

# Natural Testosterone: Hormone of the Heart



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Reprinted from

*Maximize Your Vitality and Potency For Men Over 40*

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## Continuing Education

**Goal:** To present contemporary views on the importance of testosterone and dehydroepiandrosterone (DHEA) in men's health.

**Objectives:** After reading and studying this material, the reader will be able to:

1. List eight important testosterone studies/researchers related to men's cardiovascular health.
2. List six symptoms or diseases related to impaired blood flow.
3. Name the source of DHEA and list two of its effects on the body.
4. List six testosterone-like effects associated with DHEA replacement therapy.

Diseases of the heart and blood vessels kill about half a million men (along with half a million women) in the United States each year. Everyone recognizes that the risk of developing one of these diseases grows with age, but the fact that the increased risk may be tied to male menopause and the reduction in androgens has not yet completely penetrated the walls of conventional medicine. This is a very sad situation because there is unmistakable evidence, some of it dating back more than half a century, that:

- ♥ Testosterone is a primary factor in the health of the heart and blood vessels.
- ♥ Testosterone levels decline with age.
- ♥ Restoring testosterone (and dehydroepiandrosterone [DHEA]) to youthful levels can yield significant health benefits, including protection against the various manifestations of atherosclerotic disease.

This is not to say that testosterone replacement can cure or prevent all heart disease. Nevertheless, there is good reason to believe that declining testosterone levels may lay the groundwork for some of the destructive changes that ultimately lead up to a heart attack or stroke.

## Keeping the Blood Flowing

The most common form of cardiovascular disease is atherosclerosis – the accumulation of fatty plaque deposits in arteries all over the body. Narrowing of arteries caused by plaque restricts the flow of blood to such vital organs as the heart, brain, kidneys, and penis, as well as to the limbs, fingers and toes. Blood, of course, supplies these organs with life-giving oxygen and nutrients, while it carts away metabolic products and other substances for excretion or recycling elsewhere in the body. Restricting the flow of blood to these locations can only be detrimental to health.

Depending on the location of the restriction, atherosclerosis can manifest in a variety of ways. A blockage in one or more of the coro-

nary arteries that supply the heart muscle is called *coronary atherosclerosis*; if the blockage is complete, it will cause a heart attack. If the blockade is not quickly removed, the muscle that depends on that artery may die (myocardial infarction, or MI). A blockage in the arteries supplying the brain is called a *cerebrovascular occlusion*; if the occlusion is not rapidly cleared away, it will cause a stroke, in which the brain tissue served by the blocked (occluded) blood vessel dies. Restricted blood flow in the legs, known as *claudication*, interferes with the ability to walk and can cause pain and disability. When the restriction or blockage is complete, infection and gangrene may follow, often leading to amputation of the toes, feet and even parts of the legs. Restricted or blocked arteries in the penis can cause impotence. Fortunately, for us men, the entire organ doesn't die and require amputation!

The chest pain of angina pectoris is a signal that too little blood is getting through narrowed coronary arteries to meet the heart's current needs, especially during physical or emotional stress. Angina is often treated with drugs, such as nitroglycerin, which rapidly, but temporarily, dilate coronary arteries, allowing more blood through to the starving heart muscle. Nitroglycerin works because it "donates" molecules of nitric oxide, which functions as a potent vasodilator.

Surgical methods of treating angina are also quite popular these days. These methods include balloon angioplasty (inserting a deflated balloon on the end of a long, flexible tube into the coronary arteries, and inflating it at the appropriate location, which literally flattens the plaque). At best, this tends to be a temporary solution, since these arteries often close up again, sometimes within a few months. Considering the short-term benefit, the risks of balloon angioplasty are quite high.

Another risky, costly and temporary – yet extremely common – "solution" to coronary heart disease is coronary artery bypass graft surgery (CABG). In this procedure, a length of vein is removed from the patient's leg and transplanted (grafted) into the heart to replace a length of diseased coronary artery. As with angioplasty and vasodilating drugs, bypass grafts often become occluded again,

requiring further surgery. Despite a (media-influenced) widespread favorable impression of CABG surgery, no well-researched scientific evidence shows that CABG surgery saves more lives than less drastic procedures. In the long run, the only people who seem to benefit from CABG procedures are the surgeons who perform them. (At \$50,000 or more per procedure, it may be with good reason that heart surgeons commonly pronounce the abbreviation *CABG* as “cabbage.”)

Preventing atherosclerosis in the first place is obviously a better solution than any of the above. Thus, we are urged to give up smoking and start taking expensive drugs to lower cholesterol and reduce high blood pressure. Physicians and public health agencies remind us incessantly to eat more fiber; fruits; vegetables; and oats; and less red meat and fat; and, of course, to exercise. If a physician is really current with biomedical research, he or she may also recommend taking antioxidant supplements, including vitamins C and E and B vitamins, especially vitamins B6, B12 and folic acid, all of which have been clearly shown to significantly reduce the risk of having a heart attack or stroke.<sup>1-10</sup> While some of this is good advice, some of it – like cholesterol-lowering drugs and margarine (e.g., hydrogenated fats) – may do more harm than good.

Most physicians practicing in this country today completely ignore the role of testosterone and other hormones in maintaining men's cardiovascular health. In fact, it was only until relatively recently that most physicians believed that elevated testosterone was actually dangerous for the heart. This view seems to be based on two misconceptions. First, elevated testosterone levels in women can be dangerous. This may be true, but women are not men, and there is no logical reason why both sexes should react to testosterone in precisely the same way. Second, careless use of anabolic steroid drugs, such as the especially dangerous methyl-testosterone – but not physiological amounts of natural testosterone – by some athletes and bodybuilders has been associated with serious heart disease.

## How Testosterone Protects the Heart

Evidence that testosterone might be good for the circulation goes back to World War I. At that time, a Danish surgeon named Thorkild Rosing encountered a young soldier who had died a sudden and violent death. His testicles were intact, however, and Dr. Rosing decided to transplant them into the body of an old man suffering from gangrene in one of his limbs. Remarkably, the man's gangrene healed completely.<sup>11</sup>

In the years leading up to World War II, most work on testosterone was conducted in Germany. Researchers showed, for example, that “testosterone” treatment (primarily using testosterone esters) could normalize faulty glucose metabolism (a major coexisting condition with cardiovascular disease), relieve angina and improve leg pain in men suffering from intermittent claudication.<sup>11</sup>

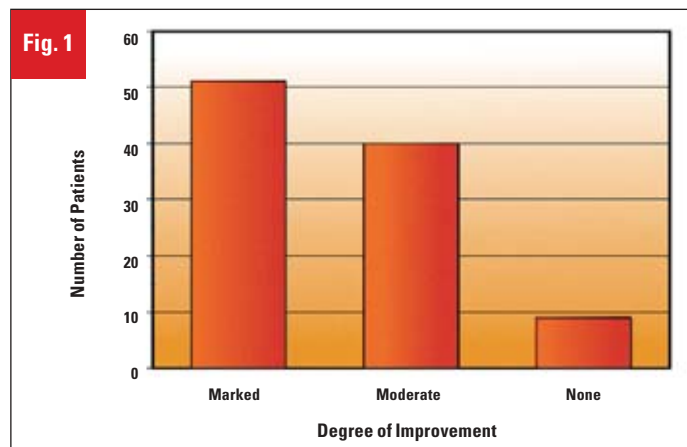
In 1939, Edward A. Edwards, MD, a surgeon at the Tufts Col-

lege Medical School in Boston, MA, published a preliminary report in the *New England Journal of Medicine* suggesting circulatory benefits of testosterone.<sup>12</sup> During his treatment of castrated men, Dr. Edwards had noticed that the skin of these men seemed to not be getting enough blood. On the contrary, blood seemed to be collecting in lower portions of the men's bodies, like the legs and lower abdomen. Was this poor circulation related to their lack of testosterone? Treatment of these men with “testosterone” (testosterone propionate) injections led to impressive improvement. “After treatment with testosterone propionate, there was an increase in “arterialization” and blood volume in those regions normally containing many arteries, such as the head, palms of the hands and soles of the feet,” Edwards reported. Would “testosterone” produce similar results in men with intact testes but poor circulation due to age-related diseases such as atherosclerosis or other organic vascular disease?

Based on the first seven such patients Edwards treated, the answer was clearly “yes.” Not only did “testosterone” restore arterial circulation to the skin, it appeared to normalize blood pressure in two cases, heal or improve two cases of gangrene, relieve leg pain in two patients and improve walking ability in all seven patients. “Subjectively, the patients reported an increased activity and feeling of optimism,” Edwards wrote, noting also that these results were similar to those reported by other researchers treating patients with male hormone.

A leading testosterone researcher during the 1940s was Maurice A. Lesser, MD, of the Boston University School of Medicine. In 1946, Dr. Lesser published the results of 100 consecutive angina pectoris patients (92 men and eight women, aged 34 to 77 years) treated with “testosterone” (testosterone propionate) for as long as four or five months.<sup>13</sup> Prior to treatment, all patients had a “clearly established” diagnosis of angina pectoris based on a history of chest pain precipitated by physical exertion or emotion and relieved by rest or nitroglycerin treatment. The results were striking, with 91 of 100 patients showing improvement (Fig. 1).

Fifty-one patients showed “marked improvement,” which was defined as the ability to increase physical activity without precipi-



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tating an anginal attack for up to two months after discontinuing “testosterone” therapy.

Forty patients showed “moderate improvement,” defined as a reduction by at least 50% in the number of anginal attacks compared with the pretreatment rate.

Dr. Lesser was aware that a placebo effect might be at work here, thus rendering any conclusions regarding the clinical value of testosterone invalid. To discount that possibility, prior to starting them on “testosterone” treatment, he gave six consecutive injections of sesame oil (the vehicle in which testosterone propionate was dissolved) to five different patients – without their awareness. None of these patients showed any improvement during the placebo phase, but once switched to “testosterone,” they all began showing progressive improvement.

Dr. Lesser pointed out that the relief provided by testosterone propionate was “not instantaneous,” in contrast to nitroglycerin, the only other successful treatment of angina at the time. In fact, it took a mean of 28 days to achieve “definite” improvement with “testosterone” treatment, and 43 days for “marked” improvement. On the other hand, relief could be long-lasting, ranging from two to 34 months after discontinuation of treatment. Treatment

with nitroglycerin lasts only as long as the drug levels remain at an active level.

These results can be questioned due to their lack of adequate experimental controls and objective measures; not so a study by Martin D. Jaffee, MD, which was published in the *British Heart Journal* in 1977.<sup>14</sup> Using a randomized, double-blind, placebo-controlled design, Dr. Jaffee treated 50 men with postexercise ST segment depression (an early electrocardiographic – ECG – sign of angina) with either weekly injections of “testosterone” (testosterone cypionate) or placebo. While attached to an ECG recorder, the men took an exercise stress test at baseline and again after four weeks and eight weeks of treatment.

The results left no doubt that “testosterone” was having a beneficial effect. As shown in Fig. 2, the placebo had no effect on post-exercise ST segment depression. By contrast, “testosterone” treatment resulted in highly significant decreases of 32% after four weeks and 51% after eight weeks.

A Chinese study also found that “testosterone” (testosterone undecanoate) treatment could benefit cardiac function in elderly men diagnosed with coronary heart disease.<sup>15</sup> Of the 62 men who participated, 60 had had a heart attack between three months and five years prior to the study. The other two had had complete occlusion of at least one major coronary artery. At the start of the study, the 62 patients had significantly lower testosterone levels compared with 50 age-matched controls. The researchers used a crossover design, in which the men took either “testosterone” or

## The Trouble with Anabolic Steroid Drugs

Much of the hesitation to use natural testosterone to prevent or treat cardiovascular diseases arises from a fear that the hormone will actually cause heart problems, not cure them. Where does this fear come from? There’s only one possible place – the misuse of anabolic steroid drugs.

Most studies show natural testosterone to be beneficial or, at worst, neutral with regard to cardiovascular health. Anabolic steroid drugs are a completely different story. Since they resemble the testosterone molecule in some ways but not in others, they work like testosterone in some ways but not in others. One of the ways they don’t work like testosterone is in terms of toxicity. Although there are many such drugs, each with its own risk:benefit profile, it can generally be stated that those anabolic steroid drugs that do not also cause liver damage outright may be laying the foundation for a heart attack or stroke, even in young, well-conditioned athletes with no other risk factors. In addition to promoting blood clots, high-dose anabolic steroids have also been found capable of increasing cholesterol levels.<sup>24</sup>

### Promoting Blood Clotting

Anabolic steroids have long been known to enhance the synthesis of both pro- and anticlotting proteins, such as fibrino-

gen and plasminogen.<sup>40</sup> The clue to which predominates in a given individual may lie with the dose. At low doses, some anabolic steroid drugs have been shown to enhance fibrinolytic activity, much as testosterone itself does.<sup>41-43</sup> At high doses, however, they clearly promote clotting.

It appears that high doses of anabolic steroid drugs increase the tendency of certain blood cells – called *platelets* – to glue themselves together. This process, known as *platelet aggregation*, is a necessary step in the formation of blood clots. In a study of 28 weightlifters, high-dose anabolic steroid drug use was associated with a greater tendency toward platelet aggregation.<sup>44</sup>

### Increasing Cholesterol

Anabolic steroid drugs, but not natural testosterone, can disrupt lipid levels. This was demonstrated in studies in which an anabolic steroid drug, such as stanozolol or methyltestosterone, caused large reductions in HDL cholesterol, as well as striking increases in LDL cholesterol and other proatherosclerotic factors. By contrast, “testosterone” (testosterone enanthate) decreased HDL by only a small amount. Other studies have found no change in HDL and decreases in LDL following treatment with testosterone enanthate.<sup>45-47</sup>

placebo for a period of time and then were switched to the opposite treatment.

During the two and a half months the men were taking “testosterone,” their angina was markedly relieved. Self-reported anginal symptoms were reduced by 77% in the “testosterone” group, compared with 7% in the placebo group. Objective measures supported the patients’ perceptions. Electrocardiographic recordings both in the laboratory and in the “real” world (as measured by a portable ECG monitor) indicated significant improvement: 69% vs 8% on ECG, and 75% vs 8% on the portable monitor, respectively. The authors reported no obvious unwanted effects of the treatment.

Despite all these encouraging results, though, no one had ever confirmed that low testosterone could actually lead to atherosclerosis and/or coronary heart disease. It was still considered possible, for example, that the low testosterone levels sometimes (but not always) found in men who had suffered a heart attack were a result of the disease, not a cause of it.

This connection was finally made in 1994 in a study by Gerald B. Phillips, MD, and his colleagues at Columbia University College of Physicians and Surgeons.<sup>16</sup> Dr. Phillips conducted what amounted to a cross-sectional study of 55 consecutive men (mean age, about 61 years) who were undergoing coronary angiography (a very common diagnostic test in which a radiopaque dye injected into a patient’s coronary arteries makes those arteries visible on x ray) because they had chest pain and/or an abnormal stress test. None of the men had ever had a heart attack or stroke. At the time of the angiography, the researchers took blood samples from the men, which they later analyzed for the levels of hormones, lipids (fatty substances, like cholesterol and triglycerides), clotting factors and other clues to the men’s health.

Phillips found a clear inverse relationship between testosterone levels and the degree of coronary artery disease. The lower the testosterone, the more occluded the men’s arteries were. When they looked only at the level of free testosterone, the relationship was even more

dramatic (Fig. 3). Phillips found that testosterone levels also correlated with several important risk factors for heart attack. Men with low testosterone had a greater tendency for their blood to clot (due to lower levels of the clot inhibitor PAI-1 [plasminogen activator inhibitor-1] and higher levels of the clot promoter fibrinogen), higher insulin levels, a sign of insulin resistance and abnormal glucose metabolism, and lower levels of high-density lipoprotein (HDL) (“good”) cholesterol. In previous studies, Phillips had found that, in men who had not yet had a heart attack, low testosterone was associated with such risk factors as diabetes, high blood levels of glucose, cholesterol, and triglycerides, high blood pressure, obesity, an increased waist-to-hip ratio (the “love handle/spare-tire syndrome”), and increased blood-clotting factors.<sup>17</sup>

Based on these results, Phillips suggested that low levels of testosterone – especially free testosterone – could lead to atherosclerosis and might be an early sign of impending heart attack. Moreover, he proposed that the converse was also true, that testosterone may protect against atherosclerosis in men.<sup>16</sup>

## Decreasing Risk Factors

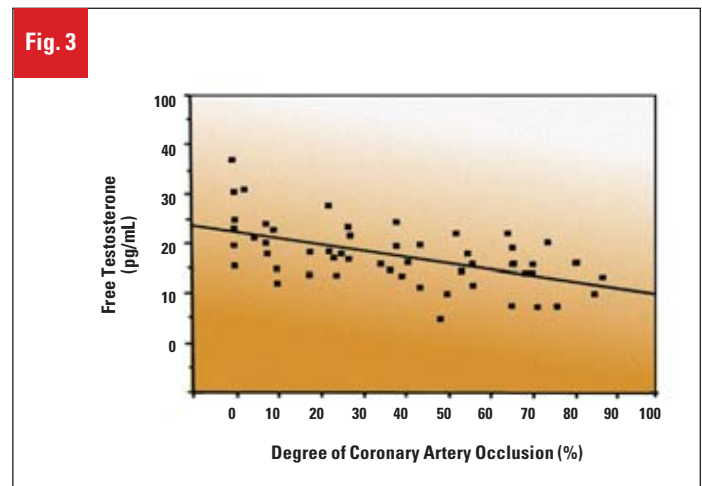
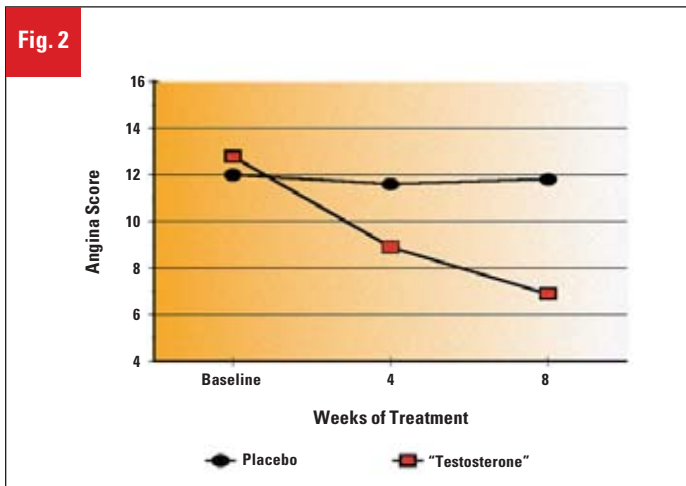
A number of studies have demonstrated that testosterone minimizes several important risk factors for heart attack, including:<sup>11,18-22</sup>

- ♥ Reducing cholesterol and triglycerides
- ♥ Reducing blood glucose levels
- ♥ Decreasing visceral fat mass
- ♥ Normalizing blood clotting

Of these, the two that have probably received the most study are blood clotting and cholesterol.

## Reduced Tendency of Blood to Clot

The tendency of blood to clot increases as men age.<sup>23</sup> Could this be due to the age-related decline in testosterone? Quite possibly, and here’s why. Blood contains some factors that promote clotting and others that inhibit it. In a highly oversimplified sketch of the



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extremely complex clotting process, blood clots form when an insoluble protein – fibrin – is formed from fibrinogen, with the help of many different substances. Fibrin forms the essential portion of all blood clots.

Modulating blood clotting is a process called *fibrinolysis* (*lysis*, from the Greek word for *dissolve*), which literally dissolves blood clots. Key among the blood’s fibrinolytic factors is the enzyme tissue plasminogen activator (t-PA), which promotes the rapid dissolution of fibrin. So potent is t-PA that it is now being produced by genetic-engineering techniques and successfully used as a “clot-busting” drug. Typically, bioengineered t-PA is given to people in the early stages of a heart attack in order to dissolve the clot before it has a chance to do too much damage.

The release of endogenous t-PA into the circulation from the endothelial cells that line the inside of arteries is partly under the control of a substance identified as plasminogen activator inhibitor (PAI 1). High levels of PAI-1 inhibit t-PA release, reducing fibrinolytic activity and increasing the risk of clot formation and decreasing the chances of surviving a heart attack.<sup>24</sup> Testosterone reduces PAI-1, allowing t-PA to function normally.<sup>25</sup> A study by researchers at the University of Cincinnati College of Medicine found that men with higher levels of endogenous testosterone also had higher levels of t-PA, as well as lower levels of PAI-1, fibrinogen and triglycerides.<sup>26</sup>

Administration of testosterone has been shown to enhance fibrinolytic activity in men in a manner not that different from what estrogens do in women.<sup>24</sup> In one study, high doses of testosterone enanthate were given to a group of normal men. Within 16 weeks of treatment, their fibrinogen levels, (i.e., blood-clotting ability) had dropped by about 15%.<sup>27</sup>

## Normalization of Blood Lipids

Just 10 or 15 years ago, it was the conventional wisdom in medicine that testosterone and other androgens could increase a man’s risk of heart disease, in part by disturbing the normal lipid balance, i.e., by increasing low-density (LDL) (“bad”) cholesterol and triglycerides and decreasing HDL (“good”) cholesterol. While many physicians still believe this, it has since become apparent to anyone paying attention to the scientific literature that this is nonsense. It does not make sense physiologically: if high endogenous – natural, internally produced – testosterone levels promote heart disease, why does heart disease appear most often in older men whose testosterone levels have started to fall? It became clear in the late 1980s that instances of heart disease that appeared to be associated with testosterone were really caused by use of excessively high doses of anabolic steroid drugs, which are not natural testosterone. (See box p 90.)

Most studies published throughout the 1980s repeatedly confirmed that endogenous testosterone was positively correlated with HDL (“good”) cholesterol and inversely correlated with triglycerides.<sup>28-34</sup> In a recent review of studies on the androgen-lipid relationship, one of the leading American medical “authorities” on this subject, Elizabeth Barrett-Connor, MD, of the University of California, San Diego, reported that every study that included at least 100 men had found a positive association between testosterone and HDL cholesterol. “Adult men with high normal concentrations of endogenous testosterone have more favorable levels of several major heart disease risk factors, including HDL cholesterol, a more suitable fat pattern, and lower glucose and insulin levels than do men with low testosterone concentrations,” she concluded.<sup>35</sup> Only a few small studies have examined the effects of testosterone supplementation on cholesterol levels.<sup>20,36-38</sup> In reviewing these trials, Dr. Barrett-Connor also noted, “Exogenous testosterone given parenterally (administered in a way that avoids digestion, e.g., via intravenous administration or injection) in physiologic doses to middle-aged men does not lower HDL cholesterol and may reduce visceral adiposity (“spare tire” or “love-handle” syndrome), glycemia (elevated blood glucose), and insulin resistance (a sign of diabetes and a precursor to coronary heart disease).”<sup>35</sup>

Another leading voice in testosterone research, J. Lisa Tenover, MD, of the Emory University School of Medicine, Atlanta, appears to agree. In a recent review of research on testosterone replacement in men, Dr. Tenover wrote, “Uniformly, such studies have shown either a decrease or no change in serum total cholesterol and LDL cholesterol, while only one of five studies demonstrated a decline in HDL cholesterol levels.”<sup>39</sup>

## Keeping Testosterone and Estrogen in Balance

There might be a “biological point of no return” where the normal balance between testosterone and estradiol (the most abundant and most potent human estrogen) starts tilting toward estradiol. When this happens, estradiol’s suppressive effects on testosterone production (via decreased leutinizing hormone release) begin to predominate, causing testosterone levels to drop to a new, lower level of equilibrium.<sup>48</sup>

Both low testosterone and high estradiol levels have been linked to cardiovascular disease. Indeed, there is good reason to believe that what is important to a man’s health is not necessarily the absolute values of each hormone but rather the testosterone:estradiol ratio. In one study, Norwegian researchers analyzed the blood of 42 healthy, middle-aged men judged to be at risk for coronary heart disease. They found a highly significant correlation between a low testosterone:estradiol ratio and impaired fibrinolytic capacity.<sup>49</sup>

There has been some confusion about the role of these hormones, in part because some studies have shown correlations with heart disease while others have not. In Phillips’ angiographic study of

55 men, for example, estradiol concentration was not related to coronary artery disease, despite the fact that other studies that have shown high estrogen levels were clearly associated with the risk of myocardial infarction in men – the opposite of what occurs in women.<sup>50-52</sup>

The connection between estrogen levels and the risk of MI was first demonstrated during the 1970s when Phillips compared 15 men (aged 32 to 42 years) who had had a heart attack with 15 matched healthy controls. He found that estrogen levels were significantly higher in the heart attack patients and that they had been elevated prior to the attack.<sup>51</sup> He also found that an elevation in the estrogen:testosterone ratio caused a form of “mild diabetes” that was commonly associated with MI. Dr. Phillips concluded from these data that, “An alteration in the sex hormone milieu is the major predisposing factor for myocardial infarction.”<sup>53, 54</sup>

How can high estrogen be a risk factor for MI but not for atherosclerosis, while low testosterone seems to increase the risk of both? Dr. Phillips reasons that low testosterone increases the risk of atherosclerosis and thrombosis (blood clot formation), but high estrogen only increases the risk of thrombosis and spasms of the coronary arteries.<sup>16</sup>

In women, the hormone balance goes the other way. High estrogen levels protect women against heart disease. Most women do not begin to develop serious heart disease until after menopause, when their ovaries have ceased producing estrogens. Taking supplemental estrogens (and sometimes small amounts of testosterone) after menopause significantly cuts their risk of developing heart disease during the postmenopausal years.

## The Remarkable Dr. Møller

One of the most important, yet least appreciated, advocates of the use of testosterone in the treatment of cardiovascular diseases was the Danish physician Jens Møller, MD, who lived from 1904 to 1989. According to Dr. Møller’s long-time colleague, Malcolm Carruthers, MD,<sup>55</sup> medicine was actually his second career. Until the end of World War II, Møller was a successful entrepreneur with offices in London, Paris and Berlin. It was not until after the war, when he was 45 and looking for more meaning in his life, that Møller turned to medicine. Wasting no time, he qualified for medical school in just three months, a quarter of the usual time, and began practicing just five years later.

Purely by chance, Møller found a job working with a Danish physician named Tvedegaard. Dr. Tvedegaard had already developed a controversial reputation based on his use of testosterone for treating severe arterial disease, a practice he had learned from German physicians before the war. (Germany, Møller pointed out, was the “cradle of hormones.” Nearly all the important research on testosterone and other hormones, from Berthold’s capons to the synthesis of testosterone in the 1930s, had originated in Germany. He believed that the intervention of WW II, combined with prejudice against all things German in the years afterward, probably delayed the acceptance of testosterone as a treatment for cardiovascular disease.<sup>11</sup>)

## Amazing Results

Like the Germans before him, Dr. Tvedegaard was achieving “amazing results” in patients with severe cases of “intermittent claudication,” painful leg cramps due to impaired circulation – usually from atherosclerosis – in the lower limbs. As this disease progresses, the circulation may become so poor in some areas that local tissue starts to die. If the local blood supply is too feeble to permit significant access by protective elements of the immune system, infection and gangrene may set in. The usual treatment has always been amputation of the gangrenous digit or limb.

Yet here was Dr. Tvedegaard apparently stopping and sometimes even reversing the otherwise inexorable progress of this terrible disease. “Night cramps would . . . go, which greatly improved the quality of sleep. Cold, blue, painful feet and legs would become pink and comfortable as the circulation mysteriously improved. Even gangrene would heal without surgery,” writes Dr. Carruthers, who witnessed many of these remarkable recoveries.<sup>55</sup>

Not surprisingly, the medical orthodoxy of Denmark, which had suffered mightily under the Nazi occupation just a few years earlier, looked with extreme suspicion on this unusual German therapy. He had to raise funds to support his research, often calling on his patients for help. Danish medical journals repeatedly rejected Tvedegaard’s papers, and he was denied the opportunity to speak at medical conferences. Given the lack of published support for his claims, it was easy to reject them as “unsupported,” “untested,” or simply, “quackery.” (This, incidentally, is exactly the same line of reasoning used today by the medical establishment in the United States and elsewhere to disparage and suppress natural, nutritional, and other patented nonpharmaceutical treatments.)

One day in 1957, the bureaucrats at the Danish Health Service decided that they had finally had enough of Drs. Tvedegaard and Møller. Bypassing their usual procedures for disciplining physicians who dared step out of line, they arranged to have the state police pay the two physicians a visit. They were accused of bilking the state by prescribing (and thus forcing the government to reimburse part of the cost of) testosterone for uses for which it was not “approved” (i.e., circulatory problems).

Tvedegaard and Møller were up against powerful odds and unscrupulous prosecutors who tried to seize their patient records (depriving them of the very evidence they needed to defend themselves), and who concocted false stories about supposed patient maltreatment. During a two-year struggle, Møller seized the gauntlet from the old and ailing Tvedegaard, carrying the battle not only to the courts, but to the medical community and the general public as well.

Møller was a worthy opponent for the regressive Danish medical establishment. Not only was he a creative thinker, he was also a master of medical theater. At one point, after gathering the latest research on testosterone along with the support of the leading German endocrinologists of the day, he organized a public meeting of 1,500 patients and relatives of patients in order to raise funds to continue his research. Somehow, he managed to have a group

“For physicians to treat high cholesterol or any of the other common symptoms and pretend that they are really treating cardiovascular disease is not only foolish, it may even be dangerous, according to Møller.”

of physicians from the Danish Health Service sit in the front row, where he confronted them with the latest research on testosterone and dared them to contradict him. “They couldn’t, and left the hall in a state of confusion and acute embarrassment,” writes Malcolm Carruthers.<sup>55</sup>

In the end, though, it was not public relations but good medicine that won the day. As luck would have it, one of Møller’s patients was a close relative of a minister of justice who happened to be on the state medical ethics committee. When the minister heard firsthand how his relative had benefited from their treatment, he had the court decisions against the two physicians overturned. Remarkably, Møller’s fiercest opponent, the director of the Danish Health Authority, also had friends and relatives who were taking testosterone under Dr. Møller’s care. When he saw how well they were doing, he too did a 180-degree turnabout and became director of an organization set up to promote the use of testosterone.

In 1976 Møller founded the European Organization for the Control of Circulatory Diseases, which continues to carry on his ideas. Right up until the time of his death, Møller continued to be an active researcher and vocal advocate for testosterone replacement therapy. Notes Carruthers, who worked closely with Møller in the last decade of his life, “It was difficult to keep up with him even when he entered his 80s, and it soon became apparent that he certainly took his own medicine, which was as effective for him as it was for his patients.”<sup>55</sup>

### Decades Ahead of His Time

Having come to medicine so late in life, Møller brought with him the eye of the iconoclast. This made it easier for him to discount many of the conventional ideas that are typically spoon-fed as fact to eager young doctors to be. Key among these was the nature and treatment of cardiovascular disease.

Over his 30+-year medical career, Dr. Møller reported having successfully treated thousands of patients with testosterone esters. He had seen “testosterone’s” beneficial effects with his own eyes. He knew it worked. He had little patience with the medical profession’s insistence on large, expensive double-blind, placebo-controlled trials before accepting the validity of a particular treatment. He pointed out, for example, that many patients taking “testosterone” require individualized treatment strategies that may not fit comfortably within the rigid methodological confines of such a study.

In addition, he had serious ethical concerns with withholding a treatment he knew worked from some patients (placebo controls) simply to satisfy a statistical requirement. “I do not wish to treat my patients and fellow human beings as if they were rats,” he

said. He made an analogy with insulin in diabetics. “Nobody in his right mind would dream of dividing diabetic patients into two groups, treating one with insulin and letting the other group perish, simply because insulin action and the pathogenesis of diabetes mellitus are not fully understood,” wrote Møller.<sup>11</sup>

His clinical findings using “testosterone” replacement fell into three general categories:

- ♥ Complete healing of gangrene of the upper and lower extremities
- ♥ Improvement of impaired carbohydrate metabolism
- ♥ Milder and fewer angina pectoris attacks, as well as normalized ECG findings

In one of the few studies that Møller published, he evaluated the effects on blood cholesterol levels of giving “testosterone” (testosterone enanthate) injections to 300 men (aged 41 to 82 years) with “recognizable circulatory diseases.” The study, which was carried out at the State Hospital in Copenhagen, showed that cholesterol levels dropped in 83% of the patients during testosterone treatment. The average reduction in cholesterol concentration in these men was 26%.<sup>11</sup>

Møller’s efforts to discover why “testosterone” replacement worked led him to a view of cardiovascular disease and its treatment that was radically different from what most physicians are taught. In Møller’s view, conventional medicine views cardiovascular disease as primarily a plumbing problem. The aim is to keep the pipes clear and the pump working. The focus is on symptoms of the disease – high cholesterol, hypertension, atherosclerosis, thrombosis (clot formation), intermittent claudication, angina, and other familiar manifestations – but not on what is really causing them.

This attitude has given rise to scores of drugs that attack these symptoms – lowering cholesterol, reducing blood pressure, and dilating coronary arteries – as well as surgical procedures that essentially ream out or replace clogged arteries as though they were lengths of copper tubing. “The press and medical journals have repeatedly published articles claiming that arteries are pipes which get sooted up due to butter consumption and can be cleared by pipe cleaners and margarine,” wrote Møller. “This theory does not have anything to do with the ‘prevention and treatment’ of cardiovascular disease.”<sup>11</sup>

Without getting too deeply into his complex theorizing, Møller viewed the normal condition of a living organism as a balance between anabolic (protein-building) and catabolic (protein-destroying) processes. The primary anabolic hormone is testosterone; the primary catabolic hormone is another steroid, cortisol. Cardiovascular disease results when catabolic influences come to predominate, leading to the accumulation of excess cholesterol, impaired carbohydrate metabolism, decreased fibrinolysis, and other well-known symptoms.

“Life unfolds in protein,” wrote Møller. “Protein is the living, respiring substance that needs to be fueled and supplied with oxygen to sustain combustion and provide energy for the unique material that is life itself – performing physical activity, expressing

itself in the actions of every enzyme, regulating every function of the body. Protein is the substance on which all the biochemical and physiological activity of life is based. And testosterone is the hormone whose major role is to build up this core substance.”<sup>22</sup>

For physicians to treat high cholesterol or any of the other common symptoms and pretend that they are really treating cardiovascular disease is not only foolish, it may even be dangerous, according to Møller. He argued, first, that cutting dietary cholesterol made no sense, pointing out that the daily cholesterol content in the diet has no appreciable effect on plasma cholesterol levels. Moreover, drastically reducing cholesterol levels, whether by a low-fat diet or drugs, may cause more harm than good. “Organisms cannot exist without cholesterol, which takes part in all cell functions,” Møller wrote. “If we interfere with this system, e.g., medically, the result may be that we decrease resistance to infection; we may even accelerate the aging process.”<sup>22</sup>

Møller was particularly opposed to the use of drugs that lower cholesterol levels, which have since become very popular. Recall that testosterone itself (as well as all other steroid hormones) is derived from cholesterol. Cholesterol is also a vital component of cell membranes. He argued that many cholesterol-lowering drugs available at that time caused more cholesterol to be excreted than the body was able to synthesize. “The result is a negative cholesterol balance, which can lead to impotence and impaired cardiac function, resulting, for instance, in angina pectoris and other signs of serious cardiovascular disease such as claudication,” he stated.<sup>22</sup>

Møller claimed that the occurrence of impotence in some men taking cholesterol-lowering drugs was a direct confirmation of his theory. “The cholesterol is wasted by going down the drain instead of building testosterone,” he said. “Decreasing the cholesterol level alone may in fact result in a decrease in the production of testosterone, which plays an important role in maintaining normal circulation. It is totally incomprehensible to me how such a substance can be used by serious practitioners of medicine, who inflict cardiovascular disease on their patients instead of curing it.”<sup>22</sup>

## Dr. Møller’s Legacy

A decade after his death, it’s a safe bet that hardly any physicians in the United States have ever heard of Dr. Jens Møller or his theories about the nature and treatment of cardiovascular diseases. Yet, it is becoming increasingly apparent that Møller was right on target.

During the late 1980s, even before Møller died, medical scientists were starting to recognize that many seemingly independent biochemical abnormalities are actually symptoms of an underlying cause of much cardiovascular disease. It is now accepted as fact that many cases of atherosclerosis, along with its correlates and clinical consequences, are part of a syndrome that includes increased insulin resistance and insulin levels, poor blood sugar regulation, elevated cholesterol and triglyceride levels, high blood pressure, and abdominal obesity.<sup>56</sup> For lack of a better name – or understanding – of this syndrome, it has been labeled “syndrome x” or “metabolic syndrome.”

While scientists have known for decades that these symptoms tend to occur together, or “cluster,” in certain individuals, they tended to look at them as independent risk factors for the really serious diseases of the heart and blood vessels. The reality of “syndrome x” suggests that much, if not most, coronary heart disease, intermittent claudication, diabetes, hypertension, along with blood lipid aberrations, clotting problems, obesity and so on, are all different manifestations – or symptoms – of the same disease.

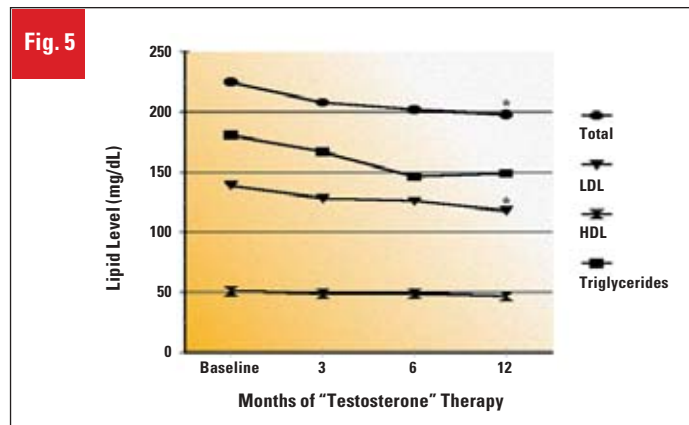
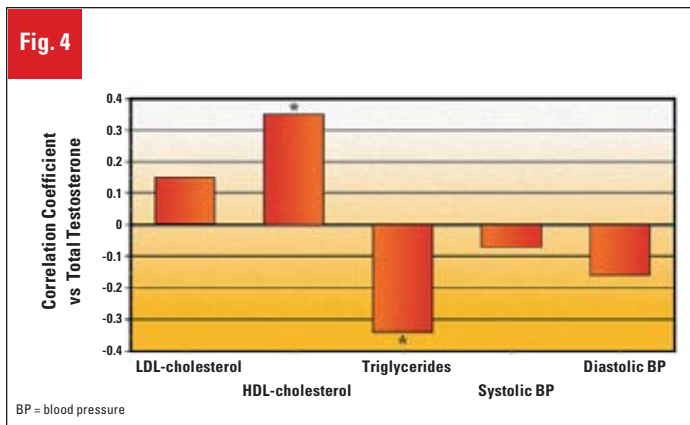
If this all sounds familiar, it should, because Jens Møller said basically the same thing for 25 years. Møller was convinced that cardiovascular disease is basically a metabolic disturbance, exactly what is implied by syndrome x. If you compare the symptoms that comprise syndrome x with those associated with low levels of testosterone, you find an almost perfect correspondence. Not surprisingly, these are the same symptoms that respond to treatment with testosterone. Is testosterone the ideal treatment for syndrome x?

We have no doubt that Møller would think so. The medical community, however, still has a way to go to catch up with him. Current thinking regarding the cause of syndrome x is leaning toward a defect – possibly inherited – in the body’s ability to produce and process insulin. It’s true that long-term insulin resistance and elevated insulin levels are associated with diabetes, hypertension, atherosclerosis, coronary heart disease and all their blood-clotting and cholesterol disturbances. As yet, no consideration is given to another metabolic step, a step involving testosterone. Testosterone, as many studies have demonstrated, can affect all these same processes including insulin resistance.

Because of its incomplete view of circulatory system diseases, conventional medicine continues to treat patients symptomatically – usually with drugs that lower cholesterol, reduce blood pressure, normalize heart beat, dilate coronary arteries, and now, help maintain insulin function. We are told to exercise and to lose weight, and often we are offered more drugs to help accomplish the latter.

Unfortunately, men are almost never offered testosterone to prevent or treat heart disease associated with male menopause. The patches being marketed today by pharmaceutical companies are aimed primarily at men with low libido or impotence as a result of a testosterone deficiency, not to treat or prevent heart disease. While physicians are free to prescribe testosterone to any patient for any reason, most are locked into the conventional treatment of cardiovascular disease, and few are aware how beneficial testosterone might be for prevention or treatment. (It is interesting that Tvedegaard and Møller were prosecuted for prescribing testosterone for just such an “off-label” use.)

Awareness will grow as more and more men begin using the new natural testosterone products that are becoming increasingly available. It is only a matter of time before someone does the study demonstrating that men who use them have less cardiovascular disease than those who do not. Already, the results of a major longitudinal epidemiologic study by Dr. Joseph M. Zmuda and colleagues at the University of Pittsburgh and Wayne State University suggest that Møller was on the right track.<sup>47</sup>



This study followed men enrolled in the large, long-running Multiple Risk Factor Intervention Trial for 13 years, monitoring their testosterone levels as well as a wide range of other health-related variables. The men were divided into two groups. One group received “special intervention” consisting of drug treatment for hypertension, counseling to help them stop smoking, if necessary, and dietary advice for lowering blood cholesterol. The other group received only their usual health care.

Zmuda and coworkers found that total testosterone levels decreased gradually over the 13 years of the study. Although various cross-sectional studies had suggested a decline in testosterone with advancing age, this was the first time it had been demonstrated in a longitudinal study. The average rate of decline was small but significant, about -0.2% per year.

The decline in testosterone levels was particularly marked in men who had a type-A personality. Type-A men are intense, hard-driving, competitive, in a hurry and easily angered. Hormonally, they respond to stress or challenges with exaggerated increases in the adrenal steroid cortisol, the effects of which are primarily catabolic. As Møller theorized, cortisol suppresses testosterone levels, which may help explain why: (1) these men have lower testosterone levels, and (2) they are at much greater risk for coronary heart disease.

One of the most surprising results in this study was the finding that the men in the “special intervention” group experienced greater reductions in total testosterone than did the men in the usual care group. There were no differences between the two groups in cigarette smoking (which was also associated with lower testosterone), body weight at baseline, or weight change over the 13 years.

How did Zmuda and colleagues explain this puzzling difference? (Jens Møller would not have been puzzled!) Apparently, drastically cutting fat intake, as these men were encouraged to do in accord with orthodox medical thinking, can be harmful. They wrote: “It is possible that this sustained reduction in dietary fat consumption contributed to a greater decrease in total testosterone levels during follow-up.” They supported this conclusion by citing research done in the 1980s showing that a decrease in dietary

fat consumption reduces levels of total testosterone, free testosterone, and androstenedione.<sup>57</sup>

Another important question Zmuda and his colleagues were attempting to answer was whether the increased incidence of atherosclerotic cardiovascular disease associated with aging is related to the decline in testosterone. Previous cross-sectional studies had clearly pointed in this direction.<sup>18,35,58,59</sup> Zmuda and colleagues found that the decline in testosterone over 13 years was independently and significantly correlated with a decrease in HDL cholesterol and an increase in triglycerides, both of which are considered to be traditional “risk factors” for atherosclerosis and coronary heart disease (Fig. 4). In other words, as testosterone levels fell, so did HDL, and triglyceride levels rose.

More importantly, replacing testosterone seems to have a beneficial effect on lipoproteins. In a 1992 study, Dr. Joyce S. Tenover assessed the effects of three months of “testosterone” (testosterone enanthate) therapy in 13 healthy men (aged 57 to 76 years) who had low-to-borderline endogenous testosterone levels. “Testosterone” replacement resulted in significant declines in total cholesterol and LDL cholesterol of about 11%. Dr. Tenover noted that these changes in lipoproteins “. . . are in marked distinction to changes seen with oral anabolic steroids.”<sup>36</sup>

A similar result was achieved by a group of Polish researchers. In a recent study, they gave “testosterone” (testosterone enanthate) to 11 healthy elderly men with low testosterone levels and monitored their cholesterol levels for 12 months. They found that “testosterone” supplementation caused a significant decline in total cholesterol and LDL cholesterol, a nonsignificant decline in triglycerides, and no change in HDL cholesterol (Fig. 5).<sup>60</sup>

## DHEA and the Heart

Although we’ve been focusing primarily on testosterone, we cannot end this discussion without at least a brief mention of another androgen that has received a great deal of attention in recent years, particularly with respect to heart disease. That androgen is DHEA.

Dehydroepiandrosterone, which is produced mainly in the adrenal glands, lies at the heart of the steroid family. Descended from cholesterol by way of pregnenolone, DHEA is a direct precursor of androstenedione and androstenediol, both of which are metabolized to make testosterone.

Despite the fact that DHEA is abundant throughout the human body, it was, until just a few years ago, considered a “junk hormone,” with no apparent purpose of its own. In fact, research on DHEA, which is still in its infancy, suggests that nothing could be farther from the truth. William Regelson, MD, of the Medical College of Virginia, in his book *The Superhormone Promise*, calls DHEA “the superstar of superhormones” and “one of the most powerful tools” available for enhancing and extending life.<sup>61</sup>

Considering that DHEA is an androgen, it should come as no surprise that DHEA has some very testosterone-like behavior. First, like testosterone, DHEA reaches its peak levels during a man's early 20s and then begins an inexorable decline. Unlike testosterone, the decline of DHEA is relatively rapid. By age 40, men have only about half the DHEA they had in their 20s, and the decline continues well into the ninth decade. By age 80, a man may have only 15% and by 90, only 5%.<sup>61</sup>

Dehydroepiandrosterone replacement has also been shown to be associated with such beneficial testosterone-like effects as:

- ♥ Feelings of energy and well-being<sup>62</sup>
- ♥ Improved insulin sensitivity and glucose tolerance<sup>63</sup>
- ♥ Reduced death from coronary heart disease<sup>64</sup>
- ♥ Lower obesity/waist-to-hip ratio<sup>65</sup>
- ♥ Slowed progression of atherosclerosis<sup>66,67</sup>
- ♥ Enhanced libido and erectile ability<sup>61</sup>
- ♥ Reduced depression and enhanced cognition<sup>68</sup>

Dehydroepiandrosterone may diverge from testosterone in the type of cardiovascular protection it provides. While testosterone raises HDL cholesterol slightly and lowers LDL cholesterol and triglycerides, DHEA does not seem to affect blood lipids very much. Some research, however, suggests that DHEA prevents platelet aggregation (as does testosterone), and it may also have other actions that interfere with the formation and progression of atherosclerosis, including preventing the oxidation of LDL cholesterol.<sup>69</sup>

*Maximize Your Vitality and Potency* can be purchased direct from Smart Publications – tel: 707-769-8308, fax: 707-763-3944, or email: info@smart-publications.com. Wholesale pricing is available for pharmacies wishing to resell the book to customers (a good way to educate about the value of natural hormones.)

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