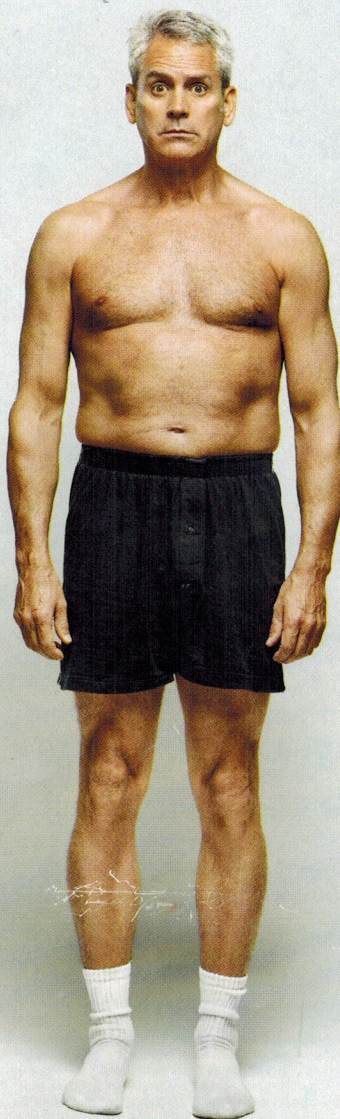


TIME

Manopause?!

Aging, insecurity and the \$2 billion testosterone industry

BY DAVID VON DREHLE



DISPLAY UNTIL
AUGUST 15, 2014

\$4.99US \$5.99CAN



0 70989 10090 9

33>



On the black market, you will always pay for them. Yet Char is fighting to protect themselves.

HEALTH

Feeling Deflated? The low-T industry wants to pump you up.

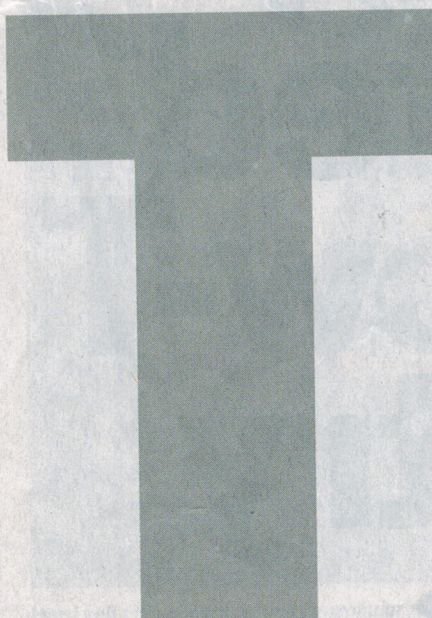
Men are showing up at doctors' offices in droves asking for scrips. But are the drugs safe?

The promise. The science. The risk.

By David Von Drehle



Salesman to a T Mike Sisk, owner of the Low T Center chain, with two staff members at a Southlake, Texas, outpost



THE SIGN OVER THE CLINIC DOOR SAYS Low T Center, as in low testosterone, as in not enough man juice in the tank. Inside, the place is musky with masculinity. The spacious suite is situated in a handsome office building in the prosperous North Texas suburb of Southlake, staffed by attractive female receptionists who welcome patients into the “man cave.” ESPN plays on the flat-screen near a bar stocked with drinks and snacks. The rooms are decorated with autographed football jerseys and other sports memorabilia. A he-man with a firm handshake named Mike Sisk is the proprietor, but he’s no doctor. Instead, Sisk is enough of a businessman to realize that America’s beer bellies could be worth their weight in gold.

Aging men by the millions are finding themselves soft where they would prefer to be firm and dull when they really need to be sharp. And although the Food and Drug Administration (FDA) doesn’t exactly approve of it, a growing number of men have come to believe that hormone therapy is the answer. Sisk is happy to oblige. With 49 clinics in 11 states—and more to come—his chain of Low T Centers serves 45,000 patients, he says, at an average price per patient of about \$400 per month.

Sisk can meet these clients’ needs because he knows how they feel. A self-

described former “gym rat,” he found himself around the age of 40 feeling run-down in the afternoon. At work and at play, he just wasn’t killing it like before. His doctor recommended Zoloft, but he worried it might cloud his thinking. He met another doctor who suggested testosterone therapy, which promises to elevate mood, melt away flab and heat things up in the bedroom. This was precisely the sort of jolt Sisk had in mind, and when a blood test indicated his T levels were drooping—which is, admittedly, a normal sign of aging—he was eager to give it a try.

Five years later, Sisk, a former FedEx sales manager, is a Midas of manliness, and his empire is worth an estimated \$100 million—a drop in the bucket of the multibillion-dollar business in hormone therapy for aging men. Fully half the patients who consult a doctor at one of Sisk’s centers for initial screenings are diagnosed with low testosterone, and thousands of other men are diagnosed by their primary-care physician, urologist or endocrinologist. U.S. prescription-testosterone sales hit \$2.4 billion in 2013, and the market is expected to swell to \$3.8 billion by 2018, according to Global Industry Analysts.

That this is happening without explicit FDA approval has the agency a bit flustered. Testosterone therapy is approved only for adult males who suffer from “medical conditions associated with a deficiency or absence of endogenous testosterone (primary or secondary hypogonadism),” in the words of agency spokesperson Andrea Fischer. A slow and gradual decline in testosterone production is normal as men age. Hypogonadism

is something different: the systemic failure of a man’s body to produce adequate testosterone to begin with. Fischer continued in a statement for *TIME*, “There are no testosterone drugs approved as a treatment for low testosterone levels, often referred to as ‘low T,’ without an associated medical condition.”

But thousands of doctors are prescribing testosterone off-label for men with borderline low or even low-normal T levels. According to an ambitious study published last year by University of Sydney researcher David Handelsman in the *Medical Journal of Australia*, the number of testosterone prescriptions written in the U.S. grew nearly tenfold from 2000 to 2011, part of a worldwide boom. At the same time, online pharmacies in Canada filled millions of additional prescriptions, many of them for Americans, the study suggested. Still more men are bypassing doctors altogether to purchase T-boosting supplements, which are not regulated by the FDA, from retailers like GNC and the Vitamin Shoppe.

Earlier this year, after several studies found indications that certain men were more prone to heart attacks and strokes while taking testosterone—and with dozens of lawsuits being filed across the country alleging harm from the drugs—the FDA announced a review of T safety.

A few months later, the agency called on testosterone manufacturers to warn patients about possible risks of blood clots in veins—a finding not directly related to the heart-attack and stroke concerns. Most recently, the agency has scheduled a meeting of experts for September to sort out red flags from red herrings in the disputed science of T therapy. The questions, however, will remain unsettled until large-scale, randomized clinical trials can provide stronger evidence.

In the meantime, the low-T bandwagon will keep collecting passengers, fueled by a 2,800% increase in marketing dollars and the fathomless fear and loathing among men staring time in the face.

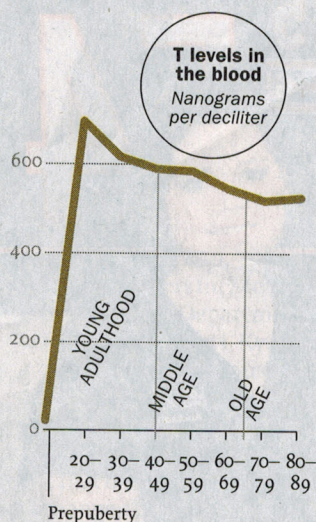
The Search for Endless Youth

IN THE LIFE OF EVERY MAN LUCKY ENOUGH to live beyond his youth, there comes the ultimate betrayal. Not betrayal by a

Whether injected, implanted or absorbed, testosterone promises, in the words of one pitch, ‘power, performance, passion’

The Lowdown On Low T

Testosterone levels normally peak in a man's 20s, then fall by 1% to 2% per year. They fluctuate from morning to afternoon and from day to day



How Low T Is Diagnosed

These are some symptoms of testosterone deficiency—some of which are also associated with other illnesses and normal signs of aging

BREAST DISCOMFORT

Tender or enlarged breasts could be a sign of hormone imbalance in men.

FRAIL BONES

Bones that lose minerals become prone to fracture.

HAIR LOSS

Shaving may become less necessary. Armpit and pubic hair may fall out or thin.

DIMINISHED SEX DRIVE

Low T could result in depressed sexual desire and fewer spontaneous erections.

DEPRESSION

It may also dampen energy, motivation, initiative and confidence.

REDUCED MUSCLE MASS

Physical activity may be more challenging with diminished muscle strength.

LOW SPERM COUNT

Men may not be able to father children. They may also experience shrinking testes.

Sources: Endocrine Society; Framingham Heart Study; Mayo Clinic; Hormone Health Network; Merck; Androgens and the Aging Male; Kantar Media; IMS Health; Global Industry Analysts; FDA
Graphic by Emily Barone and Lon Tweeten

false friend or an inconstant lover. Such backstabbing pales beside the “inevitable hour,” to borrow from the poet Thomas Gray, when the body betrays itself.

In tragic cases, it happens without warning, as when the heart of a seemingly healthy man stops beating. More typical, though, is slow-dawning treachery. Pizza and beer that once burned away quickly begin to cling to the belly. Aches and pains that used to vanish overnight linger a few days, then a few weeks, then forever. The eyes start to blur. The ears muffle. Legs lose their spring. Cells mutate and cancers activate. Most distressing for many men, one's manhood itself changes personality. Once as eager as a Labrador puppy to jump up and play, more and more it resembles an old dog that would rather nap than fetch.

Eventually the realization dawns on a fellow that something systemic is afoot. Scattered clues click into place. He comes to the grim conclusion that his body—this marvelous apparatus that he thought he knew so well—is actually out to get him. He has been marked for death. His own corpus is the assassin. And the whole op-

eration is a suicide mission. His body will kill him by killing itself.

You might say the same thing happens to women, but it's not exactly the same, judging by the demographic profile of sports-car buyers. Women handle the betrayal more matter-of-factly—a nip, a tuck, a tint, maybe, but not a Vegas condo. Perhaps their own anatomy makes them more intimate with the cycles of life, more attuned to the fact that, to quote another poet, T.S. Eliot, time the healer is also time the destroyer.

In any event, what happens next is one of the oldest of human stories. Men start searching for a loophole, a hidden door behind life's bookcase. We see this anxiety threaded through the ages. It's in the *Natural History* of Pliny the Elder, who advised men of 1st century Rome that leeks and the water of boiled asparagus were good for fighting impotence and that garlic “when pounded with fresh coriander and taken in neat wine” made for an aphrodisiac. It's on the mind of the medieval friar Albertus Magnus, who counseled flaccid men to roast the penis

of a wolf, cut it into small pieces and chew a bit to reverse the effects of time.

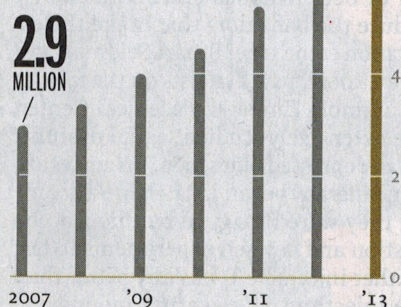
In short, the achy, the wan, the flabby and the limp have never been far from the minds of the world's scientists and hucksters. On the advice of doctors and quacks, men through the years have plunged their packages into cold baths, choked down heaping spoonfuls of wheat germ, swallowed vitamin E and stockpiled Viagra.

Meanwhile, the science of endocrinology emerged, but like all science, it was gradual. During the 1920s and '30s, chemists pinned down the role of hormones in producing the sex traits of women and men. By 1939, two scientists shared the Nobel Prize for Chemistry for their work in isolating and identifying testosterone. Proof of their findings came when the hormone passed the so-called capon test, an experiment devised by earlier researchers. Neutered chickens, known as capons, were dosed with testosterone, and in short order they developed combs and other rooster-like characteristics. The proof was in the crowing: this was a principal trigger of maleness.

The Prescription Boom

Prescription T sales are on the rise as pharmaceutical companies boost advertising efforts

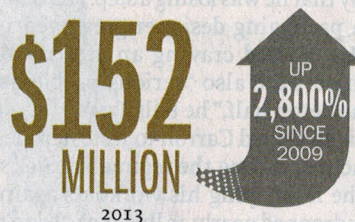
PRESCRIPTIONS



YEARLY U.S. SALES



U.S. MARKETING SPENDING



Weighing the Risks

Sleep apnea Testosterone may contribute to this disorder, in which breathing stops and starts during slumber.

Blood clots The risk of pulmonary embolism—in which blood clots lodge in the lungs—may increase.

Stroke The FDA is investigating the risk of stroke and heart attack in men taking testosterone.

For some scientists, it only stood to reason that the same hormone that makes a strapping man of 20—or 30 or 45—must also be a key to the unwelcome decline of aging. After all, as endocrinologists later observed, T levels drop gradually as men get older. Isn't it obvious that more T would mean less decline? This train of logic brings us to the frenzy of today: Men of the baby boom, top up your T levels and rock on! And give a nod to the ghost of Ponce de León as you reinhabit the hard and lusty body of your former self. Dude, I've got your fountain of youth right here.

When Doctors Disagree

THE PROBLEM IS THAT TRUSTING TESTOSTERONE to relieve men of aging amounts to a massive science experiment with unknown risks. Earlier this year, a team led by California researcher William Finkle published a survey of more than 55,000 patient records in the Public Library of Science. The data indicated that certain men were more prone to heart attacks and strokes while taking testosterone—consistent with a 2013

study of more than 8,000 patients in the Veterans Affairs system published in the *Journal of the American Medical Association*. A 2010 study of testosterone therapy for elderly and frail men came to an early end when the risk of "adverse cardiovascular events" proved too high, according to the *New England Journal of Medicine*. Canada's health authorities, after a safety review, issued a warning in July that testosterone should not be prescribed without careful consideration, because of risks of "serious and possible life-threatening heart and blood-vessel problems, such as heart

attack, stroke, blood clots and increased or irregular heart rate."

No matter what you think of testosterone therapy, however, some scientist somewhere has data to back you up. The July 2 issue of the *Annals of Pharmacotherapy* featured a review of Medicare-patient records in which more than 6,000 testosterone users were compared with some 19,000 similar men who were not on T therapy. A team led by Jacques Baillargeon of the University of Texas Medical Branch at Galveston found no elevated risk of heart attack. "This is a rigorous analysis of a large number of patients," Baillargeon says. "Our findings did not show an increased risk of heart attack associated with testosterone use in older men."

There is also the question of cancer risk. Some doctors fear that testosterone could inflame undetected tumors. Testosterone is believed to accelerate the growth rate of known prostate cancers, and suppressing the hormone is a standard part of treating advanced cases of the disease. Given that prostate cancer is a leading cause of death among aging men, the worry is that boosting T levels could be like dropping matches in a dry forest. However, several small samples of cancer patients who have tried T drugs have not found an appreciable increase in risk. Again, no large-scale clinical trials have been conducted.

Foggy science has not deterred Big Pharma's rush to meet the demand. Though Low-T Center prefers to give T therapy by injection, alternatives are available: topical gels, skin patches, implants—even a nasal spray was recently given the green light by federal regulators. And among marketers, who coined the catchy "low T" term, the story is crystal clear. Whether injected, implanted, inhaled or absorbed, testosterone promises, in the words of one product pitch, "power, performance, passion."

When asked about the T-drug craze, some endocrinologists recall a similar moment not long ago. Female hormone-replacement therapy was hailed as a time-stopping cure for the effects of menopause. But the estrogen boom stalled when a large-scale, well-funded study proved that

No matter what you think about testosterone therapy, some scientist somewhere has data to back you up

How

long-term treatment raised the risk of stroke and heart attack in many women. Now estrogen supplements and related therapies are limited to more narrowly targeted uses.

Testosterone therapy shares a lot of the intellectual scaffolding that once supported hormone replacement for women. Promoters theorize that the gradual ebbing of testosterone as men age is responsible for a condition known as andropause—a kind of male menopause. Though not as abrupt or complete as menopause in women, andropause may be a reason older men lose muscle mass and libido and become more prone to weight gain around their middles—all of which, it so happens, are heralded by marketers as symptoms of low T. (Hypogonadism, it bears mentioning, tends to have far more serious symptoms, including testicles that don't descend out of the body, infertility, enlarged male breasts and a lack of body hair.)

There is so little agreement about T therapy that doctors dispute even the most basic concepts. For example: What level of T in the blood counts as low? And what's the proper way to measure levels to begin with? Is low T actually the cause of andropause symptoms? Or is it a symptom itself, caused by other factors? Advertising assures men that dwindling testosterone levels invite belly flab. But some experts argue that the reverse is true, that the flab comes first and is the cause of lower hormone levels and more exercise and a healthier diet will bring the levels up naturally.

"Have you considered other reasons why you may be experiencing fatigue, low sex drive and other symptoms?" *Harvard Men's Health Watch* recently asked. "Do you eat a balanced, nutritious diet? Do you exercise regularly? Do you sleep well? Address these factors before turning to hormone therapy."

T Drugs in Action

FURTHER CONFOUNDING THE SUBJECT IS the role played by mankind's most cherished organ. No, not that one—the brain. The catalog of complaints triggering T therapy is well known to be a tangle of

both physical and mental factors. Take the case of Chuck Carroll, 51, a patient at the Southlake Low T Center. A two-time All-America runner in his younger years, Carroll began to worry around his 50th birthday that he was losing a step. His travels as a packaging designer grew wearisome. He started craving an afternoon nap. There were also "serious problems with the better half," he tells *TIME*.

A friend tipped Carroll to testosterone, and since beginning the regimen at Sisk's clinic, he is enjoying his workouts again and has dropped nearly 20 lb. (9 kg). "I don't feel so worn out, and my wife is happy too," he says. When his grown kids drop by and ask where Dad is, "Dad isn't on the couch."

Carroll might be describing any one of a million low-T patients. A man in his 50s or 60s or 70s finds himself feeling sluggish and low. He's eating or drinking too much, and his body doesn't burn calories as fast as it used to. Next thing he knows, he's overweight. The combination of mood and weight makes it difficult to stir up the energy for exercise, while lack of exercise only worsens his other problems. This dismal cycle wreaks havoc on his libido too.

Testosterone represents new hope and a fresh start. For the first time in years, he expects to feel happier and more energetic. After all, marketers are spending millions to raise those expectations. Believing that he will feel better, he does. He starts exercising and watching what he consumes. The dismal cycle reverses. Soon all sorts of systems, from head to heart to groin, begin operating at a higher level.

What works for one man may not work for others. A treatment that is benign when used briefly may become toxic with long use

Calling the shots Testosterone can be administered through topical gels, injections, nasal sprays and patches

Is it the hormones, or is this a classic placebo effect? Does the simple expectation of better moods and more energy produce the behaviors that make the expectation come true? Stuart Seidman and Steven Roose, psychiatrists on the faculty of Columbia University Medical Center, have extensively studied sexual dysfunction in depressed older men. When testosterone therapy began to catch fire a decade ago, they were intrigued by this placebo question and devised experiments to test whether injectable T was any better than fake injections at elevating moods and stimulating erections.

In a randomized, double-blind test of 30 men, they gave T shots to some of the subjects and harmless sesame-oil injections to the others. All the test subjects were experiencing depression and erectile dysfunction. Many of them reported improvements in their mood and function after treatment. But the doctors found no statistically significant difference in the progress of the T takers over the placebo group. Whether real or fake, the injections had the same effect on the patients.

Which is not to say testosterone is all in the mind. High doses of male hormones produce physical and emotional changes. Just look at the lads at your local high school, who sprout from wisps to hulks in a matter of months. At puberty, a rush of testosterone courses through an unsuspecting boy, signaling that the time has come to sprout his beard, swell his muscles, lower his voice and fire his loins. The body responds with a total transformation.

"Testosterone is not a silver bullet," Sisk says. "Testosterone makes a guy feel better. He starts working out a little more, drops a couple of pounds. But if you're going to sit home and drink beer and eat pretzels, this is not gonna help you."

But given the unknowns of testosterone therapy, should aging men by the millions be juicing themselves with substances powerful enough to keep Barry Bonds and Roger Clemens out of the Hall of Fame? Not to mention the risk to people close to them: men who apply the gel should be careful not to let it come into contact with others. In pregnant women, T-gel exposure can



cause birth defects, and in all women it can cause abnormal hair growth and acne. In kids, it can cause enlarged genitals and, in boys, increased erections.

The Murky Path Forward

THE FDA'S ROLE IN TESTOSTERONE THERAPY began as evidence suggested that hormone supplements would help address hypogonadism in otherwise healthy young men. But from there, the picture has grown more complicated, even as mass marketing has oversimplified the low-T message. The human gizmo starts to run down, so we slap in new batteries, but what that alluring promise misses is the exquisite complexity of human life. The natural decline in testosterone in older men doesn't happen in a vacuum. It's part of a delicate endocrine system governed by interactions of the brain with various glands—the

hypothalamic-pituitary-gonadal system. It's impossible to tease out the effects of a single ingredient from the cocktail.

Furthermore, the changes that men experience as they age are not simply expressions of hormone levels. Genes play a potent role, as do psychology and environment. Because there is no single cause of depression, there is no single cure. Likewise, weight gain happens for all sorts of reasons, and each one demands a different solution. Sexual desire is such an individual and fugitive fancy that it makes a better subject for artists than scientists, and erectile dysfunction (ED) can be an expression of boredom, chronic or acute illness, reduced blood flow, anxiety—the list goes on.

It's no wonder the FDA decided to gather the experts for a T summit. But any attempt by scientists to isolate the effect of testosterone will likely be foiled by the complexity

of the human machine. What works for one man may not work in others. A treatment that is benign when used briefly might become toxic with long use. We have more guesses and theories than we have answers or knowledge. We are closer to Pliny and Albertus than we like to admit.

Perhaps T therapy will prove as flawed as blanket hormone-replacement therapy has been for women, or maybe it will follow the path of another wonder cure: the little blue pill. When Viagra hit the market in 1998, it was hailed as the fix for ED. A second sexual revolution was declared, this one throwing off the chains of age. Within a decade, annual Viagra sales were approaching \$2 billion, even as a raft of similar medications entered the marketplace.

Then an odd thing began to happen. Doctors noticed that large numbers of their patients weren't refilling their prescriptions. Sales of Viagra, Cialis, Levitra and other ED drugs leveled off, then began to fall. Abraham Morgentaler, a urologist on the faculty at Harvard Medical School, explored this reality in the book *The Viagra Myth*. "As I listened to my patients, I came to see that our culture had taken Viagra and created a legend out of it that went far beyond its actual pharmacological properties," he wrote. "People had come to expect that taking a little blue pill could solve their personal and relationship problems, no matter how complex those difficulties were."

Mike Sisk has a somewhat different explanation for why men search for a magic pill or potion. He thinks about it now and then, when he's not busy working on the charity that he and his wife are setting up or the \$16 million gift he has pledged to the University of Tennessee athletic department or the possibility of taking his company public in 18 months or so. Andrew Marvell, yet another poet, got close to the gist when he wrote, "Though we cannot make our sun stand still, yet we will make him run."

Sisk puts it this way: "Our dads' generation went quietly into the night." Smiling broadly, he continues, "My generation is not going quietly."

—WITH REPORTING BY HILARY HYLTON IN SOUTHLAKE