section was very short, noting that "no active principle of the testes [has] yet been isolated" and that testicular transplants had a brief and uneven effect.[79]

The 1940 edition, with synthetic testosterone on the market, was

lengthier, more factual, and far more optimistic about outcomes. Now Cecil's included several "before" and "after" close-up photographs of a eunuchoid's penis, demonstrating growth after testosterone administration. It also devoted an entire section to "The Male Climacteric." Although noting that it was not a common occurrence, "some waning of sexual activity occurs with advancing years," and along with it, as Brown-Séquard (very respectfully referenced in the text) and others had observed, "the fatigue and decreased vitality of advancing age." Without great elaboration or supporting data, Cecil's declared that "the male sex hormone has also been reported . . . to rejuvenate old men." Its bottom line was a hedge with a tilt to treatment. "While there probably is in some men a true climacteric which is relieved by the administration of testosterone propionate, the characteristics of this disorder and the details of its treatment are still to be worked out."[80]

Thus, a standard medical text instructed clinicians that testosterone was a reasonable if not yet proven treatment option. It was not snake oil and had very few adverse side effects.[81] Later editions of Cecil's included a section on "Complications," but the problems, such as edema, were not considered severe. The possibility that testosterone had cancer-causing effects received even less attention than in the case of estrogen. Cecil's advised that a patient who already had prostate cancer not be given male hormones. Since the hormones stimulated cell growth, it was "not desirable to employ them when malignant tendencies are known to be present."[82] But that did not mean that testosterone caused cancer, and no one should be concerned about prescribing it to cancer-free patients. The physician who believed that some of his elderly patients might be suffering from a "true climacteric" was well within the bounds of professional practice in dispensing the hormone.[83]

Then why did testosterone not become the male equivalent of HRT? With all these promotional engines running, why did it not rival estrogen? For one thing, men do not experience a dramatic menopause, a relatively fixed moment in time when a change of life is apparent. For another, men simply do not go to doctors as often as women do. They remain more distant from medical purview, whether the case involves a very specific ailment or a more general malaise. Third, it is possible that word of mouth worked against testosterone. Whatever the company

claims for its use for erectile dysfunction, personal networks may have reported little to no success. (Compare this with contemporary conversations about Viagra.)

Finally, and perhaps most important, when men do visit physicians, they see a general practitioner, not a specialist. Unlike gynecology, there is no specialty devoted to male reproductive and sexual capacity. Urology, which emerged at the end of the nineteenth century, was essentially a surgical specialty, concerned more with physical problems than with performance or feelings. Urologists focused on the prostate and urethra, on incontinence, prostate disease, and venereal diseases. A few exceptions aside, they had never been drawn to the likes of a Steinach or Benjamin.[84] Thus, it would be highly unusual for a man complaining of fatigue or loss of libido to go to a urologist's office.

What would he be told were he to visit a general physician? In a man-to-man conversation, he would learn that testosterone might reduce his fatigue and improve his sense of well-being, and perhaps hear that it would not correct erectile dysfunction, impotence, or sterility. He would not likely be told of a risk of cancer, but he was certain to learn how expensive the drug was, far more so than estrogen. In 1943, Roche and Schering sold 25 milligrams of the compound to pharmacists for $6.25 or, adjusted to 1999 dollars, $60. Were a patient to receive injections three times a week in a doctor's office—the oral forms were less potent—the cost in today's dollars would be almost $900 a month.[85] In sum, it may have been weak demand that kept testosterone from becoming standard treatment. It was the patients, not the physicians, who kept testosterone from emulating estrogen.

VIII

Despite the weakness of consumer interest in testosterone and the lack of medical evidence to support claims of efficacy, researchers, anti-aging physicians, and pharmaceutical companies have not abandoned the drug. Testosterone still occupies a murky territory, with proponents encouraging its use, skeptics not taking a position, and opponents emphasizing its harmful side effects.

In the 1990s literature, as earlier, the most compelling argument for using testosterone in normal older men cites the results with abnormal younger men. The impulse to generalize from the pathological to the healthy continues to be irresistible. Journal articles promoting testosterone typically open with reports of how young men with a marked shortage of testosterone evince decreased sexual drive, inability to concentrate, reduced muscle mass, and loss of strength and stamina; once they receive testosterone, they experience improved libido, better mood, and increased muscle mass and greater stamina. Two assertions then move testosterone treatment from the young to the old. First, noting that testosterone levels in older men average 50 percent to 75 percent lower than in younger men, proponents maintain that "there is no reason to think that the tissues of older men require less [testosterone] than those of young men." Second, they justify interventions on the well-trod grounds that symptoms of aging resemble the symptoms of sexual underdevelopment. Thus, one geriatric center in St. Louis used a questionnaire to learn whether patients were suffering from "low testosterone syndrome." "Are you sad or grumpy? Are your erections less strong? Have you noticed a recent deterioration in your ability to play sports?" Were the answers yes, testosterone should be given.[86]

But even within this framework, prescribing the hormone is problematic. In the overwhelming majority of older men, testosterone levels are in the "low but normal" range for younger men. Someone with these scores who was in his twenties or thirties would not be diagnosed as "sexually underdeveloped." So too, almost all older men have approximately the same levels of testosterone, making it more difficult (but not impossible) to define a common condition as pathological. Others respond by casting doubt on the accuracy of the laboratory measurements. Joyce Tenover of Emory's School of Medicine contends that "the definitive diagnosis of testosterone deficiency . . . for this age group has not been established." In one type of test, only 5 percent of men over sixty had levels altogether below the normal range for younger men. But in a second type of test, 11 percent to 36 percent were testosterone-deficient, and using a third technique, "as many as 50 percent of men aged more than 60 years could be testosterone deficient." But then how should a clinician or patient proceed? Assume the best or

assume the worst? Laboratory-hop until one has the desired finding, confirming or disconfirming a need for a testosterone supplement?[87]

An even more basic question is whether older men actually benefit from receiving testosterone. Some investigators report that normal elderly men given testosterone do demonstrate an increase in muscle mass, a loss of body fat, and, according to some studies, increased strength as measured by a hand grip. Others find improvements in mood. Still others cite studies in mice that point to improved memory, suggesting "a potentially important role for testosterone in modulating age-related cognitive decline." But critics discount these findings. Although muscle mass increased, there is no evidence that testosterone actually improved day-to-day performance; recipients were not able to walk farther, or quicker, or carry heavier packages, or carry out any one of life's daily functions better than those not receiving testosterone. So too, although testosterone did appear to promote "some aspects of sexual arousability," that is, men receiving it thought more about sex, sexual performance was unaffected.[88]

Even physicians who believe that older men should receive testosterone concede a paucity of supporting data. Tenover calculates that "the total number of older men treated in all published studies combined is somewhat less than 75, and the length of therapy has varied from 1 to 18 months."[89] Others concede the weak design of the studies. Selection criteria differ on what precisely constitutes a testosterone deficiency; the means of administering the hormone are not the same—some researchers inject the hormone, others use a skin patch. There is not even agreement on what testosterone levels are needed to produce any benefits.

However dubious the gains, the risks are not trivial. The major concern has been prostate cancer. Testosterone's relationship to prostatic tissue is like estrogen's relationship to uterine tissue—both stimulate growth and, therefore, potentially, cancer cell growth. Indeed, one treatment for prostate cancer is chemical castration, used expressly to reduce testosterone levels. Does testosterone itself cause prostate cancer? No one is certain. Most of the studies are too short-term. Prostate cancer cells are slow-growing, often taking months and years to spread, and so to conclude that elderly men in a three-month trial of testosterone did not develop prostate cancer is to say almost nothing. What about such surrogate markers as the level of prostate-specific antigens (PSA)? Again, the evidence is inconclusive. One study did find elevated PSA levels in subjects taking testosterone after three months (92 percent of 13 subjects); and even after the testosterone was stopped, the levels did not drop back. (It is worth noting that proponents of testosterone more often cite this particular study for its findings that muscle mass increased than that PSA scores climbed.)

Given the stimulating effect of testosterone on cell growth and the weakness of the data on benefits, the medical literature is replete with advice to be cautious in dispensing testosterone. "Supplementation in older men," Tenover concludes, "can not be currently recommended, and more data are needed . . . before clinical decisions regarding T therapy can be rationally based." As would be expected from the estrogen story, calls for more research continue. "Larger and longer term studies . . . [are needed] to determine both the risks and benefits." But for now, the case for "enhanced survival and improved function" through testosterone has not been demonstrated.[90]

Given the state of the data and the principle of do no harm, one might have anticipated that practicing physicians would not be prescribing testosterone for healthy older men. That is not the case. The drug, which is FDA approved for testicular injuries or malfunction, is dispensed "off label" to older men, and rough estimates are that its use has doubled in recent years. The drug companies do their best to promote it. FDA rules prohibit them from advertising or marketing testosterone as an anti-aging therapy but there is ample room for improvisation. The Web site for Androderm notes that men over fifty experience a gradual reduction in testosterone and then purposely links the treatment of sexual underdevelopment to aging. Observing that "men with age-related testosterone deficiency represent the largest group of hypogonadal men . . . it is reasonable to wonder if [testosterone] can be used to halt or reverse some problems of male aging." It hedges on the question of "whether symptoms . . . are a normal part of getting older or should be considered evidence of a medical condition," but leaves no doubt that physicians would be wise to write a prescription for testosterone.

The media promotes testosterone as well. Although the tone of many

newspaper stories on testosterone is cautious, the press cannot resist capturing reader attention through a notable case of success. The *Cleveland Plain Dealer* reports that one man who had lost his desire to "kick butt" went on the Internet, found a doctor willing to prescribe testosterone, and is now enjoying a "new life." *USA Today* tells about a man who suffered from fatigue, hot flashes, and mood swings; after taking testosterone, he jogs six miles and has an active sex life. There is another man whose memory improved, another who took testosterone and was inspired to start a new business, and still another who "has more energy, can stay up late, and, as he puts it, does 'pretty well in the sack.' "[91]

The so-called anti-aging clinics make testosterone one of their staples. The Life Extension Institute promotes testosterone for a lean body mass, and uses a Charles Atlas–like figure as the logo for its pages explaining how it works. Web sites pitch and provide. SmithKline set up the Web site testosteronesource.com, where visitors could raise their Awareness and get an Education about the drug, read Patient Stories, learn about their Options, Ask the Expert, and take advantage of the "Physician Referral Service" to obtain the names of doctors who treat "testosterone deficiency." Enter testosterone on one search engine and Cenegenics, dedicated to "youthful aging" (whatever that means), comes up first. It will schedule a free physician consultation and evaluation: all you need do is call 888-Younger and give them your name, e-mail address, telephone number, and (for some unstated reason) tell them whether your annual household income is below $50,000, between $50,000 and $100,000, or above $100,000. Of course, there is no shortage of Web sites providing herbal alternatives to testosterone, including Testron, that will maximize virility, potency, and serve as a "natural aphrodisiac."[92]

In sum, testosterone is easily available to anyone who wants it. There are physicians in private practice or in anti-aging clinics or available online or by telephone for a quick "consultation," who will write the prescription. They face no reprimands from medical societies or state boards of professional conduct or the FDA. If consumers believe that aging is a form of sexual underdevelopment, they will have no trouble obtaining the hormone. In one sense, their use of testosterone will be following an old tradition that began with Brown-Séquard. In another sense, they will be following a new path, giving us a glimpse of how future enhancements will enter the market. If consumers confront profound medical ambiguities about a substance that in one form or another has been around for more than one hundred years, imagine what they will face when new genetic techniques and novel drugs promise to deliver extraordinary advantages.