CHAPTER 5

NATURAL HORMONE REPLACEMENT FOR MEN

While the casual observer may assume that bio-identical hormone replacement is something that is strictly for women, the truth is very different. Many men need hormone replacement too.

I speak from personal experience. For the early part of my life I never really believed in male menopause, also known as andropause. Like most men, I was ill-informed when the time approached, and perhaps a bit in denial. It was very evident that my female patients were experiencing this change, but we are the hunters, the stronger of the sexes; this was just normal gradual aging, wasn't it?

In my early forties, I knew I was getting older, and my body and mind began changing. I was getting sleep deprived, my sexual performance was declining, and the urge to hit the gym was no longer a priority. Late nights and early mornings delivering babies was exhausting. Work wasn't enjoyable anymore; it was irritating. My workouts were much less productive. I was developing belly fat. My cholesterol was on the rise. Trying to remember things that were once a snap now seem to take forever.

Despite the obvious signs, entering into the "season" of andropause was not a consideration. Unlike women, we really don't talk about our aging bodies. However, after hearing years

of symptoms and concerns from our talkative counterparts, although each unique, the underlying chief complaints were drawing a very straight and narrow line. Knowing that they were experiencing real hormonal changes, how are we any different?

Once I opened up to the possibility my testosterone could be low, that my symptoms were not permanent, and that my mind and body could be rejuvenated, I sought out the solution.

WHAT TESTOSTERONE IS AND WHAT IT DOES

Of all the human hormones, testosterone is wrapped in the most myth and mystery. Many men—and women—simply see it as the "sex hormone" that gives men their sex drive. In this simplistic belief, high testosterone equals high sex drive. Low testosterone equals poor bedroom performance.

Of course, this image of testosterone as being the he-man hormone is a vast oversimplification. Before we discuss the complex ways in which testosterone levels affect the minds and bodies of men, let's make sure that we know what this stuff is, where it comes from, and what it does in your body.

Found in mammals, reptiles, birds, and other vertebrates, testosterone is a steroid hormone from the androgen group. Steroid hormones help control metabolism, inflammation, immune functions, development of sexual characteristics, and the ability to withstand illness and injury—hence the popular use of the term "steroids" for the stuff that athletes inject. In male mammals, testosterone is secreted primarily by the testicles, although small amounts are also secreted by the adrenal glands.

In men, testosterone aids in the development of male reproductive organs such as the testes and prostate, and promotes secondary sexual characteristics including the growth of body hair and increased muscle and bone mass.

Males produce more than females; on average, in adult males, levels of testosterone are eight times as great as in adult females.

When the higher rate of metabolic *consumption* of testosterone in males is taken into account, the actual daily production of testosterone is about twenty times greater in men than in women.

Testosterone levels can be measured by a simple blood test. In males, the first physical signs of increased testosterone are apparent during puberty. A boy's voice changes, his shoulders broaden, and his facial structure becomes more masculine. Testosterone levels are at their highest during adolescence and early adulthood. The normal range of testosterone levels in healthy males is between 800 and 1,200 nanograms per deciliter (ng/dL). After age thirty, testosterone levels in men decline—sometimes precipitously.

The History of Testosterone Therapy

Over the centuries, medical researchers have been keen to uncover the secret to male sexual function—how it began in puberty and why it seemed to wane as men reached middle age and later. After all, reproduction is a key mystery of life, and if you could unlock its secrets the effects on human life could be profound.

The history of testosterone therapy has, and continues to, resemble a mystery novel. There has long been intrigue and controversy. Some of the first experiments involving testosterone were conducted on chickens. In 1767, John Hunter transplanted testes from roosters into the abdomen of a hen. While the testes adhered to the hen's intestine, they produced no noticeable change in the hen.

In 1849, Arnold A. Berthold tried a similar experiment but with a twist. Of six roosters, two were used as a control group, two were castrated but had their testes transplanted back into their own bodies at a distant location, and the remaining two were castrated and left to develop with no testes. Unsurprisingly, Berthold found that the two castrated chickens never developed adult male characteristics. However, the two chickens with the transplanted testes developed into mature adult roosters. This suggested that the location of the organ was not crucial to how

these internal secretions worked; the secretions must travel freely through the bloodstream.

In 1889, Harvard University professor Charles Edouard Brown-Séquard contributed an article in the *London Lancet* entitled, "The Effects Produced on Man by Subcutaneous Injections of a Liquid Obtained From the Testicles of Animals." He wrote, "There is no need of describing at length the great effects produced on the organization of man by castration, when it is made before the adult age. It is particularly well known that eunuchs are characterized by their general debility and their lack of intellectual and physical activity.... It is known that well-organized men, especially from twenty to thirty-five years of age, who remain absolutely free from sexual intercourse or any other causes of expenditure of seminal fluid, are in a state of excitement, giving them a great, although abnormal, physical and mental activity. These two series of facts contribute to show what great dynamogenic power is possessed by some substance or substances which our blood owes to the testicles. For a great many years I have believed that the weakness of old men depended on two causes—a natural series of organic changes and the gradually diminishing action of the spermatic glands."

His article throws into perfect relief the three most persistent beliefs that people have had about testosterone (the "Elixir of Life"): that lack of it makes a young man weak; that if a man "saves it" by celibacy he will become stronger; and that the decline of old age is due to a loss of the magical elixir.

Of the first belief I'll reserve judgment, and the second we now know is laughable. But the third is no laughing matter to millions of men as they open that invitation to join AARP for the first time.

Brown-Séquard injected testicular extract into himself, and then claimed amazing physical and mental improvements. Of course there was no proof that it worked, and it was later discovered it was merely a placebo effect. No matter! By the end of 1889, more than 12,000 physicians were selling the "Elixir of Life" throughout Europe and North America.

The idea that some mysterious substance in animal testicles could offer performance-enhancing benefits in athletes has been firmly planted in the research community ever since 1896, when Austrian physiologist Oskar Zoth published a paper in which he hypothesized that injections of steroid-based testicular extracts could enhance athletic performance. He somewhat presciently wrote, "The training of our athletes offers an opportunity for further research and a practical assessment of our experimental results."

In the 1920s came our next testosterone pioneer, Eugene Steinach, a Viennese physiologist, who invented the "Steinach operation" (or "Steinach vasoligature"), the goals of which were to reduce fatigue and the consequences of aging, and to increase overall vigor and sexual potency in men. It consisted of a half- (unilateral) vasectomy, which would cause the sperm-producing tissue to back up and atrophy, making more room for the interstitial or Leydig cells that are also produced in the testicles, which would then flood the bloodstream with hormones and new energy. He trained numerous surgeons in the art of "Steinaching" eager patients. In the Roaring Twenties, thousands of Steinach operations were performed in the US and around the world, from Chile to India.

Any apparent results were a placebo effect. The biological ideas that underlay Steinaching have long been discredited; a vasectomy doesn't stimulate the overproduction of Leydig cells, as Steinach supposed.

Steinach was followed by a Swiss genitourinary surgeon, Paul Niehans, who ingeniously transferred live testicular cells to increase "testicular secretions." But what were these "secretions"? What was helping these "middle-aged, listless individuals"?

In 1935, researchers K.G. David, E. Dingemanse, J. Freud and E. Laqueur, who were backed by the Organon Pharmaceutical Company in Oss, The Netherlands, published the now classic paper "*Über krystallinisches mannliches Hormon aus Hoden*

(Testosteron) wirksamer als aus harn oder aus Cholesterin bereitetes Androsteron," or, "On crystalline male hormone from testicles (testosterone) effective as from urine or from cholesterol." They named the hormone "testosterone" from the stems of "testicle" and "sterol," and the suffix of "ketone."

Thanks to the breakthrough by Organon, the testosterone industry was born. The synthesis of testosterone came later by Leopold Ruzicka, and the researchers applied for a patent. In 1939, Ruzicka shared the Nobel Prize for chemistry with Adolf Friedrich Johann Butenandt, another researcher in the field of human hormones.

These great pioneers from all parts of the world had discovered the "secretion." Since then, the question has been who to treat, with which problems, with how much testosterone, and whether should it be bio-identical or synthetic.

In 1945, Paul Henry de Kruif, an American biologist, wrote a book on testosterone, *The Male Hormone*. There were a number of studies in the "golden age of steroids" from 1940-1960. They mostly were haphazard, using synthetic injections or oral methyl testosterone. In California, bodybuilders experimented with testosterone and helped develop the multi-million-dollar black market in testosterone supplements that flourishes today.

In 1966, a physician named Robert Wilson wrote *Feminine Forever*, which was the stimulus for women to start getting their hormones replaced. This book sparked discussions about testosterone replacement in men. The products were "synthetic" testosterone compounds, and without guidance as to dosing, a number of males became aggressive, blaming testosterone, and its use quickly diminished. In the 1980s, the World Health Organization performed a study to see if anabolic steroids could be used as a male contraceptive. The results were very efficacious and with minimal side effects. It is interesting and perplexing that the doses used for contraception in the male exceed those used by Olympic sprinter Ben Johnson for which he was banned from the Olympics. It wasn't until the new millennium that testosterone was re-evaluated as a "healthy aging" drug.

THE MODERN TESTOSTERONE INDUSTRY

Today, physicians write more than seven million prescriptions per year for testosterone products. It's a two-billion-dollar-a-year business for the pharmaceutical industry—a "blockbuster" for sure.

The pioneers have given way to big pharmaceutical companies vying for that two-billion-dollar gold mine. Meanwhile, the black market for anabolic steroids has staked its claim. It has found its way into modern houses, where men self-diagnose and administer this dangerous drug, all trying to stay ahead of the inevitable aging process. This has caused men to suffer horrendous side effects including aggression, heart disease, and testicular atrophy. Major sports athletes from pro football, cycling, baseball and bodybuilding have fallen from fame and have had their careers tarnished permanently.

As with all great mysteries, there must be a problem to solve. What is the right drug, at the right dose, given by the best route of administration? Where is our solution? Is it synthetic or bio-identical? Where is the hero who actually wants to improve the health and vitality of men as they age, rather than sell out to commercial profiteering? This book and this chapter help solve the mystery of hundreds of years.

Age and Testosterone

Male andropause can begin any time after age thirty-five. It has also been termed androgen deficiency in the adult male (ADAM). Each year thereafter, men lose between one and five percent of their testosterone production. That means on average men lose twenty percent of their testosterone per decade. Many men lose it much more quickly.

In conjunction with this *decrease* in testosterone as we age, there is an *increase* in sex hormone binding globulin (SHBG), the protein that binds up our useable testosterone (T). So we make less T, and more of it gets sucked up like a sponge by the SHBG. Unlike

female menopause, which occurs more as an event or rapid loss of hormone production, the "season" of andropause can be indolent, and therefore harder to pinpoint, in its onset. Aging in males, like females, is multi-factorial. Some men have great genes and long-lasting hormone balance. Others have genetic alterations, stressful lives, sub-optimal immune systems, and early hormone imbalances leading to accelerated, unhealthy aging.

The symptoms are an easy way to help make the diagnosis. Men feel fatigued (especially after noon), experience insomnia, and have decreased memory, focus, and concentration. They have "presenteeism," where they go to work and they are present and accounted for, but their performance is sub-par. Workouts are less productive, and in fact they begin losing muscle mass. Sexual performance is decreased. This is most noticeable by a loss of morning erections and loss of erections after ejaculation. Some men even lose their libido. These symptoms have deleterious effects on a man's relationship with his partner. It is by no coincidence that the peak years for divorce correspond to the early years of andropause.

Over the long term, men with low testosterone have an increased risk for heart disease, stroke, diabetes mellitus, Alzheimer's disease, prostate cancer, arthritis, osteoporosis and fractures, and sarcopenia (muscle loss).

Testosterone Replacement Choices

What responsible and safe steps can males entering andropause take to protect their bodies and minds?

There are a number of choices—many of them questionable and unstudied. Because men produce twenty times more testosterone daily compared to woman, men require obviously higher doses to treat their symptoms and for long-term prevention of the diseases listed above.

- Anabolic steroids that cannot be metabolized to estrogen are not part of a healthy aging plan. They have deleterious side effects, including aggression, and can damage the

heart, liver and kidneys.

- The creams and gels commercialized by the pharmaceutical companies, albeit bio-identical, have erratic absorption, and do not achieve blood levels adequate to treat the symptoms of low testosterone. They certainly are not capable of preventing heart disease, Alzheimer's disease, diabetes, or osteoporosis. They are, however, a great example of the commercialization of medicine and the lack of concern by pharmaceutical companies for treating the aging male with something that might make them healthier, not just generate profits.

  It is prudent to recall the study published in the journal *Circulation* in 2007, the official journal of the American Heart Association. They looked at more than 11,000 men between the ages of forty and seventy-nine. The levels of testosterone before therapy, if low, had increased risk of heart disease, cancer, and all causes of death. Based on this study and numerous others, it is prudent to achieve higher levels of testosterone similar to those seen in our twenties.

  As of this writing, a growing number of men throughout the United States are pursuing potential AndroGel lawsuits, Testim lawsuits, Axiron lawsuits, and other testosterone drug lawsuits. All of the complaints filed in state and federal courts nationwide involve similar allegations that men suffered heart attacks, strokes, blood clots or other serious and sometimes fatal injuries as a result of heart problems from Androgel and other testosterone drugs, and that inadequate warnings have been provided to men and the medical community.

- Synthetic injections including testosterone cypionate, testosterone enanthate, and the new longer-acting testosterone undecanoate.

  The first two, testosterone cypionate and testosterone enanthate, must be administered at least weekly, if not twice a week. This could require 104 shots per year per patient. In my experience, this leads to a compliance problem, and

men simply will not stay on the therapy. These products are also produced in an oil base, typically cottonseed oil. This allows for a "time release" of the synthetic testosterone, which then must go to the liver for conversion to the active compound testosterone. Many men have experienced allergies to the cottonseed oil and have developed scar tissue from the oil at the injection sites. Even though cypionate and enanthate can achieve successful blood levels, there is a "roller coaster" effect with blood levels going up and down on a weekly basis. Additional problems from these two medications include: a lowering of the HDL cholesterol levels (good cholesterol), an excessive increase in red blood cells, and—most disturbing—an increase of a substance from our platelets called thromboxane A2. This substance has been associated with increasing platelet "stickiness" and constriction of blood vessels. It is not known but surmised that this may lead to increase in heart attacks in the elderly, especially if they have pre-existing heart disease.

The final drug in this category is testosterone undecanoate. It has been recently approved by the FDA for the treatment of hypogonadism in males. It is a "synthetic" and has all the pitfalls described for the other injectable testosterone preparations. It also has two additional issues. Most importantly, patients have had pulmonary oil micro-embolisms. This where small oil droplets have travelled to the lung and caused fatalities. There has also been anaphylactic reactions to the oil. Currently, AVEED, as the product is known as, is only available on a restricted program.

- The final, and best choice is treatment with subcutaneous hormone pellets. While I'll present an entire chapter devoted to this therapy, here's an overview. Each testosterone "pellet" is tiny—only about the size of a grain of rice. As in the female, it is implanted painlessly beneath the skin in the buttock or sometimes the abdomen.

  The pellets are natural bio-identical testosterone. Their benefits are many and side effects few. Most important,

they maintain relatively constant blood levels, avoiding the "roller coaster" effect of injections and creams. They also achieve adequate blood levels to be beneficial to the symptoms of low testosterone, and more importantly are a great proactive step to avoiding the serious maladies that await us in each decade as we get older. This therapy is made even more fascinating because men only have to receive the therapy usually twice a year. They are therefore the *sine qua non* needed for "healthy aging."