The New Yorker
Issue of July 29, 2002

[MEDICAL DISPATCH]

HORMONES FOR MEN
Is male menopause a question of medicine or of marketing?

by JEROME GROOPMAN

It goes by many names. “Male menopause” is perhaps the most popular, but “andropause” is the term that many doctors favor, and PADAM (“partial androgen deficiency in aging men”) has its partisans, too. The condition may afflict millions of Americans, and, if they do not yet recognize the symptoms, a public-awareness campaign has been launched to help them. A two-page ad that ran in *Time* not long ago showed a car’s gas gauge pointing to Empty and beside it the words “Fatigued? Depressed mood? Low sex drive? Could be your testosterone is running on empty.” The ad explains that “as some men grow older, their testosterone levels decline,” and that such men should consult their doctors about testosterone therapy. At the bottom of the page, the gas gauge points to Full.

Physicians have been targeted with similar ads. One that appeared in a recent issue of a primary-care journal calls on them to “identify the men in your practice with low testosterone who may benefit from clinical performance in a packet.” The photographs are eye-catching: there’s a well-built fellow in his middle years beside the words “improved sexual function”; a smiling man in shorts and a T-shirt who is standing next to a mountain bike (“improved mood”); a policeman directing traffic (“increased bone mineral density”). Doctors are told to “screen for symptoms of low testosterone” and “restore normal testosterone levels.”

These ads were paid for by Unimed, a division of the Belgian conglomerate Solvay. Unimed makes AndroGel, a drug that was approved by the F.D.A. two years ago, and is the fastest-growing form of testosterone-replacement therapy for men. Pills, introduced in the sixties, often caused liver damage. Intramuscular injections, particularly favored by bodybuilders and competitive athletes, produce a sharp spike of the hormone, and then a fall, and these fluctuations are often accompanied by swings in mood, libido, and energy. In the late eighties, a transdermal patch was developed, and its use is still widespread. The patch provides safer and steadier dosing, but often causes skin irritation, and sometimes falls off during exercise. AndroGel, by contrast, delivers testosterone in a colorless, drying gel that is simply rubbed on an area of the body -- usually the shoulders -- once a day. It has thus made testosterone available in a form that almost any man can use conveniently.

If hormone-replacement therapy for andropause becomes as common as such therapies have been for menopause -- and this seems to be the ambition of some drug companies -- the consequences, both medical and financial, could be dramatic. Given the popular desire to reverse human aging with a simple nostrum and the growing intimacy between commercial and clinical

concerns, the trend may prove to be irresistible. The pharmaceutical industry is, of course, in the business of inventing treatments. Some people wonder whether it may help invent diseases, too.

To be treated for andropause, you first need physicians who can confidently make the diagnosis. One of them is Dr. Abraham Morgentaler, the director of Men's Health Boston. He is forty-six years old, with thick black hair and deep-set eyes. Trained as a urologist, he specializes in male sexual dysfunction and infertility. He views testosterone deficiency in older men as a silent epidemic, and worries that, of the perhaps five million American men who suffer from it, ninety-five per cent go undiagnosed. Replacing missing testosterone, he believes, will help restore youthful muscle tone, bone strength, potency, and general vigor. He recently put an ad in the Boston *Globe* urging men who were experiencing "low sex drive" or "low energy" to have their testosterone level tested at his clinic. The costs of both the ad and the tests were underwritten by a Unimed educational grant.

Men's Health Boston is in a modern brick-and-glass office building at a busy intersection in Brookline. It has a well-appointed waiting room with soft lighting and upholstered chairs; photographs of famous local athletes adorn the walls. The men who came to see Morgentaler on a recent afternoon had all been given a questionnaire provided by Unimed:

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Among the patients was a real-estate broker in his late fifties. He had answered "Yes" to questions 1, 2, 3, 5, 7, and 10. "I'm just exhausted by the end of the afternoon," he said, after Morgentaler gave him a physical. "And my brain often feels foggy." He likes to shoot pool, and he remarked that his game wasn't what it used to be.

"Have you noticed any change in sexual performance?" Dr. Morgentaler asked.

"Well, I'm not a kid anymore," the patient said, but he had no real complaints.

Morgentaler then showed the man the results from his blood assay. His testosterone levels were "somewhat low," Morgentaler said. "Now, if I had a magic wand and I could do anything for you, what would it be?"

"Fix the energy thing."

“I have good news for you,” Dr. Morgentaler said. “There is an excellent chance that giving you testosterone will help to restore your energy. And, in terms of being foggy, I can’t promise, but I have several men in my practice who are professors. They take testosterone, and they say it makes their brains much sharper.”

Dr. Morgentaler explained that, while testosterone would not cause prostate cancer, if the patient had a hidden tumor the hormone would “act like food, nourishing the cancer.” For that reason, his P.S.A. (prostate-specific antigen) level would be checked, and Morgentaler would take six biopsy samples of the prostate gland to make sure that there was no malignancy.

“I’ll give you a prescription now, and you can get started once we complete these tests,” Dr. Morgentaler said. “When I give men back testosterone, some say ‘Whoa!’ ”

The patient liked the sound of that. “Maybe I’ll be a stallion again,” he said.

Testosterone, an androgen, is a steroid hormone derived from cholesterol. It is produced primarily by the testes, but the signal to produce it comes from the pituitary gland, in the form of two other hormones, which arrive in pulses at certain times of the day. As men age, the response of the testes becomes more muted; for men over the age of forty, the levels of testosterone in the bloodstream decline, on average, by about 1.2 per cent each year.

Morgentaler’s next patient was a construction worker in his forties. The man was on cardiac medication and had an implanted defibrillator, because he was prone to life-threatening arrhythmias, and occasionally he received electric jolts from the device. His wife had died some three years before, but in the previous six months he had been in a stable relationship. He had come to the clinic because he had difficulty reaching orgasm.

Morgentaler asked about other symptoms.

“I used to be able to play racquetball non-stop, but I'm tired now after four games.”

Morgentaler nodded. “We caught it just at the right time.” “But my primary-care doctor checked my testosterone and said it was 800, which is normal. He told me he couldn’t do anything about my problem.”

Morgentaler looked at the results of the man’s blood assay. Total testosterone was in the normal range, at 509 nanograms per decilitre. But his free testosterone, Morgentaler told him, was another matter. At any moment, about two per cent of circulating testosterone is “free” -- unbound to any protein -- and thus biologically active. The patient’s free testosterone was a little under the lower limit of normal. (“Normal” testosterone levels refer to what’s normal for men in their twenties.) “If I had a magic wand and I could do anything for you, what would it be?” Morgentaler asked.

“Get rid of the problem with orgasm.”

"Well, I believe we have a very good chance of helping you." Morgentaler wrote out a prescription for AndroGel. "We'll check your P.S.A. today, but we don't need to do biopsies of your prostate gland until after the age of fifty. So you can get started right away."

"I can't thank you enough," the patient said.

When the F.D.A. decides to permit the sale of a new drug, it specifies a list of "indications" -- particular medical conditions for which the drug has been approved. "The F.D.A. never approved AndroGel for andropause," says Dr. Dan Shames, the director of the Division of Reproductive and Urological Drug Products at the F.D.A. "We're not sure what 'andropause' is. The intention was that AndroGel would be for people with conditions like Klinefelter's and pituitary dysfunction." Klinefelter's syndrome is a congenital disorder in which men have an extra X chromosome and underdeveloped testes. Other suitable candidates for therapy are men whose testes have been scarred by viral inflammation. Still others have had a tumor that damaged the hypothalamus or the pituitary gland, so the brain no longer sends activating signals to the testes. In such men, muscle strength, libido, and bone density are diminished, and testosterone replacement is an effective treatment.

The trouble is that there aren't very many of these people -- they number only in the tens of thousands. But there are some thirty-five million men in the United States over the age of fifty, and, if the andropause movement takes off, annual revenues for the producers of testosterone-replacement drugs could reach billions of dollars. Estrogen-replacement therapy in menopausal women -- a comparable market -- has generated more than two billion dollars a year in revenue, largely for Wyeth, the maker of Premarin, the most popular estrogen-replacement drug.

This is where marketing and medical science may part ways. Pharmaceutical companies often obtain F.D.A. approval of a new product for a niche population with a relatively rare disease, hoping to expand later to a larger and more profitable market. Once a drug is approved for sale, a physician can legally prescribe it for any clinical condition he thinks would benefit from it. The F.D.A. prohibits drug companies from advertising "off label" uses -- those other than the approved indications -- but they can pursue alternative strategies. They can run ads that "raise awareness" of a condition without mentioning the proprietary therapy by name. And they can align themselves with so-called "opinion leaders," well-known physicians whose views are thought to have influence among their peers, by financing their research, say, or offering them consulting agreements.

If you're hoping to expand the medical "indications" for a drug regimen, there are few greater boons than the endorsement of a major medical society. Unimed's andropause campaign won a considerable victory when the Endocrine Society -- a prestigious organization of hormone specialists -- convened its First Annual Andropause Consensus Conference, in April of 2000, just six weeks before AndroGel came on the market. The conference, which was held in Beverly Hills, set out to define andropause and decide how it should be treated. The chair was Dr. Ronald Swerdloff, an endocrinologist at Harbor-U.C.L.A. Medical Center, and he assembled a panel whose task was to come up with recommendations for clinical practice. These recommendations were distributed at this year's annual meeting of the Endocrine Society, in June, and undoubtedly they will have considerable influence in the medical community.

The panel acknowledged that the benefits of testosterone replacement in aging men hadn't been established, but it nonetheless recommended that all men over the age of fifty be screened for testosterone deficiency. Screening should start with a questionnaire, like the one that Unimed had provided for Morgentaler. Patients who had symptoms, whose morning testosterone levels were under the lower limit of normal, specified as 300, and who had no conditions that would rule out testosterone replacement, like prostate cancer, "would likely benefit from treatment," the panel stated. A table accompanying the recommendations suggested that low testosterone levels would be found in more than ten per cent of men over fifty, and nearly thirty per cent of men over seventy -- in perhaps as many as seven million Americans.

There's no doubt that the panel reached its conclusions in good faith; the androgen enthusiasts are nothing if not sincere. But it's also the case that a Unimed/Solvay educational grant was the sole source of funding for the Beverly Hills conference. According to Scott Hunt, the Endocrine Society's executive director, Unimed even suggested some of the panel's members. And, of the thirteen panelists in the final group, at least nine, including Swerdloff and his co-chair, had significant financial ties to the drug company, in the form of research grants, consulting arrangements, or speaking fees. The recommendations made reference to the educational grant but not to the panelists' ties to Unimed.

The bid to medicalize middle age may be well supported by the pharmaceutical industry, but it remains poorly supported by scientific research. Is the decline in testosterone levels really responsible for most of the symptoms of aging in men? What levels of testosterone are, in fact, "normal"? Does andropause even exist? The limits of medical knowledge are starkly evident when you visit a research center like the one run by Dr. William Crowley, the chief of the Reproductive Endocrine Unit at Massachusetts General Hospital, and his associate Dr. Frances Hayes. In a laboratory crowded with centrifuges, chemical hoods, and spectrophotometers, they and their team spend hours double-checking sensitive chemical assays for hormones produced by the hypothalamus and the testes, as well as the pituitary and adrenal glands. In an adjoining clinical-research center, volunteer human subjects are hooked up to I.V.s and insulin clamps.

Several years ago, Dr. Crowley realized that, in order to study hypogonadal men, he needed a clear definition of normal testosterone levels. So he inserted catheters into the veins of healthy young subjects in their twenties and drew blood samples every ten minutes in the course of twenty-four hours. He still sounds amazed by what he found.

"We measured the size of their testes, evaluated body hair, erectile function, sperm count, muscle mass, bone density, pituitary function," Crowley recalls. "These men were completely normal from every parameter. And it was incredible: fifteen per cent had testosterone levels during the day that were well below what is set as the lower limit of normal -- more than fifty per cent below the cutoff."

Why do testosterone levels among healthy men vary so much? Hayes speculates that some men may have highly efficient testosterone receptors -- cellular traps that grab the free hormone in the blood -- so that what appears to be an abnormally low testosterone level is all the hormone they

need. But even an individual's testosterone levels can be markedly different at different times. One factor may be stress, which seems to reduce levels of sex steroids. Drug interactions, too, might alter testosterone levels in unpredictable ways. And much of the variation simply eludes explanation. Crowley studied several young men whose initial test results showed testosterone levels ranging from 150 to 200 -- well below the 300 cutoff -- over twenty-four hours. "They had a perfectly normal testosterone profile," Crowley says. "There can be a funny disconnect between one measurement and a later one" -- which means that testosterone deficiency may be easily overdiagnosed.

"This variability in testosterone levels was really a physiological curiosity until AndroGel was approved," Crowley continues. "Now every time the testosterone level is below 300 the question of prescription is raised." As for the often quoted figure of four or five million "andropausal" men -- the figure touted in the Unimed ads -- Hayes says, "Frankly, I don't know where that number comes from or how real it is."

What makes things more confusing is that the usual commercial tests that physicians use to measure testosterone levels are notoriously unreliable. The andropause movement has made laboratory assays a lucrative business, and all kinds of patented kits have come on the market. But, as Swerdloff's panel discovered, the results tend to be inconsistent. "It's really a big problem," Swerdloff says. "Practicing doctors have a great belief in the numbers, but in the past few years the assays have deteriorated." If you assayed blood samples from normal men with one proprietary test, you might find values between 300 and 900, while another test would give values between 160 and 700. So men whose tests report low total testosterone levels -- like the real-estate broker Morgentaler saw -- might actually have normal levels. The tests for free testosterone seem to be even less accurate.

Not every practitioner finds reason for concern. "The tests aren't as reliable as we want them to be, but it doesn't matter," says Morgentaler, who sometimes even prescribes AndroGel "preventatively" for middle-aged men whose testosterone levels are in the lower quarter of the normal range. "It's not credible that we aren't helping these men by giving them testosterone. The truth is, there's a deep emotional issue in some people who oppose hormone-replacement therapy, because it asks the question 'Is there hope of achieving eternal youth?' There are those who don't want to oppose Mother Nature."

And there are those who don't want to wait for scientific validation. Last year, a panel organized by the National Institutes of Health -- maybe the closest thing we have to a voice of independent scientific consensus -- released a paper concluding that the andropause hypothesis is unproved. The report that Swerdloff's group released at the Endocrine Society meeting in June contains references to sixty-two relevant publications, but omits any reference to the N.I.H. report.

Swerdloff and his colleagues reviewed the half-dozen controlled studies available on giving testosterone to healthy aging men, and were evidently impressed by those which found that it increased lean muscle mass, strength, and bone-mineral density in the spine. Unfortunately, most of these studies were small, involving forty or fifty men. The reported improvements were far from dramatic, and different studies have had contradictory findings. In fact, the largest and longest-term

study, of a hundred and eight men over three years, showed no improvements in energy level, sexual performance, or strength.

So there's a lot of uncertainty about the effects of the age-related lowering of testosterone. "There appears to be a threshold level of testosterone below which libido and sexual function are impaired," Hayes says. "Boosting above this threshold doesn't seem to enhance sexual performance." The role that testosterone plays in maintaining strong bones in healthy elderly men is highly controversial, too. Dan Shames, of the F.D.A., says, "Just because you are increasing bone density doesn't mean you prevent fractures." Even in studies that found a positive correlation between testosterone levels and bone strength, the hormone accounted for only about five per cent of age- and weight-adjusted differences. Men with severely low testosterone levels showed improvement in the spine, but no change was observed in the hips -- and it is mainly hip fractures that debilitate the elderly.

"Each pharmaceutical company wants to get up and say, 'This is the magic bullet for aging,'" Crowley says. "But it's overly simplistic to attribute such a complex process as aging to the change in the level of a single hormone like estrogen or testosterone."

If the benefits of treating "andropause" are in doubt, so, more worrisomely, is the safety. The known side effects of testosterone therapy include gynecomastia (abnormal enlargement of the breasts) and testicular shrinkage (as gonads compensate by making less of the hormone). Testosterone also raises the level of circulating red blood cells; if this level is excessive, the blood becomes viscous, which can lead to congestive heart failure or stroke. And among men who received a 100-milligram daily dose of AndroGel over a year, nearly twenty per cent developed some sort of prostate disorder, such as prostatic hyperplasia.

More troubling is how testosterone accelerates the growth of prostate cancer. The majority of men over the age of sixty-five have clusters of cancer cells in their prostate glands which are both "occult" and "indolent": they're hard to find, and they grow so slowly that they're unlikely to create any trouble by themselves. Here the perils are twofold. On the one hand, unnecessary biopsies can lead to unnecessary surgery, aimed at eradicating cancers that might have remained inactive. On the other hand, biopsies can easily miss cancers that, under a regimen of testosterone replacement, become more aggressive than they otherwise would be. Not surprisingly, Dr. Shames says that the F.D.A. has "issues of concern over the safety" of prescribing testosterone-replacement therapy for men whose hormone levels fall as part of normal aging.

Even Dr. Swerdloff acknowledges these uncertainties. "I agree that currently there are insufficient data on the long-term effects of testosterone-replacement therapy on the heart or on the development of prostate cancer, but the benefits seem considerable," he says. The andropause panel he chaired was aware that the N.I.H. is thinking of doing rigorous, placebo-controlled clinical studies that would span six or more years. "If the answer is yes, that replacement therapy causes heart damage or sparks emergence of prostate cancer, then you will know in six years or so," he says. "But older people in this age group won't wait six to ten years to have solid answers. Clinical practice will move at one rate, and the data will trail."

This is precisely what concerns many scientists. “Pharmaceutical marketing is the driver, not physiology,” Crowley complains of the andropause movement. “Maybe we’re meant to lower our testosterone levels -- maybe it’s healthy and protects us from developing prostate cancer. Of course, that’s pure conjecture, but it’s something that needs to be carefully addressed.” When you elevate the testosterone levels in a seventy-year-old man to those he had at twenty, are you really returning him to “normal”? Crowley says, “I worry that this widespread prescription of testosterone for aging men is going to precipitate an epidemic of prostate cancer.”

Of course, it will not be the first time that hormones have been heavily marketed -- in advance of the scientific evidence -- as a way to recapture youth. In the late sixties, estrogens were touted to women as their chance to be “feminine forever.” And initial data from small or uncontrolled studies were encouraging. Estrogen therapy was believed to help sustain sexual health, and mood, while protecting bones from osteoporosis and the heart from arteriosclerosis. The media were flooded with ads for estrogen therapy, and publishers churned out books celebrating its benefits. Nearly forty per cent of postmenopausal women have been prescribed hormone-replacement therapy.

As we now know, conventional H.R.T. not only increases the risk of breast cancer but can lead to heart attacks, strokes, and blood clots. A nationwide trial of sixteen thousand women -- part of the Women’s Health Initiative -- was recently terminated when the therapy was linked to a twenty-six per cent increase in invasive breast cancer and a significant increase in cardiovascular disease as well. A hormone regimen meant to reverse the effects of aging has proved to accelerate serious disease. As Dr. Swerdloff put it, the data trailed clinical practice.

Meanwhile, testosterone-replacement therapy is becoming increasingly popular. Last year alone, sales of transdermal testosterone doubled. An estimated quarter of a million American men are now taking the hormone. If the current rates continue, that number will rise to nearly a million within two years -- and, with the newly conferred imprimatur of the Endocrine Society, the rates could surge.

To date, the best published safety data we have on AndroGel as a treatment for andropause comes from a study of sixty-seven men who took the drug for an average of twenty-nine months. An accurate assessment of its effects on the heart, blood vessels, and prostate would require many years of observing many thousands of men -- a male counterpart to the Women’s Health Initiative. Until then, the attempt to reverse the gradual decline in testosterone levels in aging men can’t be considered the treatment of a disorder: it amounts to a vast, uncontrolled experiment, whose consequences remain uncertain. As Hayes says, “It would be a shame to make the same mistakes again.”