LifeExtension

Male Hormone Modulation Therapy

In terms of instant effect, the protocol you are about to read may surpass any Life Extension program described in this book.

The age-reversal premise we are espousing is the subject of three books written by highly respected medical doctors. These books provide a persuasive compilation of research findings and clinical experience to document the safety and efficacy of using this approach to treat aging. The books fail, however, to provide an aggressive therapeutic plan of action. In this protocol, the Foundation provides a novel step-by-step program to enable people to immediately take advantage of this new information.

In writing this protocol, the Life Extension Foundation reviewed several thousand published scientific studies to validate safety and anti-aging efficacy. We also received input from experts who have personally followed this system for several years.

Foundation members do not want to see their bodies ravaged by age if a documented therapy is available that can control or reverse this devastating process. In this case, proven therapies exist and many of them are FDA approved.

Implementing this protocol requires diligent medical testing, but the potential for significant age reversal is compelling.

MALE HORMONES AND AGING

As men age past age 40, hormonal changes occur that perceptibly inhibit physical, sexual, and cognitive function. The outward appearance of a typical middle-aged male shows increased abdominal fat and shrinkage of muscle mass, a hallmark effect of hormone imbalance (94-97, 271).1 Loss of a feeling of well-being, sometimes manifesting as depression, is a common psychological complication of hormone imbalance. Until recently, these changes were attributed to "growing old," and men were expected to accept the fact that their bodies were entering into a long degenerative process that would someday result in death.

A remarkable amount of data has been compiled indicating that many of the diseases that middle-aged men begin experiencing, including depression, fatigue, abdominal weight gain, alterations in mood and cognition, decreased libido, erectile dysfunction, prostate disease, and heart disease are directly related to hormone imbalances that are correctable with currently available drug and nutrient therapies. The onset of these symptoms usually appears in the early 50s, although with smokers the onset is significantly earlier (290-293).

To the patient's detriment, conventional doctors are increasingly prescribing drugs to treat depression, elevated cholesterol, angina, and a host of other diseases that might be caused by an underlying hormone imbalance.

If doctors checked their male patients' blood levels of estrogen, testosterone, thyroid, and DHEA (instead of prescribing drugs to treat symptoms), they might be surprised to learn that many problems could be eliminated by adjusting hormone levels to fit the profile of a healthy 21-year-old male.

Few physicians are familiar with the hormone blood tests that should be ordered for men, nor do they have the experience required to properly adjust hormones to reverse the degenerative changes that begin in midlife. This protocol will provide the patient and physician with the information necessary to safely modulate hormone levels for the purpose of preventing and treating many of the common diseases associated with growing older.

Too Much Estrogen

The most significant hormone imbalance in aging men is a decrease in free testosterone, while estrogen levels remain the same or increase precipitously. As men grow older, they experience a variety of disorders relating to the dual effects of having too little testosterone and excess estrogen. The result is a testosterone-estrogen imbalance that directly causes many of the debilitating health problems associated with normal aging (1-12, 28).

One cause of hormone imbalance in men is that their testosterone is increasingly converted to estrogen. One report showed that estrogen levels of the average 54-year-old man are higher than those of the average 59-year-old woman (1, 5, 13-18, 48).

The reason that testosterone replacement therapy does not work by itself for many men is that exogenously administered testosterone may convert (aromatize) into even more estrogen, thus potentially worsening the hormone imbalance problem in aging males (i.e., too much estrogen and not enough free testosterone) (21, 26). Although there are studies that show that testosterone replacement therapy does not increase estrogen beyond normal reference ranges, we will show later how the standard laboratory reference ranges do not adequately address the issue of estrogen overload (4, 8, 9, 17, 22-25, 27, 29-32).

Estrogen is an essential hormone for men, but too much of it causes a wide range of health problems. The most dangerous acute effect of excess estrogen and too little testosterone is an increased risk of heart attack or stroke (39-43, 261-270). High levels of estrogen have been implicated as a cause of benign prostatic hypertrophy (BPH) (35-44, 46, 47). One mechanism by which nettle root extract works is to block the binding of growth-stimulating estrogen to prostate cells (42-44, 48-50).

When there is too little testosterone present, estrogen attaches to testosterone cell receptor sites throughout the body and creates many problems in aging men. In youth, low amounts of estrogen are used to turn off the powerful cell-stimulating effects of testosterone. As estrogen levels increase with age, testosterone cell stimulation may be locked in the "off" position, thus reducing sexual arousal and sensation and causing the loss of libido so common in aging men (94, 99, 259).

High serum levels of estrogen also trick the brain into thinking that enough testosterone is being produced, further slowing the natural production of testosterone. This happens when estrogen saturates testosterone receptors in the hypothalamus region of the brain. The saturated hypothalamus then stops sending out a hormone to the pituitary gland to stimulate secretion of luteinizing hormone that the gonads require to produce testosterone. High estrogen can thus shut down the normal testicular production of testosterone (1, 53, 54, 271-277).

One further complication of excess estrogen is that it increases the body's production of sex hormone-binding globulin (SHBG). SHBG binds free testosterone in the blood and makes it unavailable to cell receptor sites (51, 52, 55, 56).

Based on the multiple deleterious effects of excess estrogen in men, aggressive action should be taken to reduce estrogen to a safe range if a blood test reveals elevated levels. We will discuss the appropriate blood tests and steps that can be taken to lower estrogen levels later in this protocol.

THE CRITICAL IMPORTANCE OF FREE TESTOSTERONE

Testosterone is much more than a sex hormone. There are testosterone receptor sites in cells throughout the body, most notably in the brain and heart (60-180). Youthful protein synthesis for maintaining muscle mass and bone formation requires testosterone (67, 69, 81). Testosterone improves oxygen uptake throughout the body, helps control blood sugar, regulates cholesterol, and maintains immune surveillance (82, 83). The body requires testosterone to maintain youthful cardiac output and neurological function (58, 65). Testosterone is also a critical hormone in the maintenance of healthy bone density (59, 66, 67, 84-86), muscle mass, and red blood cell production (67, 69, 91-93, 98).

Of critical concern to psychiatrists are studies showing that men with depression have lower levels of testosterone than do control subjects. For some men, elevating free testosterone levels could prove to be an effective antidepressant therapy. There is a basis for free testosterone levels being measured in men with depression and for replacement therapy being initiated if free testosterone levels are low normal or below normal.

Testosterone is one of the most misunderstood hormones. Body builders tarnished the reputation of testosterone by putting large amounts of synthetic testosterone drugs into their young bodies. Synthetic testosterone abuse can produce detrimental effects (34), but this has nothing to do with the benefits a man over age 40 can enjoy by properly restoring his natural testosterone to a youthful level.

Conventional doctors have not recommended tes-tosterone replacement therapy because of an erroneous concern that testosterone causes prostate cancer. As we will later show, fear of prostate cancer is not a scientifically valid reason to avoid testosterone modulation therapy.

Another concern that skeptical physicians have about prescribing testosterone replacement therapy is that some poorly conducted studies showed it to be ineffective in the long-term treatment of aging. These studies indicate anti-aging benefits when testosterone is given, but the effects often wear off. What physicians fail to appreciate is that exogenously administered testosterone can convert to estrogen in the body. The higher estrogen levels may negate the benefits of the exogenously administered testosterone. The solution to the estrogen-overload problem is to block the conversion of testosterone to estrogen in the body.

Numerous studies show that maintaining youthful levels of free testosterone can enable the aging man to restore strength, stamina, cognition, heart function, sexuality, and outlook on life, that is, to alleviate depression. A study in Drugs and Aging (1999) suggested that androgen therapy can result in polycythemia (increased numbers of red blood cells) causing an increase in blood viscosity and risk of clotting (303). For many aging men, however, borderline anemia is a greater concern than red blood cell overproduction. When men are deprived of testosterone during prostate cancer therapy, anemia frequently manifests. Life Extension has not seen cases in which polycythemia developed in men taking enough tes-tosterone to restore physiological youthful ranges. In other words, too much testosterone could cause problems, but replacing testosterone to that of a healthy 21-year-old should not produce the side effects that some doctors are unduly concerned about. As you will read in the section entitled "Testosterone and the Heart," it appears that testosterone replacement therapy provides significant beneficial effects against cardiovascular disease.

Why Testosterone Levels Decline

Testosterone production begins in the brain. When the hypothalamus detects a deficiency of testosterone in the blood, it secretes a hormone called gonadotrophin-releasing hormone to the pituitary gland. This prompts the pituitary to secrete luteinizing hormone (LH), which then prompts the Leydig cells in the testes to produce testosterone.

In some men, the testes lose their ability to produce testosterone, no matter how much LH is being produced. This type of testosterone deficiency is diagnosed when blood tests show high levels of LH and low levels of testosterone. In other words, the pituitary gland is telling the testes (by secreting LH) to produce testosterone, but the testes have lost their functional ability. So the pituitary gland vainly continues to secrete LH because there is not enough tes-tosterone in the blood to provide a feedback mechanism that would tell the pituitary to shut down. In other cases, the hypothalamus, or pituitary gland, fails to produce sufficient amounts of LH, thus preventing healthy testes from secreting testosterone. Blood testing can determine whether sufficient amounts of LH are being secreted by the pituitary gland and help determine the appropriate therapeutic approach. If serum (blood) testosterone levels are very low, it is important to diagnose the cause, but no matter what the underlying problem, therapies exist today to safely restore testosterone to youthful levels in any man (who does not already have prostate cancer).

As indicated earlier, a major problem that aging men face is not low production of testosterone, but excessive conversion of testosterone to estrogen. Specific therapies to suppress excess estrogen and boost free testosterone back to youthful physiological levels will be discussed later.

The Effects of Testosterone on Libido

Sexual stimulation and erection begin in the brain when neuronal testosterone-receptor sites are prompted to ignite a cascade of biochemical events that involve testosterone-receptor sites in the nerves, blood vessels, and muscles. Free testosterone promotes sexual desire and then facilitates performance, sensation, and the ultimate degree of fulfillment.

Without adequate levels of free testosterone, the quality of a man's sex life is adversely affected and the genitals atrophy. When free testosterone is restored, positive changes can be expected in the structure and function of the sex organs. (It should be noted that sexual dysfunction can be caused by other factors unrelated to hormone imbalance. An example of such a factor is arteriosclerotic blockage of the penile arteries.)

The genital-pelvic region is packed with testosterone receptors that are ultra-sensitive to free testosterone-induced sexual stimulation. Clinical studies using tes-tosterone injections, creams, or patches have often failed to provide a long-lasting, libido-enhancing effect in aging men. We now know why. The testosterone can be converted to estrogen. The estrogen is then taken up by testosterone receptor sites in cells throughout the body. When an estrogen molecule occupies a testosterone receptor site on a cell membrane, it blocks the ability of serum testosterone to induce a healthy hormonal signal. It does not matter how much serum free testosterone is available if excess estrogen is competing for the same cellular receptor sites.

Estrogen can also increase the production of SHBG, which binds the active free testosterone into an inactive "bound testosterone." Bound testosterone cannot be picked up by testosterone receptors on cell membranes. For testosterone to

produce long-lasting, libido-enhancing effects, it must be kept in the "free" form (not bound to SHBG) in the bloodstream. It is also necessary to suppress excess estrogen because this hormone can compete for testosterone receptor sites in the sex centers of the brain and the genitals.

Restoring youthful hormone balance can have a significant impact on male sexuality (99-102).

Testosterone and the Heart

Normal aging results in the gradual weakening of the heart, even in the absence of significant coronary artery disease. If nothing else kills the elderly male, his heart just stops beating at some point.

Testosterone is a muscle-building hormone, and there are many testosterone-receptor sites in the heart (57). The weakening of the heart muscle can sometimes be attributed to testosterone deficiency (103-108).

Testosterone is not only responsible for maintaining heart muscle protein synthesis, it is also a promoter of coronary artery dilation (109-113) and helps to maintain healthy cholesterol levels (81-114).

There are an ever-increasing number of studies indicating an association between high testosterone and low cardiovascular disease rates in men. In the majority of patients, symptoms and EKG measurements improve when low testosterone levels are corrected. One study showed that blood flow to the heart improved 68.8% in those receiving testosterone therapy. In China, doctors are successfully treating angina with testosterone therapy (9, 115, 116).

The following list represents the negative effects of low testosterone on cardiovascular disease:

- Cholesterol, fibrinogen, triglycerides, and insulin levels increase
- Coronary artery elasticity diminishes (30-33)
- Blood pressure rises
- Human growth hormone (HGH) declines (weakening the heart muscle)
- Abdominal fat increases (increasing the risk of heart attack)

Those with cardiovascular disease should have their blood tested for free testosterone and estrogen. Some men (with full cooperation from their physicians) may be able to stop taking expensive drugs to stimulate cardiac output, lower cholesterol, and keep blood pressure under control if they correct a testosterone deficit or a testosterone-estrogen imbalance. A compelling study of 1100 men showed that those with serum dehydroepiandrosterone-sulfate (DHEA-S) in the lowest quarter (< 1.6 mcg/mL) were significantly more likely to incur symptoms of heart disease (295), and in a review of several studies, other authors have confirmed this association (296). Dehydroepiandro-sterone (DHEA) is produced by the adrenal gland and is a precursor hormone for the manufacture of testosterone (see the DHEA Replacement Therapy protocol).

Despite numerous studies substantiating the beneficial effects of testosterone therapy in treating heart disease, conventional cardiologists continue to overlook the important role this hormone plays in keeping their cardiac patients alive (9, 30, 31, 77, 93, 111-113, 115, 116, 261-270).

Testosterone and the Prostate Gland

Many doctors will tell you that testosterone causes prostate disease. The published scientific literature indicates otherwise.

As readers of Life Extension Magazine learned in late 1997, estrogen has been identified as a primary culprit in the development of benign prostatic hyperplasia (BPH). Estrogen has been shown to bind to SHBG in the prostate gland and cause the proliferation of epithelial cells in the prostate (124, 182-184). This is corroborated by the fact that as men develop benign prostate enlargement, their levels of free testosterone plummet, although their estrogen levels remain the same or are rising. As previously discussed, aging men tend to convert their testosterone into estrogen. The published evidence shows that higher serum levels of testosterone are not a risk factor for developing benign prostate disease (8, 36, 41, 117-137).

The major concern that has kept men from restoring their testosterone to youthful levels is the fear of prostate cancer. The theory is that since most prostate cancer cell lines need testosterone to proliferate, it is better not to replace the testosterone that is lost with aging. The problem with this theory is that most men who develop prostate cancer have low levels of tes-tosterone, and the majority of published studies show that serum testosterone levels do not affect one's risk for contracting prostate cancer.

Because there is such a strong perception that any augmentation of testosterone can increase the risk of prostate cancer, we did a MEDLINE search on all the published studies relating to serum testosterone and prostate cancer. The abstracts at the end of this protocol provide quotations from the published literature as it relates to the issue of whether testosterone causes prostate disease. Of the 27 MEDLINE studies found, five studies indicated that men with higher testosterone levels had a greater incidence of prostate cancer, whereas 21 studies showed that testosterone was not a risk factor and one study was considered neutral. Before starting a testosterone replacement program, men should have a serum PSA test and a digital rectal exam to rule out prostate cancer. Nothing is risk free. A small minority of men with low testosterone and prostate cancer will not have an elevated PSA or palpable lesion detectable by digital rectal exam. If these men use supplemental testosterone, they risk an acute flare-up in their disease state. That is why PSA monitoring is so important every 30-45 days during the first 6 months of any type of testosterone augmentation therapy. If an underlying prostate cancer is detected because of testosterone therapy, it is usually treatable by nonsurgical means.

Please remember that testosterone does not cause acute prostate cancer, but if you have existing prostate cancer and do not know it, testosterone administration is likely to boost PSA sharply and provide your doctor with a quick diagnosis of prostate cancer (and an opportunity for very early treatment). We acknowledge that some aging men will not want to take this risk.

As stated above, the MEDLINE score was 21 to 5 against the theory that testosterone plays a role in the development of prostate cancer. None of these studies took into account the prostate cancer prevention effects for men who take lycopene, selenium, and vitamins A and E, nor did they factor in possible prostate disease preventives such as saw palmetto, nettle, soy, and pygeum (42-44, 145-170, 172).

In the book, Maximize Your Vitality & Potency, a persuasive case is made that testosterone and DHEA actually protect against the development of both benign and malignant prostate disease. Dr. Wright also points out that natural therapies, such as saw palmetto, nettle, and pygeum, provide a considerable degree of protection against the alleged negative effects that higher levels of testosterone might have on the prostate gland.

We eagerly await the results of more studies, but the fear of developing prostate cancer in the future should not be a reason to deprive your body today of the life-saving and life-enhancing benefits of restoring a youthful hormone balance.

Once a man has prostate cancer, testosterone therapy cannot be recommended because most prostate cancer cells use testosterone as a growth promoter. Regrettably, this denies prostate cancer patients the wonderful benefits of testosterone therapy. Men with severe BPH should approach testosterone replacement cautiously. It would be prudent for those with BPH who are taking testosterone replacement therapy to also use the drug Proscar (finasteride) to inhibit 5-alpha-reductase levels, thereby suppressing the formation of dihydrotestosterone (DHT) (171-182). DHT is 10 times more potent than testosterone in promoting prostate growth, and suppressing DHT is a proven therapy in treating benign prostate enlargement. Saw palmetto extract suppresses some DHT in the prostate gland, but its effectiveness in alleviating symptoms of BPH probably has more to do with

- Its blocking of alpha-adrenergic receptor sites on the sphincter muscle surrounding the urethra. (This is how the drug Hytrin works.)
- Its inhibition of estrogen binding to prostate cells (such as nettle)
- Its inhibition of the enzyme 3-ketosteroid (which causes the binding of DHT to prostate cells)
- Its anti-inflammatory effect on the prostate

Note: *Men with severe BPH may also consider using the drug Arimidex (0.5 mg twice a week) to suppress excess levels of estrogen. Estrogen can worsen BPH and supplemental testosterone can elevate estrogen if an aromatase-inhibiting drug such as Arimidex is not used.*

It is unfortunate that many people still think that restoring testosterone to youthful levels will increase the risk of prostate disease. This misconception has kept many men from availing themselves of this life-enhancing and life-saving hormone.

Although it is clear that excess estrogen causes benign prostate enlargement, the evidence for excess estrogen's role in the development of prostate cancer is uncertain (8, 41, 117-134, 182-217, 236). Some studies show that elevated estrogen is associated with increased prostate cancer risk, while other studies contradict this finding. For more information on testosterone, estrogen, and the prostate gland, refer to the February 1999 issue of *Life Extension Magazine* (182-217, 306).

Testosterone and Depression

A consistent finding in the scientific literature is that testosterone replacement therapy produces an increased feeling of well-being. Published studies show that low testosterone correlates with symptoms of depression and other psychological disorders (94-97, 272).

A common side effect of prescription antidepressant drugs is the suppression of libido. Those with depression either accept this drug-induced reduction in quality of life, or get off the antidepressant drugs so they can at least have a somewhat normal sex life. If more psychiatrists tested their patients' blood for free testosterone and prescribed natural testosterone therapies to those with low free testosterone, the need for libido-suppressing antidepressant drugs could be reduced or eliminated. As previously described, tes-tosterone replacement often enhances libido, the opposite effect of most prescription antidepressants.

One study showed that patients with major depression experienced improvement that was equal to that achieved with standard antidepressant drugs (97).

Androderm is one of several natural testosterone-replacement therapies that can be prescribed by doctors. A 12-month clinical trial using this FDA-approved drug resulted in a statistically significant reduction in the depression score (6.9 before versus 3.9 after). Also noted were highly significant decreases in fatigue: from 79% before the patch to only 10% after 12 months (218).

According to Jonathan Wright, M.D., co-author of Maximize Your Vitality & Potency, the following effects have been reported in response to low testosterone levels (305):

- Loss of ability to concentrate
- Moodiness and emotionality
- Touchiness and irritability
- Great timidity
- Feeling weak
- Inner unrest
- Memory failure
- Reduced intellectual agility
- Passive attitudes
- General tiredness
- Reduced interest in surroundings
- Hypochondria

The above feelings can all be clinical symptoms of depression, and testosterone replacement therapy has been shown to alleviate these conditions. Testosterone thus has exciting therapeutic potential in the treatment of depression in men.

Testosterone and Mental Decline

Evidence indicates that low levels of testosterone may contribute to memory impairment and increase the vulnerability of the brain to Alzheimer's and related disorders. Beta-amyloid, a peptide that may accumulate in certain regions of the aging brain, is implicated in the development of Alzheimer's disease. Researchers have found that testosterone exerts neuroprotective benefits from the effects of toxic beta-amyloid. An article published in Brain Research describes a study in which cultured neurons were exposed to beta-amyloid in the presence of testosterone. The resulting toxicity from beta-amyloid was significantly reduced by testosterone through a rapid estrogen-independent mechanism (317).

Other researchers have explored the mechanism by which testosterone may exert its protective effect in Alzheimer's disease. Their research in animals shows that testosterone decreases the secretion of harmful beta-amyloid and increases the secretion of the non-amyloidogenic APP fragment, sbetaAPPalpha, indicating that testosterone supplementation in elderly men may be beneficial in the treatment of Alzheimer's (318, 319).

Another published study examined the neuroprotective effects of estradiol, testosterone, epi-testosterone, and methyl-testosterone in neurons induced to undergo apoptosis by serum deprivation. Physiologic concentrations of testosterone were found to be neuroprotective, similar to estradiol. Methyl-testosterone showed an effect that was delayed in time, suggesting that a metabolite may be the active agent. Epi-testosterone showed a slight neuroprotective effect but not through the androgen receptor. The authors concluded that androgens may be of therapeutic value against Alzheimer's disease in aging males (302).

Researchers in Oxford, England found that lower levels of testosterone were present in men with Alz-heimer's as opposed to controls. These results were independent of confounding factors such as age, body mass index, education, smoking, alcohol abuse, and endocrine therapy. The authors recommended further studies to determine whether low levels of total tes-tosterone precede or follow the onset of Alzheimer's disease.

Testosterone and Aging

We know that many of the degenerative diseases of aging in men, such as Type-II diabetes, osteoporosis, and cardiovascular disease, are related to a testosterone deficiency. We also know that common characteristics of middle age and older age, such as depression, abdominal fat deposition, muscle atrophy, low energy, and cognitive decline, are also associated with less than optimal levels of free testosterone (58, 219).

A consistent pattern that deals with fundamental aging shows that low testosterone causes excess production of a dangerous hormone called cortisol. Some antiaging experts call cortisol a "death hormone" because of the multiple degenerative effects that it produces. Some of these effects are immune dysfunction, brain cell injury, and arterial wall damage.

A group of scientists conducted two double-blind studies in which they administered supplemental testosterone to groups of aging men and observed the typical responses of lower levels of cholesterol, glucose, and triglycerides, reductions in blood pressure, and decreased abdominal fat mass. The scientists showed that excess cortisol suppressed testosterone and growth hormone production and that the administration of testosterone acted as a "shield" against the overproduction of cortisol in the adrenal gland. Another study published in 1999 on testosterone and atherosclerosis in men showed a statistically significant correlation between low testosterone and excess serum insulin. It was noted that an elevated estradiol to testosterone ratio is connected with insulin resistance.

It is important to point out that testosterone is an anabolic (or protein building) hormone while cortisol is a catabolic hormone that breaks down proteins in the body. Normal aging consists of a progressive decrease in free testosterone with a marked increase in cortisol. As men age past 40, cortisol begins to dominate, and the catabolic effects associated with growing older begin to dominate.

These findings have significant implications in the battle to maintain youthful hormone balance for the purpose of staving off normal aging and its associated degenerative diseases.

THE TESTOSTERONE DOCTOR

Eugene Shippen, M.D. (co-author of The Testosterone Syndrome, 1998) provided extensive evidence documenting the pathology of the testosterone deficiency syndrome in men. Some excerpts follow from a lecture presented by Dr. Shippen at the American Academy for Anti-Aging Medicine Conference in December 1998:

- First, testosterone is not just a "sex hormone." It should be seen as a "total body hormone," affecting every cell in the body. The changes seen in aging, such as the loss of lean body mass, the decline in energy, strength, and stamina, unexplained depression, and decrease in sexual sensation and performance, are all directly related to testosterone deficiency. Degenerative diseases such as heart disease, stroke, diabetes, arthritis, osteoporosis, and hypertension are all directly or indirectly linked to testosterone decline (220-223). Secondly, testosterone also functions as a pro-hormone. Local tissue conversion to estrogens, dihydrotestosterone (DHT), or other active metabolites plays an important part in cellular physiology.
- Excess estrogen seems to be the culprit in prostate enlargement. Low testosterone levels are in fact associated with more aggressive prostate cancer (201, 205, 224-229). While fear of prostate cancer keeps many men from testosterone replacement, it is in fact testosterone deficiency that leads to the pathology that favors the development of prostate cancer.
- Testosterone improves cellular bioenergetics. It acts as a cellular energizer. Since testosterone increases the metabolic rate and aerobic metabolism, it also dramatically improves glucose metabolism and lowers insulin resistance (76, 80, 230).
- Another myth is that testosterone is bad for the heart. Actually, low testosterone correlates with heart disease more reliably than does high cholesterol (19, 231). Testosterone is the most powerful cardiovascular protector for men. Testosterone strengthens the heart muscle (232); there are more testosterone receptors in the heart than in any other muscle. Testosterone lowers LDL cholesterol and total cholesterol (69, 81, 111) and improves every cardiac risk factor. It has been shown to improve or eliminate arrhythmia and angina (9, 106, 113-115, 233, 266).

Testosterone replacement is the most underutilized important treatment for heart disease.

- Testosterone shines as a blood thinner, preventing blood clots (32). Testosterone also helps prevent colon cancer (235, 236).
- Previous research on testosterone used the wrong form of replacement. Injections result in initial excess of testosterone, with conversion of excess to estrogens. Likewise, total testosterone is often measured instead of free testosterone, the bioavailable form. Some studies do not last long enough to show improvement. For instance, it may take six months to a year before the genital tissue fully recovers from atrophy caused by testosterone deficiency, and potency is restored.
- Physicians urgently need to be educated about the benefits of testosterone and the delicate balance between androgens (testosterone) and estrogens. Each individual has his or her own pattern of hormone balance; this indicates that hormone replacement should be individualized and carefully monitored.

OBESITY AND HORMONE IMBALANCE

A consistent finding in the scientific literature is that obese men have low testosterone and very high estrogen levels. Central or visceral obesity ("pot belly") is recognized as a risk factor for cardiovascular disease and Type-II diabetes. Research has shed light on subtle hormone imbalances of borderline character in obese men that often fall within the normal laboratory reference range. Boosting tes-tosterone levels seems to decrease the abdominal fat mass, reverse glucose intolerance, and reduce lipoprotein abnormalities in the serum. Further analysis has also disclosed a regulatory role for testosterone in counteracting visceral fat accumulation. Epidemiological data demonstrate that relatively low tes-tosterone levels are a risk factor for development of visceral obesity (7, 237).

One study showed that serum estrone and estradiol were elevated twofold in one group of morbidly obese men. Fat cells synthesize the aromatase enzyme, causing male hormones to convert to estrogens (278). Fat tissues, especially in the abdomen, have been shown to literally "aromatize" testosterone and its precursor hormones into potent estrogens (80, 237-242).

Eating high-fat foods may reduce free testosterone levels according to one study that measured serum levels of sex steroid hormones after ingestion of different types of food. High-protein and high-carbohydrate meals had no effect on serum hormone levels, but a fat-containing meal reduced free testosterone levels for 4 hours (243).

Obese men have testosterone deficiency caused by the production of excess aromatase enzyme in fat cells and also from the fat they consume in their diet. The resulting hormone imbalance (too much estrogen and not enough free testosterone) in obese men partially explains why so many are impotent and have a wide range of premature degenerative diseases (45).

FACTORS CAUSING THE ESTROGEN-TESTOSTERONE IMBALANCE IN MEN

If your blood tests reveal high estrogen and low tes-tosterone, here are the common factors involved:

Excess "Aromatase" Enzyme

As men age, they produce larger quantities of an enzyme called aromatase. The aromatase enzyme converts testosterone into estrogen in the body (17, 240, 241, 244, 245). Inhibiting the aromatase enzyme results in a significant decline in estrogen levels while often boosting free testosterone to youthful levels. Therefore, an agent designated as an "aromatase inhibitor" may be of special value to aging men who have excess estrogen.

Liver Enzymatic Activity

A healthy liver eliminates surplus estrogen and sex hormone-binding globulin. Aging, alcohol, and certain drugs impair liver function and can be a major cause of hormone imbalance in aging men. Heavy alcohol intake increases estrogen in men and women (54, 246, 285).

Obesity

Fat cells create aromatase enzyme and especially contribute to the buildup of abdominal fat (241, 242). Low testosterone allows the formation of abdominal fat (47, 239, 248), which then causes more aromatase enzyme formation and thus even lower levels of testosterone and higher estrogen (by aromatizing testosterone into estrogen). It is especially important for overweight men to consider hormone modulation therapy.

Zinc Deficiency
Zinc is a natural aromatase enzyme inhibitor (247). Since most Life Extension Foundation members consume adequate amounts of zinc (30-90 mg a day), elevated estrogen in Foundation members is often caused by factors other than zinc deficiency.

Lifestyle Changes
Lifestyle changes (such as reducing alcohol intake) can produce a dramatic improvement in the estrogen-testosterone balance, but many people need to use aromatase-inhibiting agents to lower estrogen and to improve their liver function to remove excess SHBG. Aromatase converts testosterone into estrogen and can indirectly increase SHBG. SHBG binds to free testosterone and prevents it from exerting its biochemical effects in the body.

CORRECTING A HORMONE IMBALANCE

A male hormone imbalance can be detected through use of the proper blood tests and can be corrected using available drugs and nutrients. The following represents a step-by-step program to safely restore youthful hormone balance in aging men:

Step 1: Blood Testing
The following initial blood tests are recommended for any man over age 40:

- Complete blood count and chemistry profile to include liver-kidney function, glucose, minerals, lipids, and thyroid (TSH)
  Free and Total Testosterone
- Estradiol (estrogen)
- DHT (dihydrotestosterone)
- DHEA
- PSA
- Homocysteine
- Luteinizing hormone (LH) (optional)
- Sex Hormone Binding Globulin (SHBG) (optional)

Step 2: Interpretation of Free Testosterone, Estrogen, and Total Testosterone Blood Test Results
One can easily determine if they need testosterone replacement or estrogen suppression by adhering to the following guidelines:

Free Testosterone
Free testosterone blood levels should be at the high-normal of the reference range. We define high-normal range as the upper one third of the reference range. Under no circumstances should free or total testosterone be above the high end of the normal range.

What too often happens is that a standard laboratory "reference range" deceives a man (and his physician) into believing that proper hormone balance exists because the results of a free testosterone test fall within the "normal" range. The following charts show a wide range of so-called "normal" ranges of testosterone for men of various ages. While these normal ranges may reflect population "averages," the objective for most men over age 40 is to be in the upper one-third tes-tosterone range of the 21- to 29-year-old group. Based on the following reference range chart from LabCorp, this means that optimal free testosterone levels should be between 21-26.5 nanogram/dL in aging men.

Reference Intervals for Free Testosterone from LabCorp

20-29 years	9.3-26.5 picogram/mL
30-39 years	8.7-25.1 picogram/mL
40-49 years	6.8-21.5 picogram/mL
50-59 years	7.2-24.0 picogram/mL
60+ years	6.6-18.1 picogram/mL

An example of how this chart can be deceptive would be if a 50-year-old man presented symptoms of testosterone deficiency (depression, low energy, abdominal obesity, angina, etc.), but his blood test revealed his free testosterone to be 9 picogram/mL. His doctor might tell him he is fine because he falls within the normal "reference range." The reality may be that to achieve optimal benefits, testosterone levels should be between 21-26.5 picogram/mL. That means a man could have less than half the amount of testosterone needed to overcome symptoms of a tes-tosterone deficiency, but his doctor will not prescribe testosterone replacement because the man falls within the "average" parameters. That is why it is so important to differentiate between "average" and "optimal." Average 50-year-old men often have the symptoms of having too little testosterone. Yet since so many 50-year-old men have lower than desired testosterone levels, this is considered to be "normal" when it comes to standard laboratory reference ranges.

The Life Extension Foundation would like to point out that there is disagreement between clinicians and laboratories on the best method for measuring tes-tosterone status. There are different schools of thought as to which form of testosterone should be measured and which analytical procedure provides the most accurate assessment of metabolic activity.

To illistrate this point, the reference values for measuring free testosterone from Quest Diagnostics follow:

Adult Male (20-60+ years):	
1.0-2.7%	50-210 pg/mL
Optimal Range:	150-210 pg/mL for aging men without prostate cancer.

We believe that direct testing for free testosterone is the best way to test for testosterone activity, as free testosterone is active testosterone and consists of only 1-2% of total testosterone. Total testosterone can be good for general testing. The four main methods presently used for analyzing free testosterone are:

- Direct, Free Testosterone by Direct Analog/Radioimmunoassay (RIA)
- Testosterone Free by Ultrafiltration (UF)
- Testosterone Free by Equilibrium Tracer Dialysis (ETD)
- Testosterone Free and Weakly Bound by Radioasssay (FWRA)

The latter three test methods are older, more complicated methods that are technically demanding. The direct RIA test has a number of commercial test kits available, and they are better used in today's automated equipment, making this test less tedious and requiring a smaller (less) sample. These advantages have convinced many laboratories and clinics to prefer direct RIA testing for free testosterone. The Life Extension Foundation agrees with this assessment, and therefore uses and recommends the direct free testosterone test with the above-mentioned reference levels.

Consequently, if your doctor tests your free tes-tosterone, be sure you know the analytical method used. If your test results have a reference range as follows, you have probably been tested with one of the other test methods:

Male Reference Range	***Test Type***
66-417 nanogram/dL	FWRA
12.3-63%	%FWRA
5-21 nanogram/dL	UF or ETD
50-210 picogram/mL	UF or ETD
1.0-2.7%	% of free by UF or ETD

No matter what test method is used to determine your free testosterone status, the optimal level (where you want to be) is in the upper one-third of normal for a 20-29 year old male.

Estrogen

Estrogen (measured as estradiol) should be in the mid- to lower-normal range. If estradiol levels are in the upper one-third of the normal reference range, or above the normal reference range, this excessive level of estrogen should be

reduced. Labcorp lists a reference range of between 3-70 picogram/mL for estradiol while Quest states a reference range of between 10-50. For optimal health, estradiol should be in the range of 10-30 picogram/mL for a man of any age.

The fact that most aging men have too much estrogen does not mean it is acceptable for a man to have low estrogen. Estrogen is used by men to maintain bone density, and abnormally low estrogen levels may increase the risk for prostate cancer and osteoporosis. The objective is to achieve hormone balance, not to create sky-high testosterone levels without enough estrogen. The problem is that, if we do nothing, most men will have too much estrogen and far too little testosterone.

Total Testosterone

Some men have their total testosterone measured. Standard reference ranges are between 241-827 nanograms/dL for most laboratories. Many older men are below 241. Optimal levels of total testosterone for most men are between 500-827 nanograms/dL. If your levels are lower than 500 nanograms/dL or even a little higher and you still have symptoms, you should check your free testosterone by the Direct (RIA) method.

For other hormone tests, the following are considered to be optimal:

Where You Want to Be	***Comment***
PSA Under 2.6 ng/mL (optimal range)	Standard reference range is up to 4, but if your level is persistently 2.6 or above, have a blood test to measure the percentage of free vs. bound PSA and a digital rectal exam to help rule out prostate cancer.
DHEA 400-560 mcg/dL (optimal range)	For older men, standard DHEA ranges are very low. It is important for men without prostate cancer to restore them to the youthful range (400-560).
DHT 20-50 nanogram/dL (optimal range)	Reference range is 30-85. DHT is 10 times more androgenic than testosterone and has been implicated in prostate problems and hair loss.
Luteinizing hormone (LH) Age 20-70: 1.5-9.3 mIU/mL 70+: 3.1-34.6 mIU/mL (standard reference ranges) Under 9.3 mIU/mL (optimal range)	If these levels are high, it is an indication of testicular testosterone production deficiency. LH tells the testes to produce testosterone. If there is too little testosterone present, the pituitary gland secretes more LH in a futile effort to stimulate testicular testosterone production. Testosterone replacement therapy should suppress excess LH levels. Low LH can also be a sign of estrogen overload, since too much estrogen can suppress LH activity. This could mean using an estrogen blocker like Arimidex could solve a testosterone deficiency problem.
Sex Hormone	Reference range is 13-71 nanomole/L. Excessive binding

Binding Under 30 nanomoles/L (optimal range)	inactivates testosterone (297).

Referring to Table 1, there are five possible reasons why free testosterone levels may be low-normal (below the upper third of the highest number of the reference range):

- Too much testosterone is being converted to estradiol by excess aromatase enzyme and/or the liver is failing to adequately detoxify surplus estrogen. Excess aromatase enzyme and/or liver dysfunction is likely the cause if estradiol levels are over 30.
- emember, aromatase converts testosterone into estradiol, which can cause estrogen overload and testosterone deficiency.
- Too much free testosterone is being bound by SHBG (sex hormone binding globulin). This would be especially apparent if total testosterone levels were in the high normal range, while free testosterone was below the upper one-third range.
- The pituitary gland fails to secrete adequate amounts of luteinizing hormone (LH) to stimulate testicular production of testosterone. Total testosterone in this case would be in the bottom one-third to one-half range. (On LabCorp's scale, this would be a number below 241-500 ng/dL.)
- The testes have lost their ability to produce testosterone, despite adequate amounts of the testicular-stimulating luteinizing hormone. In this case, LH would be above normal, and total testosterone would in very low normal or below normal ranges.
- Inadequate amounts of DHEA are being produced in the body. (DHEA is a precursor hormone to tes-tosterone and estrogen) (250).

Step 3: What to Do When Results Are Less Than Optimal

1. If estradiol levels are high (above 30), total testosterone is mid- to high-normal, and free testosterone levels are low or low-normal (at the bottom one third of the highest number on the reference range), you should:
    - Make sure you are getting 80 mg a day of zinc. (Zinc functions as an aromatase inhibitor for some men.)
    - Consume 400 mg of indole-3-carbinol to help neutralize dangerous estrogen metabolites. Cruciferous vegetables, such as broccoli and cauliflower, can also stimulate the liver to metabolize and excrete excess estrogen.
    - Reduce or eliminate alcohol consumption to enable your liver to better remove excess estrogens (refer to the Liver Degenerative Disease protocol to learn about ways to restore healthy liver function).
    - Review all drugs you are regularly taking to see if they may be interfering with healthy liver function. Common drugs that affect liver function are the NSAIDs: ibuprofen, acetaminophen, aspirin, the "statin" class of cholesterol-lowering drugs, some heart and blood pressure medications, and some antidepressants. It is interesting to note that drugs being prescribed to treat the symptoms of testosterone deficiency such as the statins and certain antidepressants may actually aggravate a testosterone deficit, thus making the cholesterol problem or depression worse.
    - Lose weight. Fat cells, especially in the abdominal region, produce the aromatase enzyme, which converts testosterone into estrogen (242).
    - Take a combination supplement providing a flavonoid called chrysin (1000 mg) along with piperine (10 mg) to enable the chrysin to be absorbed into the blood stream. Chrysin has been shown to be a mild aromatase inhibitor. This combination of chrysin and peperine can be found in a product called Super MiraForte.
    - If all of the above fail to increase free testosterone and lower excess estradiol, ask your doctor to prescribe the potent aromatase inhibiting drug Arimidex (anastrozole) in the very low dose of 0.5 mg twice a week. Arimidex is prescribed to breast cancer patients at the dose of 1-10 mg a day. Even at the higher dose prescribed to cancer patients, side effects are rare. In the minute dose of 0.5 mg twice a week, a man will see an immediate drop in estradiol levels and should experience a rise in free testosterone to the optimal range.
3. If free testosterone levels are in the lower two thirds of the highest number in the reference range, but total testosterone is high-normal, and estradiol levels are not over 30, you should
    - Consider following some of the recommendations in the previous section to inhibit aromatase because many of the same factors are involved in excess SHBG activity.

- Take 320 mg a day of the super-critical extract of saw palmetto and 240 mg a day of the methanolic extract of nettle (Urtica dioica). Nettle may specifically inhibit SHGB (42-44, 251, 252), while saw palmetto may reduce the effects of excess estrogen by blocking the nuclear estrogen receptor sites in prostate cells, which in turn activate the cell-stimulating effects of testosterone and dihydrotes-tosterone. Saw palmetto also has the effect of blocking the oxidation of testosterone to androstenedione, a potent androgen that has been implicated in the development of prostate disease (253).

5. If total testosterone is in the lower third of the reference range or below normal, and free testosterone is low, and estradiol levels are under 30, you should
   - Initiate therapy with the testosterone patch, pellet, or cream. Do not use testosterone injections or tablets.
     or
   - See if your luteinizing hormone (LH) is below normal. If LH is low, your doctor can prescribe an individual dose of chorionic gonadotropin (HCG) hormone for injection. Chorionic gonadotropic hormone functions similarly to LH and can re-start testicular production of testosterone. Your doctor can instruct you about how to use tiny 30-gauge needles to give yourself injections 2-3 times a week.
     After 1 month on chorionic gonadotropic hormone, a blood test can determine whether total testosterone levels are significantly increasing. You may also see your testicles growing larger.

Before initiating testosterone replacement therapy, have a PSA blood test and a digital rectal exam to rule out detectable prostate cancer. Once total testosterone levels are restored to a high-normal range, monitor blood levels of estradiol, free testosterone, and PSA every 30-45 days for the first 6 months to make sure the exogenous testosterone you are using is following a healthy metabolic pathway and not causing a flare-up of an underlying prostate cancer. The objective is to raise your levels of free testosterone to the upper third of the reference range, but to not increase estradiol levels beyond 30.

Excess estrogen (estradiol) blocks the production and effect of testosterone throughout the body, dampens sexuality, and increases the risk of prostate and cardiovascular disease. Once you have established the proper ratio of free testosterone (upper third of the highest number in the reference range) and estradiol (not more than 30), make sure your blood is tested every 30-45 days for the first 5 months. Test every 6 months thereafter for free testosterone, estradiol, and PSA. For men in their 40s-50s, correcting the excess level of estradiol is often all that has to be done.

THERAPIES

"Andro" Supplements

Androstenedione is a precursor to both testosterone and estrogen. Early studies showed that "andro" supplements could markedly increase testosterone levels, but more recent studies cast doubt on this concept. A study in the *Journal of the American Medical Association* (1999) reported on an 8-week study showing that androstenedione supplements increased estrogen levels in 30 men (258). No increase in strength, muscle mass, or testosterone levels was observed. Perhaps combining androstenedione with an aromatase inhibitor that would prevent it from converting to estrogen would make this precursor hormone work better in men. In the meantime, we suggest avoiding androstenedione until more definitive research is published.

Testosterone Patches, Creams, Pellets, and Tablets

Synthetic testosterone "steroid" drugs are chemically different from the testosterone your body makes and do not provide the same effect as natural testosterone. Some of the synthetic testosterone drugs to avoid using on a long-term basis are methyltestosterone, danazol, oxandrolone, testosterone propionate, cypionate, or enanthate.

The fact that testosterone is marketed as a "drug" does not mean it is not the same natural hormone your body produced. Scientists learned decades ago how to make the identical testosterone that your body produces, but since natural testosterone could not be patented, drug companies developed all kinds of synthetic testosterone analogs that could be patented and approved by the FDA as new drugs. Currently available recommended natural testosterone drugs are:

- Androderm Transdermal System (SmithKline Beecham's testosterone patch)
- Testoderm Transdermal System (Alza's testosterone patch)
- Testosterone creams, pellets, and sublingual tablets (available from compounding pharmacies)

Both synthetic and natural testosterone drugs require a prescription, and a prescription should only be written after blood or saliva tests reveal a testosterone deficiency.

Alternative physicians usually prescribe testosterone creams and other types made at compounding pharmacies, whereas conventional doctors are more likely to prescribe a box of ready-made, FDA-approved testosterone patches. All forms of natural testosterone are the same and all will markedly increase free testosterone in the blood or saliva.

If you interact with children, you may want to avoid testosterone creams. There is a report of a young male child going through premature puberty after the child made contact with the testosterone cream on his father's body and on weightlifting equipment in the home. This unique case is a testament to the powerful effects that testosterone exerts in the body.

Caution: Do not use testosterone replacement if you have prostate cancer.

Men with existing prostate cancer should follow an opposite approach as it relates to testosterone. Prostate cancer patients are normally prescribed testosterone ablation therapy (using a drug that blocks the pituitary release of LH and another drug that blocks testosterone-receptor sites on the cells). Early-stage prostate cancer cells can often be controlled by totally suppressing testosterone in the body. Late-stage prostate cancer patients are sometimes put on drugs that produce estrogenic effects to suppress prostate cancer cells that no longer depend on testosterone for growth. Regrettably, prostate cancer patients on tes-tosterone ablation therapy often temporarily have many of the unpleasant effects of low testosterone that have been described in this article. Before initiating a therapy that boosts your free testosterone level, a blood PSA test and digital rectal exam are recommended for men over age 40. While restoring free testosterone to healthy physiological levels does not cause prostate cancer, it can induce existing prostate cancer cells to proliferate faster.

Natural Testosterone-Boosting/Estrogen-Suppressing Approaches

Chrysin

A bioflavonoid called chrysin has shown potential as a natural aromatase-inhibitor. Chrysin can be extracted from various plants. Bodybuilders have used it as a testosterone-boosting supplement because by inhibiting the aromatase enzyme, less testosterone is converted into estrogen. The problem with chrysin is that because of its poor absorption into the bloodstream, it has not produced the testosterone-enhancing effects users expect.

In a study published in Biochemical Pharmacology (1999), the specific mechanisms of chrysin's absorption impairment were identified, which infers that the addition of a pepper extract (piperine) could significantly enhance the bioavailability of chrysin (304). Pilot studies have found that when chrysin is combined with piperine, reductions in serum estrogen (estradiol) and increases in total and free testosterone result in 30 days. Aromatase-inhibiting drugs are used to treat women with estrogen-dependent breast cancers. The rationale for this therapy is that estrogen is produced by fat cells via a process known as aromatization. Aging men often have excess aromatase enzyme activity, and the result is that too much of their testosterone is "aromatized" into estrogen.

In a study published in the *Journal of Steroid Biochemical Molecular Biology* (1993), chrysin and 10 other flavonoids were compared to an aromatase-inhibiting drug (aminoglutethimide) (298). The study tested the aromatase-inhibiting effects of these natural flavonoids (such as genistein, rutin, tea catechins, etc.) in human fat cell cultures. Chrysin was the most potent aromatase-inhibitor, and was shown to be similar in potency and effectiveness to the aromatase-inhibiting drug. The scientists conducting the study concluded by stating that the aromatase-inhibiting effects of certain flavonoids may contribute to the cancer preventive effects of plant-based diets.

Two studies have identified specific mechanisms by which chrysin inhibits aromatase in human cells. These studies demonstrate that chrysin is a more potent inhibitor of the aromatase enzyme than phytoestrogens and other flavonoids that are known to have aromatase-inhibiting properties (299, 300). The purpose of these studies was to ascertain which fruits and vegetables should be included in the diet of postmenopausal women to reduce the incidence of breast cancer. Excess levels of mutagenic forms of estrogen have been linked to a greater risk of breast cancer, and scientists are studying dietary means of naturally reducing levels of these dangerous estrogens. Flavonoids such as chrysin are of considerable interest because they suppress excess estrogen via their aromatase-inhibiting properties. Although this cancer preventing effect is most important for women, inhibiting aromatase in aging men has tremendous potential for naturally suppressing excess estrogen while boosting low levels of testosterone to a youthful state.

Since chrysin is not a patentable drug, do not expect to see a lot of human research documenting its effects. There are many FDA-approved drugs that inhibit aromatase (such as Arimidex), and there is not much economic interest in finding natural ways of replacing these drugs. Although prescription aromatase-inhibiting drugs are relatively free of side effects, aging men who are seeking to gain control over their sex hormone levels sometimes prefer natural sources, rather than

trying to convince a physician to prescribe a drug (such as Arimidex) that is not yet approved by the FDA as an antiaging therapy. (Arimidex is prescribed to estrogen-dependant breast cancer patients to prevent testosterone and other hormones in the body from converting, i.e., aromatasing, into estrogen.)

An advantage to using plant extracts to boost tes-tosterone in lieu of drugs is that the plant extracts have ancillary health benefits. Chrysin, for example, is a potent antioxidant that produces vitamin-like effects in the body. It has been shown to induce an anti-inflammatory effect, possibly through inhibition of the enzymes 5-lipooxygenase and cyclooxygenase inflammation pathways. Aging is being increasingly viewed as a proinflammatory process, and agents that inhibit chronic inflammation may protect against diseases as diverse as atherosclerosis, senility, and aortic valve stenosis. Chrysin is one of many flavonoids being studied as a phyto-extract that may prevent some forms of cancer. If chrysin can boost free testosterone in the aging male by inhibiting the aromatase enzyme, this would provide men with a low-cost natural supplement that could provide the dual antiaging benefits of tes-tosterone replacement and aromatase-inhibiting drug therapy. Pilot studies indicate that chrysin increases total and free testosterone levels in the majority of men who take it with piperine.

Chrysin has one other property that could add to its libido-enhancing potential. A major cause of sexual dissatisfaction among men is work-related stress and anxiety. Another problem some men have is "sexual performance anxiety" that prevents them from being able to achieve erections when they are expected to. In a study published in Pharmacology Biochemistry and Behavior (1994), mice were injected with diazepam (Valium), chrysin, or placebo to evaluate the effects these substances had on anxiety and performance levels. Chrysin was shown to produce antianxiety effects comparable with diazepam, but without sedation and muscle relaxation. In other words, chrysin produced a relaxing effect in the brain, but with no impairment of motor activity. The mechanism of action of chrysin was compared to diazepam, and it was shown that unlike diazepam, chrysin can reduce anxiety without inducing the common side effects associated with benzodiazepine drugs.

A common problem with benzodiazepine drugs is memory impairment. In a study published in Pharmacology Biochemistry and Behavior (1997), chrysin displayed potent antianxiety effects in rats, but did not interfere with cognitive performance. In this study, diazepam was shown to inhibit neurological function, but chrysin (and other antianxiety flavonoids) had no effect on training or test session performance. The scientists conducting this study pointed out that chrysin selectively inhibits anxiety in the brain but, unlike diazepam, does not induce the cognitive impairment (302).

Chrysin may therefore offer libido-enhancing effects in the aging male by

- Increasing free testosterone
- Decreasing excess estrogen
- Producing a safe antianxiety effect

Chrysin is being sold to bodybuilders by commercial supplement companies that do not know if their product is favorably modulating testosterone and estrogen levels in men. The Life Extension Foundation, on the other hand, has conducted studies to evaluate the effects of chrysin (combined with piperine to facilitate absorption) on aging men.

Nettle

About 90% of testosterone is produced by the testes; the remainder is produced by the adrenal glands. Tes-tosterone functions as an aphrodisiac hormone in brain cells and as an anabolic hormone in the development of bone and skeletal muscle. But testosterone that becomes bound to serum globulin is not available to cell receptor sites and fails to induce a libido effect. It is therefore desirable to increase levels of "free tes-tosterone" in order to ignite sexual arousal in the brain.

As discussed already, a hormone that controls levels of free testosterone is called SHBG. When testosterone binds to SHBG, it loses its biological activity and becomes known as "bound testosterone," as opposed to the desirable "free testosterone." As men age past age 45, SHBG's binding capacity increases almost dramatically--by 40% on average--and coincides with the age-associated loss of libido.

Some studies show that the decline in sexual interest with advancing age is not always due to the amount of testosterone produced, but rather to the increased binding of testosterone to globulin by SHBG. This explains why some older men who are on testosterone replacement therapy do not report a long-term aphrodisiac effect. That is, the artificially administered testosterone becomes bound by SHBG and is not bioavailable to cellular receptor sites where it would normally produce a libido-enhancing effect.

It should be noted that the liver also causes tes-tosterone to bind to globulin. This liver-induced binding of testosterone is worsened by the use of sedatives, antihypertensives, tranquilizers, and alcoholic beverages. The overuse of drugs and alcohol could explain why some men do not experience a libido-enhancing effect when consuming drugs and plant-based aphrodisiacs. An interesting review entitled "How Desire Dies" (Nature, 381/6584, 1996) discusses how frequently prescribed drugs, such as beta-blockers and antidepressants, cause sexual dysfunction. Prescription drugs of all types have been linked to inhibition of libido.

Logically, one way of increasing libido in older men would be to block the testosterone-binding effects of SHBG. This would leave more testosterone in its free, sexually activating form.

A highly concentrated extract from the nettle root provides a unique mechanism for increasing levels of free testosterone. European research has identified constituents of nettle root that bind to SHBG in place of testosterone, thus reducing SHBG's binding of free testosterone (309-313). As the authors of one study stated, these constituents of nettle root "may influence the blood level of free, i.e., active, steroid hormones by displacing them from the SHBG binding site."

The prostate gland also benefits from nettle root. In Germany, nettle root has been used as a treatment for benign prostatic hyperplasia (enlargement of the prostate gland) for decades. A metabolite of testosterone called dihydrotestosterone (DHT) stimulates prostate growth, leading to enlargement. Nettle root inhibits the binding of DHT to attachment sites on the prostate membrane.

Nettle extracts also inhibit enzymes such as 5-alpha reductase that cause testosterone to convert to DHT. It is the DHT metabolite of testosterone that is known to cause benign prostate enlargement, excess facial hair, and hair loss at the top of the head.

Muira Puama

French scientists have identified an herbal extract that has shown libido-enhancing effects in two human clinical studies. Muira puama comes from the stems and roots of the Ptychopetalum olacoides plant and is widely used in the Amazon region of South America as an aphrodisiac, tonic, and cure for rheumatism and muscle paralysis.

Muira puama has been the subject of two published clinical studies conducted by Dr. Jacques Waynberg, an eminent medical sexologist and author of 10 books on the subject. The first study, conducted at the Institute of Sexology in Paris under Waynberg's supervision, was reported in the November 1994 issue of the *American Journal of Natural Medicine*. The study population consisted of 262 men complaining of lack of sexual desire or inability to attain or maintain erection. After 2 weeks, 62% of patients with loss of libido rated the treatment as having a dynamic effect, while 52% of patients with erectile dysfunction rated the treatment as beneficial. The article goes on to compare muira puama favorably to yohimbine, stating, "Muira puama may provide better results than yohimbine without side effects."

Dr. Waynberg's second study, entitled "Male Sexual Asthenia," focused on sexual difficulties associated with asthenia, a deficiency state characterized by fatigue, loss of strength, or debility, all symptoms of a testosterone deficiency. The study population consisted of 100 men over 18 years of age who complained of impotence or loss of libido or both. A total of 94 men completed the study and were evaluated. Muira puama treatment led to significantly increased frequency of intercourse for 66% of couples. Of the 46 men who complained of loss of desire, 70% reported intensification of libido. The stability of erection during intercourse was restored in 55% of patients and 66% of men reported a reduction in fatigue. Other beneficial effects included improvement in sleep and morning erections.

Treatment with muira puama was much more effective in cases with the least psychosomatic involvement. Of the 26 men diagnosed with common sexual asthenia without noticeable sign of psychosomatic disorder, the treatment was effective for asthenia in 100% of cases, for lack of libido in 85% of cases, and for inability of coital erection in 90% of cases.

The latter finding confirms the broad tonic action of muira puama on conditions of fatigue and stress-related sexual dysfunction. Since muira puama is not an artificial stimulant, it fortifies the system over a period of time. Some men report increased vitality within 2 weeks, while the full effects build over several weeks.

Dr. Waynberg notes that his toxicology studies and observations corroborate the conclusions of the scientific literature on the absence of toxicity of muira puama, which is well tolerated by men in general good health.

One of the earliest scientific studies of muira puama was conducted by another French doctor, Dr. Rebourgeon. His research found the plant to be effective in "gastrointestinal and circulatory asthenia as well as impotence." Three of the

most respected scientific authorities on medical herbalism recommend muira puama. In published books, James Duke, Ph.D., chief of the United States Department of Agriculture's Medical Plant Laboratory (314), and Michael Murray, M.D. (315) recommend muira puama for erectile dysfunction or lack of libido. In addition, Daniel Mowrey, Ph.D., in Herbal Tonic Therapies (316), stated: "Based on the clinical reports documenting the libido and energy enhancing effects of muira puama, it is possible that this herb induces these positive changes by favorably altering the hormone balance in aging men, i.e., increases free testosterone and/or suppresses excess estrogen" (316).

HUMAN HORMONE MODULATION STUDIES USING NUTRIENTS

In order to ascertain the safety and efficacy of nutrients that are purported to modulate male hormone levels, The Life Extension Foundation sponsored clinical studies to assess the effects of specific supplements on blood levels of testosterone, estrogen, and SHBG (307). The nutrients tested included various combinations of chrysin, nettle root, maca, ginger root, muira puama, and zinc, along with piperine to enhance the absorption of the chrysin.

The results from the first pilot study showed that nine out of 10 men experienced a significant reduction in serum estradiol (estrogen) levels after only 30 days, compared to baseline. In this brief study, total testosterone increased in seven out of 10 men, but free testosterone increased in only four of the 10 men studied. Other blood parameters were not statistically altered.

A more comprehensive study incorporating a different combination of nutrients resulted in eight out of eight men experiencing increases in free testosterone while levels of the undesirable SHBG declined in seven out of eight men, compared to baseline. Estrogen and other blood parameters were not significantly altered in this study.

A third study was undertaken to evaluate still another combination of nutrients. It revealed that after 30 days, 12 out of 17 men experienced an increase in total testosterone and 11 out of 17 showed an increase in free testosterone, compared to baseline. Again, other blood parameters were not significantly altered.

Based on the results of these studies, a formula called Super MiraForte was developed that contains the combination of chrysin, nettle root, muira puama, piperine, and other nutrients that showed the most potent effects in boosting free testosterone and suppressing estrogen in aging men. For those who would prefer to avoid testosterone-boosting and estrogen-suppressing drugs, 4 capsules a day of Super MiraForte may be considered.

Mandatory Testing

When embarking on a hormone modulation program, medical testing is critical. First, a baseline blood PSA must be taken to rule out existing prostate cancer. Then free testosterone and estradiol tests are needed to make sure that too much testosterone is not being converted into estradiol (estrogen). If estrogen levels are too high, the use of aromatase inhibitors can keep testosterone from converting (aromatizing) into estrogen in the body. Follow-up testing for testosterone, estrogen, and PSA are needed to rule out occult prostate cancer and to fine-tune your program. It is possible that testosterone patches and creams can increase testosterone levels too much. In that case, blood or saliva testing could save you money by allowing you to use less of the testosterone drug.

There are now natural dietary supplements in development that boost free testosterone levels and suppress excess estrogen. Even when these supplements become available, PSA testing is still mandatory because any substance that increases testosterone should be avoided by most prostate cancer patients.

TESTOSTERONE CAVEATS

Please, after reading all of this, do not just "treat a number." In dealing with sexual function and libido, there is always a large psychological component to enhancing or regaining performance. There are also many physical causes of dysfunction. Do not assume that a certain test number means guaranteed results or you may end up with performance anxiety over that. If you have genuine symptoms, definitely try this protocol; it is well thought out and proven. But remember to include all the other stressors and factors in your life-style into the equation.

CORROBORATING STUDIES

Because of the highly controversial nature of this article, Life Extension has taken the unprecedented step of publishing more than 180 pages of scientific abstracts on our website that are numerically matched to the statements made in this article. This may be the first time for such a massive undertaking, and it reflects the urgent need to convey this information

to skeptical physicians so that they will prescribe tes-tosterone and aromatase-inhibiting drugs to individuals whose blood tests indicate a need for these therapies.

PUBLISHED STUDIES

Studies Indicating That Testosterone Does Not Cause Prostate Cancer

Study 1

"This nested case-control study was based on the cohort of men who donated blood to the Janus serum bank at Oslo University Hospital between 1973 and 1994. Cancer incidence was ascertained through linkage with the Norwegian Cancer Registry. The study included sera from 59 men who developed prostate cancer subsequent to blood donation and 180 men who were free of any diagnosed cancer in 1994 and were of similar age and had similar blood storage time. Neither testosterone, DHT, nor the ratio of testosterone to DHT was associated with risk of developing prostate cancer. These results showed no association, positive or negative, between androgens measured in serum and the subsequent risk of developing prostate cancer" (Vatten et al. Cancer Epidemiology Biomarkers Prev. 1997 Nov; 6(11): 967-9 (212). Study conducted at Department of Community Medicine and General Practice, University Medical Center, Trondheim, Norway [lars.vatten@medisin.ntnu.no]).

Study 2

"We conducted a nested case-control study in a cohort of 6860 Japanese-American men examined from 1971 to 1975. At the time of examination, a single blood specimen was obtained, and the serum was frozen. After a surveillance period of more than 20 years, 141 tissue-confirmed incident cases of prostate cancer were identified, and their stored sera and those of 141 matched controls were assayed for total testosterone, free testosterone, dihydrotestosterone, 3-alpha-androstanediol glucuronide, androsterone glucuronide, and androstenedione. The findings of this study indicate that none of these androgens is strongly associated with prostate cancer risk" (213) (Nomura et al. Cancer Epidemiol. Biomarkers Prev. 1996 Aug; 5(8): 621-5. Study conducted at Japan-Hawaii Cancer Study, Kuakini Medical Center, Honolulu, HI 96817).

Study 3

"Prostate cancer was identified in 14% (11/77) of the entire group and in ten men (29%) aged 60 years or older. The median age for men with cancer was 64 years. No significant differences were noted between the cancer and benign groups with regard to PSA level, PSA density, prostate volume, total testosterone level, or free testosterone level. A high prevalence of biopsy-detectable prostate cancer was identified in men with low total or free testosterone levels despite normal PSA levels and results of digital rectal examination. These data suggest that (1) digital rectal examination and PSA levels are insensitive indicators of prostate cancer in men with low total or free tes-tosterone levels, and (2) PSA levels may be altered by naturally occurring reductions in serum androgen levels" (213) (Morgentaler et al. J. Am. Med. Assoc. 1996 Dec 18; 276(23): 1904-6. Study conducted at Division of Urology, Beth Israel Hospital, Harvard Medical School, Boston, MA 02215).

Study 4

"We conducted a prospective nested case-control study to evaluate the relationships of serum androgens and estrogens to prostate cancer using serum collected at baseline for the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. None of the individual androgens or estrogens was significantly related to prostate cancer. These results do not support a strong relationship of serum androgens and estrogens with prostate cancer in smokers" (189) (Dorgan et al. Cancer Epidemiol. Biomarkers Prev. 1998 Dec; 7(12): 1069-74. Study conducted at Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892-7374 [jd7g@nih.gov]).

Study 5

"We report a nested case-control study of serum bio-markers of 5-alpha-reductase activity and the incidence of prostate cancer. From a cohort of more than 125,000 members of the Kaiser Permanente Medical Care Program who underwent multiphasic health examinations during 1964-1971, we selected 106 incident prostate cancer cases. A control was pair matched to each case on age, date of serum sampling, and clinic location. The adjusted odds ratios and 95% confidence intervals for a one quartile score increase were 1.00 for total testosterone (1.00 = no increased risk), 1.14 for free testosterone, 1.13 for androsterone glucuronide, and 1.16 for 3-alpha-diol G" (190) (Guess et al. Cancer Epidemiology Biomarkers Prev. 1997 Jan; 6(1): 21-4. Study conducted at Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC 27599-7400).

Study 6
"Serum samples were obtained from 6860 men during their study examination from 1971-1975. After a surveillance period of about 14 years, 98 incident cases of prostate cancer were identified. Their stored sera and that of 98 matched controls from the study population were tested for the following: testosterone, dihydrotestosterone, estrone, estradiol, and sex hormone globulin. There was a suggestion that serum dihydrotestosterone levels were lower and the testosterone/dihydrotestosterone ratios were higher in the prostate cancer cases compared with their controls. However, none of these associations or that of the other hormones was strongly significant" (191) (Nomura et al. Cancer Res. 1988 Jun 15; 48(12): 3515-7. Study conducted at Japan-Hawaii Cancer Study, Kuakini Medical Center, Honolulu, HI 96817).

Study 7
"A case-control study of prostatic cancer was carried out to examine the association between selected physical characteristics and factors related to sexual development and behavior and the risk for this disease. The levels of testosterone (T), dihydrotestosterone, salivary testosterone and T/SHBG (sex hormone binding globulin) did not vary with age. Older men had higher estradiol (estrogen) levels. Further, little association between hormone levels and risk factors was found, except for married subjects having increased serum androgens and heavy subjects having decreased serum androgens (not significant)" (192) (Hayes et al. Eur. J. Cancer Prev. 1992 Apr; 1(3): 239-45. Study conducted at Department of Urology, Erasmus University, Rotterdam, the Netherlands).

Study 8
"A population-based nested case-control study was conducted to determine the relation of prediagnostic serum levels of testosterone, dihydrotestosterone, prolactin, follicle-stimulating hormone, luteinizing hormone, estrone, and estradiol to the risk of subsequent prostate cancer. Serum specimens of study subjects were available from a blood collection campaign in Washington County, Maryland, in 1974. There were no significant differences in levels of these hormones between cases and controls, although elevated levels of luteinizing hormone and of testosterone/dihydrotestosterone ratios were associated with mild increased risks of prostate cancer" (194) (Hsing et al. Cancer Epidemiol. Biomarkers Prev. 1993 Jan-Feb; 2(1): 27-32. Study conducted at National Cancer Institute, Division of Cancer Etiology, Bethesda, MD 20892).

Study 9
"The possible relationship between changes in peripheral hormone levels and the occurrence of prostatic pathology was studied in a case-control study involving estimation of various plasma hormones in 368 Dutch and 258 Japanese men, who were grouped as controls and patients with benign prostatic hyperplasia, focal prostatic carcinoma, or clinically evident prostatic carcinoma. There were no significant differences in plasma androgen levels between Japanese or Dutch prostate cancer cases and their respective control subgroups. These findings do not support a correlation between the lower plasma testosterone levels and a lower incidence of prostate cancer in the Japanese men. Furthermore, no significant differences were found between salivary levels of testosterone or the ratio between testosterone and SHBG in the various Dutch subgroups. In Japanese benign prostatic hyperplasia patients, the testosterone to SHBG ratio was significantly increased. In conclusion, the results of this retrospective, cross-sectional study do not indicate that hormonal levels play a primary role in the origin or promotion of prostatic abnormalities" (195) (de Jong et al. Cancer Res. 1991 Jul 1; 51(13): 3445-50. Study conducted at Department of Endocrinology and Reproduction, Erasmus University, Rotterdam, the Netherlands).

Study 10
"Frozen serum samples were analysed for PSA, DHT, testosterone and SHBG, and compared to the diagnosis and tumor stage, grade, and ploidy. DHT levels were slightly lower in patients with prostate cancer but the difference was not statistically significant. There was a trend towards lower DHT values in more advanced tumors. Testosterone levels were lower in patients with cancer than in the control group, but the differences were not significant. There was no correlation between testosterone levels, tumor stage, and ploidy. The testosterone/DHT ratio tended to be higher in patients with more advanced tumors. SHBG levels were lower in patients with cancer than in controls, but the differences were not statistically significant. There were no systematic variations of tumor stage, grade, and ploidy. Within a group, DHT levels tended to be lower among cases and in those with more advanced tumors. No systematic variation was found in the levels of testosterone or SHBG" (197) (Gustafsson et al. Br. J. Urol. 1996 Mar; 77(3): 433-40. Study conducted at Department of Urology, Karolinska Institute at Stockholm Soder Hospital, Sweden).

Study 11
"Index cases and their brothers and sons had a significantly lower mean plasma testosterone content than controls of comparable age. Preliminary data suggest that the metabolic clearance rate of testosterone and the conversion ratio of testosterone to estradiol are relatively high in probands. The observations indicate that familial factors are potent risk

factors for the development of prostatic cancer. They also suggest that plasma androgen values in families with prostatic cancer cluster in the lower range of normal and that plasma sex-steroid content is more similar in each brother with or without prostatic cancer than among non-brothers" (198) (Meikle et al. Prostate 1985; 6(2): 121-8).

Study 12
"Baseline sex hormone levels were measured in 1008 men ages 40-79 years who had been followed for 14 years. There were 31 incident cases of prostatic cancer and 26 identified from death certificates with unknown dates of diagnosis. In this study, total testosterone, estrone, estradiol, and sex hormone-binding globulin were not related to prostate cancer, but plasma androstenedione showed a positive dose-response gradient" (199) (Barrett-Connor et al. Cancer Res. 1990 Jan 1; 50(1): 169-73. Study conducted at Department of Community and Family Medicine, University of California, San Diego, La Jolla, CA 92093).

Study 13
"The hypothesis that serum concentrations of pituitary hormones, sex steroid hormones, or sex hormone-binding globulin (SHBG) affect the occurrence of prostatic cancer was tested in a consecutive sample of 93 patients with newly diagnosed, untreated cancer and in 98 population controls of similar ages without the disease. Remarkably close agreement was found for mean values of total testosterone (15.8 in cases and 16.0 in controls), and free testosterone (0.295 and 0.293, respectively), with corresponding odds ratios for the highest vs. lowest tertile of 1.0 (1.00 = no increased risk) for testosterone and 1.2 for free testosterone. Similar close agreement between cases and controls was found for serum concentrations of estradiol, androstenedione, and SHBG, although the mean estradiol level was nonsignificantly lower among cases" (200) (Andersson et al. Br. J. Cancer 1993 Jul; 68(1): 97-102. Study conducted at Department of Urology, Orebro Medical Center Hospital, Sweden).

Study 14
"Modest depression of serum testosterone and estradiol was noted for prostate cancer patients compared to clinic controls, although the differences were not statistically significant. This depression was interpreted to be a likely result of the malignant process rather than a cause of it" (202) (Hulka et al. Prostate 1987; 11(2): 171-82. Study conducted at Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, NC 27514).

Study 15
"The prostate cancer patients had a slightly lower mean free testosterone and mean estradiol/free T ratio than the BPH patients. The mean estradiol/free tes-tosterone ratio was significantly higher in the BPH patients and in the PC patients than in the young controls. It seems possible that the observed age-dependent significant increase in plasma estrogen concentration in the BPH patients may act as a protective factor against prostatic cancer" (203) (Rannik-ko et al. Prostate 1983; 4(3): 223-29).

Study 16
"A fourfold higher relative risk for the development of prostatic cancer was observed for brothers of prostatic cancer cases compared to their brothers-in-law and males in the general population of the state of Utah. Probands and their brothers, and sons of the patients with the disease, had significantly lower plasma tes-tosterone levels than controls of comparable age. This is the first documentation indicating that familial (possibly genetic) factors are potent risk factors for predisposing men to the development of prostatic cancer and in regulating the plasma content of androgens. Our results indicate that plasma androgen levels in families with prostatic cancer are clustered in the lower range of the normal population. They also suggest that plasma androgen content is more similar within each family with cancer than among families without cancer" (204) (Meikle et al. J. Clin. Endocrinol. Metabol. 1982 Jun; 54(6): 1104-1108).

Study 17
"Pretreatment hormone levels were determined in 222 patients with prostatic cancer and their prognostic value assessed. The patients were grouped into yearly survival categories and only those whose cause of death was due to the disease were included in the study. Low concentrations of testosterone in plasma at the time of diagnosis related to a poor prognosis. Patients who died within 1 year of diagnosis had the lowest mean plasma levels of this steroid. The pretreatment mean plasma testosterone concentrations were found to be higher as the survival period of the various groups lengthened. The indications from this study are that poor testicular function is associated with early death from prostatic carcinoma and that the measurement of blood levels of testosterone at diagnosis could provide a prognosis of subsequent life span" (205) (Harper et al. Eur. J. Cancer Clin. Oncol. 1984 Apr; 20(4): 477-82).

Study 18

"Pretreatment plasma concentrations of total tes-tosterone, prolactin, and total estradiol were measured in 123 prostatic cancer patients who were categorized into groups according to the UICC classification. The mean follow-up time was 48 months. Higher pretreatment estradiol and testosterone levels were associated with better survival" (207) (Haapiainen et al. Scand. J. Urol. Nephrol. Suppl. 1988; 110: 137-43. Study conducted at Second Department of Surgery, Helsinki University Central Hospital, Finland).

Study 19

"This cross-sectional study was undertaken to determine whether serum hormones (free testosterone, androstenedione, luteinizing hormone, or prolactin) have any influence on serum prostate specific antigen (PSA) levels in patients with stage A-C prostate cancer. None of the hormones in any of the analyses showed any association to serum PSA values. Serum free testosterone, androstenedione, and luteinizing hormone appeared to have no influence on serum PSA values in nonmetastatic cancer patients" (208) (Vijayakumar et al. J. Natl. Med. Assoc. 1995 Nov; 87(11): 813-19. Study conducted at Department of Radiation Oncology, Michael Reese Hospital, Center for Radiation Therapy, University of Chicago).

Study 20

"Serum levels of testosterone, DHT, androsterone, 5 alpha-androstane-3 alpha, 17-beta-diol (5 alpha-diol), and estradiol were measured by radioimmunoassay in the sera of 9 patients with untreated prostatic cancer and in 11 with benign prostatic hypertrophy (BPH). Although no specific changes in steroid hormone levels in either disease group were found, response patterns of serum T, DHT, and E2 were shown to be those characteristic of male senescence, suggesting a relative predominance of estrogens over androgens" (211) (Isurugi et al. Prostate Suppl. 1981; 1: 19-26).

Study 21

"We studied the effect of exogenous testosterone administration on the serum levels of PSA (prostate-specific antigen) and PSMA (prostate-specific membrane antigen) in hypogonadal men. Serial serum PSA, serum PSMA, and serum total testosterone levels were obtained at intervals of every 2-4 weeks in ten hypogonadal men undergoing treatment with exogenous testosterone, delivered as testosterone enanthate injection or by testosterone patch. A two-tailed, paired t-test failed to demonstrate a significant correlation between serum PSA or PSMA and serum testosterone levels. This study suggests that in hypo-gonadal men, neither PSMA nor PSA expression is testosterone-dependent" (185) (Douglas et al. J. Surg. Oncol. 1995 Aug; 59(4): 246-50. Study conducted at Department of Surgery, Walter Reed Army Medical Center, Washington, D.C. 20307-5001).

Study 22

"Blood samples were collected from 52 incident cases of histologically confirmed prostate cancer and 52 age- and town of residence-matched healthy controls in Athens, Greece. DHT was associated inversely, significantly, and strongly with the risk of prostate cancer, whereas testosterone was associated marginally positively, and E2 was associated non-significantly inversely with the disease" (Signorello et al. Cancer Causes Control 1997 Jul; 8(4): 632-36. Study conducted at Department of Epidemiology and Harvard Center for Cancer Prevention, Harvard School of Public Health, Boston, MA 02115).

Studies Indicating that Testosterone Causes Prostate Cancer

Study 1

"We conducted a prospective, nested case-control study to investigate whether plasma hormone and sex hormone-binding globulin (SHBG) levels in healthy men were related to the subsequent development of prostate cancer. No clear associations were found between the unadjusted levels of individual hormones or SHBG and the risk of prostate cancer. However, a strong correlation was observed between the levels of testosterone and SHBG (r = 0.55), and weaker correlations were detected between the levels of testosterone and the levels of both estradiol (r = 0.28) and DHT (r = 0.32) (all P < 0.001). When hormone and SHBG levels were adjusted simultaneously, a strong trend of increasing prostate cancer risk was observed with increasing levels of plasma testosterone (ORs by quartile = 1.00, 1.41, 1.98, and 2.60 [95% CI = 1.34-5.02]; P for trend = .004), an inverse trend in risk was seen with increasing levels of SHBG (ORs by quartile = 1.00, 0.93, 0.61, and 0.46 [95% CI = 0.24-0.89]; P for trend = 0.01), and a nonlinear inverse association was found with increasing levels of estradiol (ORs by quartile = 1.00, 0.53, 0.40, and 0.56 [95% CI = 0.32-0.98]; P for trend = 0.03). No associations were detected between the levels of DHT or prolactin and prostate cancer risk. High levels of circulating tes-tosterone and low levels of SHBG--both within normal endogenous ranges--are associated with increased risks of prostate cancer. Low levels of circulating estradiol may represent an additional risk factor" (214) (Gann et al. J. Natl. Cancer Inst. 1996 Aug 21; 88(6): 1118-26. Study conducted at Department of Medicine, Brigham, and Women's Hospital, Harvard Medical School, Boston, MA).

Study 2
"Basal serum concentrations of sex steroids, sex hormone-binding globulin (SHBG), and gonadotrophins, and the basal levels and response to adrenocorticotropic hormone (ACTH) of adrenocortical steroids, were measured before treatment in 72 patients with prostate cancer and in 42 age-matched healthy controls. Patients aged <60 years with prostate cancer had significantly elevated levels of total testosterone and unconjugated (E1) and total (tE1) oestrone, while patients aged > or = 60 years had significantly elevated levels of total and non-SHBG-bound testosterone (NST), 17-alpha-hydroxyprogesterone and tE1. Gonadotrophins, SHBG levels and relationships between total testosterone and SHBG were normal in both age groups of patients, as were basal levels and ACTH-induced increments of adrenocortical steroids. The patients had normal age-related variations in SHBG and NST and in basal levels and ACTH-induced increments of adrenocortical steroids. There was a significant age-related increase in serum E1 in the control subjects but not in the patients. Patients with metastatic disease had significantly lower E1 levels than had patients without metastases. The results suggest an increased sensitivity of the testes to gonadotrophic stimulation, as well as an increased peripheral oestrogen synthesis in patients with prostate cancer, the latter being most pronounced in younger subjects. Men developing prostate cancer may have been exposed to a combination of elevated endogenous oestrogen and androgen levels for a long time. These findings support the theory of a synergism between oestrogens and androgens as an important factor in the aetiology of prostate cancer" (196) (Carlstrom et al. Br. J. Urol. 1997 Mar; 79(3): 427-31. Study conducted at Department of Obstetrics and Gynaecology, Karolinska Institute, Huddinge University Hospital, Sweden).

Study 3
"A blinded, case-control study was undertaken to determine if hair patterning is associated with risk of prostate cancer, as well as specific hormonal profiles. The study accrued 315 male subjects who were stratified with regard to age, race, and case-control status (159 prostate cancer cases/156 controls). Free testosterone was greater among cases than in controls (16.4 +/-6.1 vs. 14.9 +/-4.8 picogram/mL, P = 0.02). Conversely, DHT-related ratios were greater among controls. Data suggest that increased levels of free testosterone may be a risk factor for prostatic carcinoma" (216) (Demark-Wahnefried et al. J. Androl. 1997 Sep-Oct; 18(5): 495-500. Study conducted at Division of Urology, Duke University Medical Center, Durham, NC 27710).

Study 4
"We present the case of a hypogonadal patient in whom a 20-fold increase in prostate-specific antigen and a palpable prostatic nodule developed 6 months into the administration of intramuscular testosterone" (217) (Curran et al. Urology 1999 Feb; 53(2): 423-4. Study conducted at Department of Urology, Lahey Clinic Medical Center, Burlington, MA 01805).

Study 5
"The metabolic clearance and production rates of tes-tosterone were significantly higher in (prostate cancer) patients than in controls. These results indicate that men with prostatic cancer have elevated clearance and production rates of testosterone without an alteration of estradiol production or clearance" (215) (Meikle et al. J. Steroid Biochem. 1989 Jul; 33(1): 19-24. Study conducted at Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT 84132).

SUMMARY

Before beginning testosterone replacement, comprehensive blood testing is necessary to determine liver-kidney function, and levels of glucose, minerals, lipids, thyroid, free and total testosterone, estadiol, DHT, DHEA, PSA, homocysteine, LH (optional), and SHBG (optional). These tests may be done at your doctor's office or they can be performed directly at a laboratory in your area. Call 1-800-208-3444 for information about ordering these tests on your own. A digital rectal exam is also recommended to eliminate the possibility of prostate cancer. Natural testosterone is highly recommended over synthetic types. Nutritional supplements may be added to the diet depending upon test results that can prevent testosterone from cascading into estrogen and DHT.

The following supplements are recommended:

1. Super MiraForte containing chrysin, piperine, nettle, and muira pauma boosts free testosterone and suppresses estrogen by acting as a mild aromatase inhibitor, 4 capsules daily.
2. Saw Palmetto/Nettle Formula helps to inhibit SHGB and reduce the effects of excess estrogen, 2 capsules daily.
3. Indole-3-carbinol (IC3) helps neutralize dangerous estrogen metabolites (16-hydroxyestrone), 200-400 mg daily.
4. Zinc functions as an aromatase inhibitor in some men, 80-90 mg daily.

FOR MORE INFORMATION

The best source for actual case histories of men who successfully used hormone modulation is Dr. Eugene Shippen's book entitled The Testosterone Syndrome (260). Dr. Shippen provides many interesting details too numerous to be covered in this concise protocol. Another book, Maximize Your Vitality & Potency, by Dr. Jonathan Wright, also contains historical and more technical data about the benefits of testosterone that are, again, too numerous to include in this protocol. These two books are available from the Life Extension Foundation.

PRODUCT AVAILABILITY

Indole-3-carbinol, OptiZinc, Super MiraForte, and Saw Palmetto/Nettle Formula are available by calling (800) 544-4440 or by ordering online. To order your own blood tests, call 1-800-208-3444.

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