
Masculine Vitality: Pros and Cons of Testosterone in Treating the Andropause



An Interdisciplinary Workshop of the
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Canyon Ranch-International Longevity Center closed workshops are modeled after National Institutes of Health Consensus Workshops. We bring together scientists on particular critical topics to decide what can be agreed upon and, when a consensus is reached, to develop a research agenda. The participants are then asked to determine what information should be provided to the public and, finally, what messages are pertinent to policymakers at the foundation, business, and governmental levels. Previous workshops have included *Prescription for Longevity, Maintaining Healthy Lifestyles, Achieving and Maintaining Cognitive Vitality With Aging, Biomarkers of Aging, and Longevity Genes.*

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Preface

A huge national drug experiment is under way. It affects hundreds of thousands of men, it is unsupervised and uncontrolled, and its subjects are unaware that they are taking a drug with unknown and potentially life-threatening side effects. The drug is testosterone replacement, and, increasingly, men are using it in an attempt to regain youthful vitality, sexuality, mental alacrity, and bone and muscle mass.

Women already have a long history of hormone replacement therapy use, beginning in 1948 when Robert Wilson first published *Feminine Forever*. Based on theories unsupported by research, the book nevertheless fed the fantasies of many women (and their partners) that by ingesting an estrogen pill youthful femininity could be prolonged indefinitely. After it was reported that women who took the hormone developed uterine cancer in larger numbers than women who hadn't taken it, combined estrogen-progesterone hormone therapy was developed, which protects the uterus. However, it wasn't until 50 years after *Feminine Forever* was published that women had a comprehensive body of information about the benefits and long-term risks of hormone replacement.

Today, men face a similar situation, but they are in a position to learn from women's experiences. What is needed is a longitudinal clinical trial that addresses the benefits and risks of testosterone

replacement therapy. A Men's Health Initiative at the National Institutes of Health comparable to the Women's Health Initiative would provide valuable information about the safety and efficacy of male hormone replacement.

Thus far, the National Institutes of Health and Veteran's Administration have decided against undertaking the large clinical trial because of understandable concern regarding the possibility of promoting prostate cancer. However, since thousands of men daily appear to be willing to take their chances on unproven hormone replacement, surely they should be allowed to give informed consent to volunteer in a randomized, double-blind clinical trial that would answer questions about the pros and cons of replacement therapy on bone, muscle, sexuality, and central nervous function, as well as its long-term safety.

A large-scale clinical study of benefits and risks of both short- and long-term testosterone replacement therapy conducted in multiple centers would involve 6,000 men, examined over six years, at a cost of over \$100 million. The price is high, but not as high, in the long run, as inaction.

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Executive Summary

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INTRODUCTION

As our population ages, concerns about frailty and disability, as well as the all-too-human desire to remain young for as long as possible have led increasing numbers of women and men to the questionable practice of restoring diminishing hormone levels. Recent research findings have alerted women to the potential health risks of estrogen replacement therapy, but to date no serious long-term studies have been conducted to examine the effects on men of testosterone replacement.

The lack of information about testosterone should be of particular concern because testosterone use in this country has skyrocketed, with sales reaching \$400 million in 2002. While men whose testosterone levels have greatly diminished often experience a decline in muscle mass or strength and reduced bone mass that frequently leads to frailty and disability, it is not known whether testosterone replacement can delay or prevent this loss. Nor have the long-term effects of this hormone replacement therapy been studied. For example, little is known about the effect testosterone replacement has on the risks of prostate and heart disease.

On May 16-19, 2002, a group of eminent researchers gathered at Canyon Ranch Health Resort in Tucson, Arizona. The purpose of this consensus workshop was to determine what is known about testosterone and the effects of testosterone replacement therapy, to propose a research agenda for future work, and to identify other steps that might be taken in the realm of public information and policy.

It is extremely important to understand the health risks of testosterone deficiency and whether testosterone replacement therapy is safe and effective. The academic community is in agreement that large-scale definitive studies are needed to obtain realistic estimates of the long-term clinical benefits and risks of testosterone replacement in older men.

WHAT IS TESTOSTERONE?

Testosterone is a vital sex hormone that is produced in the testes, the male reproductive glands that also produce sperm. Testosterone is the major determinant of male sexual differentiation in the fetus and male secondary characteristics and function in boys and men. Production of testosterone peaks during adolescence and early adulthood, and it declines progressively with age at the rate of about 1 percent per year beginning in the fourth decade of life. The extent to which this contributes to loss of bone, lean body/skeletal muscle mass, gain in body fat, and frailty remains to be determined. Little proof exists to support the hypothesis of andropause—the so-called “male menopause.” Unlike women, whose estrogen levels precipitously decline beginning in their fourth decade, men exhibit a large range of normal testosterone levels throughout life.

MUSCLE MASS

A number of studies have shown an increase in muscle mass with testosterone treatment in older men without a concomitant increase in muscle strength. However, doses were not consistent and

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the hormone levels of many men studied were not sufficiently diminished. It has also been suggested that upper-limb muscles may be more sensitive to testosterone effects than lower-limb muscles. Carefully designed studies with consistent subjects and dosages are needed to clarify the results.

BONE DENSITY

During puberty, bone mineral density increases dramatically in boys. As men age, bone mineral density declines, and they become vulnerable to fractures. It is unclear whether this decline is due to age-related declines in testosterone or to other bone-regulating factors (e.g., parathyroid hormone, vitamin D, growth hormone). One study conducted to determine testosterone's role in increasing spinal bone density, found that only in men whose serum testosterone levels were particularly low before treatment did the hormone therapy improve bone density. Another study found that testosterone given to healthy older men with low testosterone levels prevented femoral neck bone loss, decreased body fat, and increased lean body mass and lower-extremity muscle strength. Although these findings suggest that testosterone replacement may benefit some older men, further studies are needed, particularly studies that examine fracture rates over time.

BRAIN FUNCTION AND COGNITION

The results of basic science investigations corroborate those of clinical trials and epidemiological studies. Although not universally confirmed, administration of testosterone to men with low testosterone levels has been shown to enhance cognitive function in the majority of clinical studies. It must be noted that this enhancement is confined to specific areas. In several independent studies, weekly administration of testosterone, either by injection or scrotal patch, significantly enhanced spatial memory, working memory, and verbal fluency of healthy older men. Again,

findings of these clinical studies are preliminary and need to be systematically confirmed in larger clinical studies before the therapeutic potential of testosterone can be firmly established.

PROSTATE AND ERECTILE FUNCTION

One of the greatest fears of supplementing older men with testosterone is an increased risk for benign hyperplasia and/or prostate cancer. Dozens of reports on prospective testosterone replacement studies over the last 20 years have shown no increase in prostate cancer. However, no definitive conclusions can be drawn yet because of methodological shortcomings of the studies available to date. These include short duration of follow-up; studies were not designed to take into account that incidence of prostate cancer is closely linked to age, race and ethnicity; lack of consistency in evaluation of prostates (e.g., only a few studies use biopsies of the prostate for assessment.) Testosterone clearly improves libido when administered to older men.

RESEARCH AGENDA

To date a number of small-scale randomized trials of testosterone replacement therapy in older men have been conducted with reports of positive effects on bone mineral density, muscle strength, and increase in lean body mass with a decrease in body fat. However, none have included a sufficient number of subjects to adequately assess risks and benefits of testosterone replacement. A large-scale study with approximately 6,000 subjects has been estimated as necessary to ascertain changes in the incidence of prostate cancer and coronary events and to firmly establish possible benefits.

Better technology is needed to determine normal ranges of testosterone and to identify abnormally low levels in individuals who might benefit from testosterone replacement. The development of accurate diagnostic testing would also aid in this process.

Masculine Vitality: Pros and Cons of Testosterone in Treating the Andropause

INTRODUCTION

Increasing frailty with age is a major problem for the older American population and increases the risk for adverse health outcomes such as falls, hospitalization, institutionalization, and eventually mortality (Fried et al. 2001). Unfortunately, neither an adequate definition of nor means of assessing frailty is available. Gillick (2001) suggests that frailty is “so ill-defined that some gerontologists dispute that it is any more than a synonym for disability.” Nevertheless, there is certainly consensus that a biological understanding of what causes older persons to become frail could provide a link between aging and the diseases of old age and could lead to interventions to delay and/or prevent disability among older persons. Such interventions are already being suggested based on known age-related changes in levels of circulating hormones, but most of these suggested interventions are based on insufficient knowledge of the full implications of the hormone replacement therapy suggested. One of these potential interventions is testosterone supplementation in older men. An epidemiological study has suggested that declining function in old age is related to low levels of bioavailable testosterone (Perry et al. 2000), and a single small study found that testosterone therapy enhanced function in older males undergoing rehabilitation (Bakhshi et al. 2000).

Serum testosterone levels decline with age in men, and in some men testosterone declines to such a large extent as to classify these men as “hypogonadal.” As observed in both cross-sectional (Gray et al. 1991) and longitudinal (Morley et al. 1997a;

Zmuda et al. 1997; Harman et al. 2001; Feldman et al. 2002) studies, beginning in the third decade age is associated with a gradual and progressive decline in serum testosterone levels at a rate of approximately 1 percent per year. About 98 percent of serum testosterone is either tightly bound to sex hormone binding globulin or weakly bound to serum albumin. Thus, only about 1 percent to 2 percent of testosterone circulates freely in the plasma unbound to proteins. The bioavailable testosterone, comprised of the free testosterone plus the testosterone weakly bound to albumin, is thought to be responsible for testosterone’s biologic effect in most tissues. Bioavailable testosterone declines even more with age than does total testosterone because of a concomitant age-related increase in sex hormone binding globulin (Figure 1). Men with total and/or bioavailable testosterone levels below the normal range for young men, are classified as “hypogonadal” (see following section). Rather than utilize this type of statistical construct to define hypogonadism, workshop participants recommended that, where possible, the definition of hypogonadism should be based on functional as well as biochemical criteria, i.e., low serum levels of testosterone that are associated with physiological changes consistent with androgen deficiency, such as reduced muscle mass or strength, reduced bone mass, etc. Such a definition would follow the analogy of hyperlipidemia, where normal levels of total cholesterol (as high as 260) previously were defined on the basis of a statistical construct but now are based on levels associated with cardiovascular disease (normal levels less than

200). Unfortunately, at the time of this report insufficient data exist to rigorously identify levels of testosterone that define physiological or functional hypogonadism for most target organs and tissues. The participants agreed that priority should be given to allocating resources for research aimed at addressing this problem.

It remains unclear what role the observed decline in total and bioavailable testosterone plays in male aging. Matsumoto (2002) has recently reviewed the clinical implications of the decline in testosterone with aging, but the long-term clinical beneficial effects of testosterone replacement in older men remain poorly defined, and its long-term effects on the risks of prostate and heart disease remain largely unknown. Because of these uncertainties about the clinical utility of hormone replacement in older men, the academic community is in agreement that large-scale definitive studies are needed to obtain realistic estimates of the long-term clinical benefits and risks of testosterone replacement in older men.

In contrast to the academic community, the media and the public at large appear to have moved beyond science in this field. As a result, testosterone sales have been growing at an alarming rate in the last several years. A review of prescription sales data indicates that testosterone sales had been steady at about \$18 million until 1988. In that year, ALZA Corporation introduced the Testoderm scrotal testosterone patch. In 1993, GlaxoSmithKline started marketing the Androderm patch developed by TheraTech Inc. Since 1993, testosterone sales have been growing at 25 percent to 30 percent per annum, increasing from \$23 million in 1993 to \$71 million in 1999. In 2000, when Androgel, was introduced into the market, testosterone sales more than doubled to \$150 million. A recent market analysis of prescription sales indicates that testosterone sales had reached \$250 million in the year 2001 and

are expected to reach \$400 million in 2002, based on current projections (Anderson et al. 2002).¹ These sales data refer to the dollar amount of prescription sales at the retail level and do not include all the sales of the product, particularly at the wholesale level. Therefore, although these sales data derived from IMS and BMC corporations are considered reliable and widely used by the pharmaceutical companies for making sales projections, they likely underestimate the total sales volume.

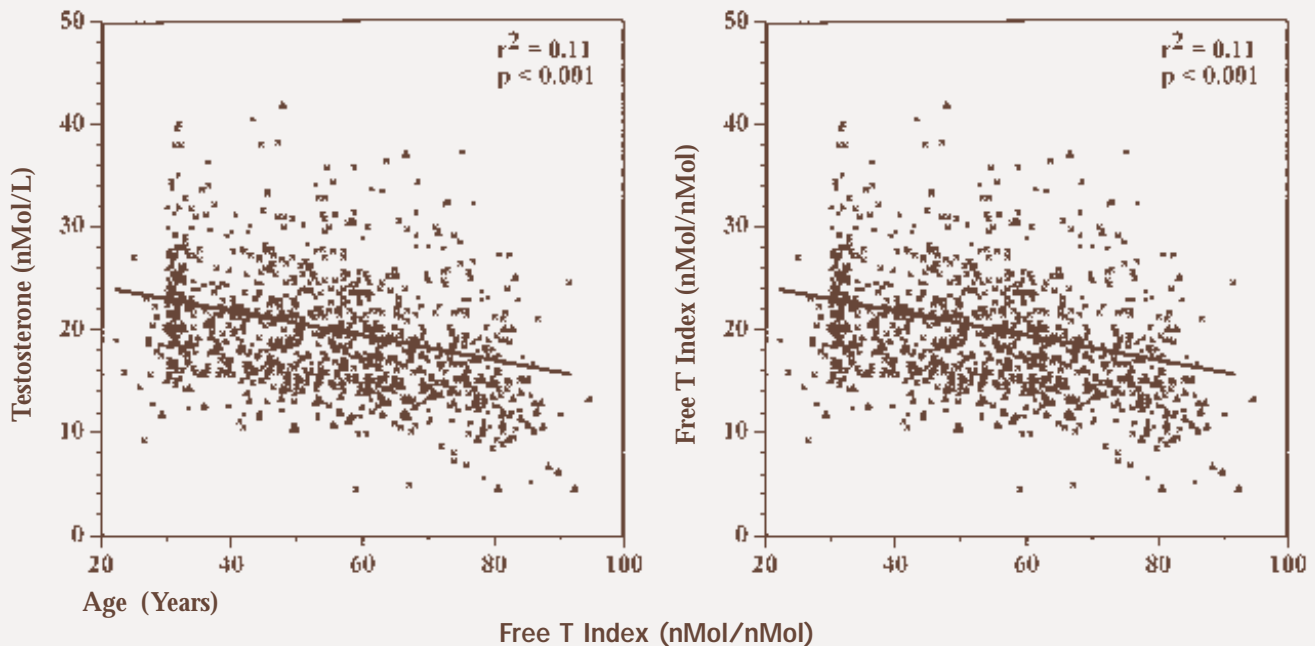
This explosive growth in testosterone prescription and usage has spawned enormous interest in the pharmaceutical industry in developing new testosterone formulations. At the present time, at least 12 different androgen formulations are in various phases of clinical development. These developmental efforts by the industry suggest that the upward pressures on the sales of testosterone products are likely to persist and even grow in the foreseeable future. Thus, it is extremely important for the scientific community to develop a consensus about the health benefits and safety of these products. The purposes of this report are to: (1) summarize what we already know about the andropause and the effects of testosterone replacement therapy; (2) propose a research agenda for future work; and (3) identify other steps that might be taken in the realm of public information and policy.

WHO IS HYPOGONADAL?

The following statement about “normal” testosterone levels is taken from the report of the Second Annual Andropause 2001 meeting sponsored by the Endocrine Society. This report is available to members of the Endocrine Society at www.endo-society.org/membership/membersonly.cfm.

¹ These data and projections were provided to Dr. Bhasin by officials at GlaxoSmithKline, IMS Corporation, ALZA Corporation, and Solvay-Unimed Corporation.

Figure 1



Effects of age on serum testosterone (left panel) and free testosterone index (right panel) in Baltimore Longitudinal Study of Aging men (Harman et al. 2001). Individual data points for testosterone (upper panel), sex hormone binding globulin (middle panel), and free testosterone index (lower panel) from the earliest available (usually first) visits during 1963–1994 are shown as crosses (x), and the additional set of 120 serum samples from later visits (1995–1998) are plotted as closed triangles. Best-fit regression lines, r^2 , and p values are also shown. Total testosterone concentrations and free testosterone index values decreased linearly with increasing age.

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“The normal range for serum total testosterone levels in early morning hours in healthy young men 20 to 40 years of age is approximately 300 ng/dL to 1,000 ng/dL. The recommendations of this Consensus Panel were predicated on this range for normal serum testosterone. Assuming that a patient has signs or symptoms consistent with androgen deficiency and no contraindications exist, men who fall below the lower limit of this range would likely benefit from treatment independent of age.

“Total testosterone levels < 200 ng/dL clearly indicate hypogonadism, and in most instances indicate that benefits may be derived from testosterone replacement therapy. Total testosterone levels between 200 ng/dL and 400 ng/dL should be repeated and followed up by calculation of free testosterone from total testosterone and sex-hormone binding globulin concentrations, or

by measurement of free testosterone levels by the dialysis method, or bioavailable testosterone by the ammonium sulfate precipitation method. If a healthy man has a serum testosterone level > 400 ng/dL, it is unlikely he is testosterone deficient and, therefore, clinical judgment should guide the next steps, even if he has symptoms suggestive of testosterone deficiency.” However, recent data suggest that an upper value of 500 ng/dL should be used (Morley et al. 2002).

The Consensus Panel went on to conclude that based on this definition, 49 percent of men over 80, 28 percent of men 70–79 years old, and 19 percent of men 60–69 years old could be considered to have low total testosterone levels. Thus, it is extremely important to understand what the health risks of testosterone deficiency are and whether testosterone replacement therapy is both safe and effective. The following sections

of this document discuss what is known about the role of testosterone in various physiological systems and what changes occur with aging.

There are three screening tests using symptoms and/or epidemiological factors currently in use to detect hypogonadism, i.e., androgen deficiency in aging males (Morley et al. 2000), Massachusetts Male Aging Study (III) Screen (Smith et al. 2000) and the Aging Men's Survey (Heineman et al. 1999). The first two tests have undergone some degree of validation. The androgen deficiency in aging males test has undergone independent validation in Belgium (Legros and Delhez 2002). There is an overwhelming need for independent epidemiologically appropriate validation of these questionnaires. Although androgen deficiency in aging males is widely utilized throughout the world to screen for older hypogonadal men, a better test based on known symptoms of hypogonadism is needed.

BIOCHEMISTRY AND METABOLISM OF TESTOSTERONE

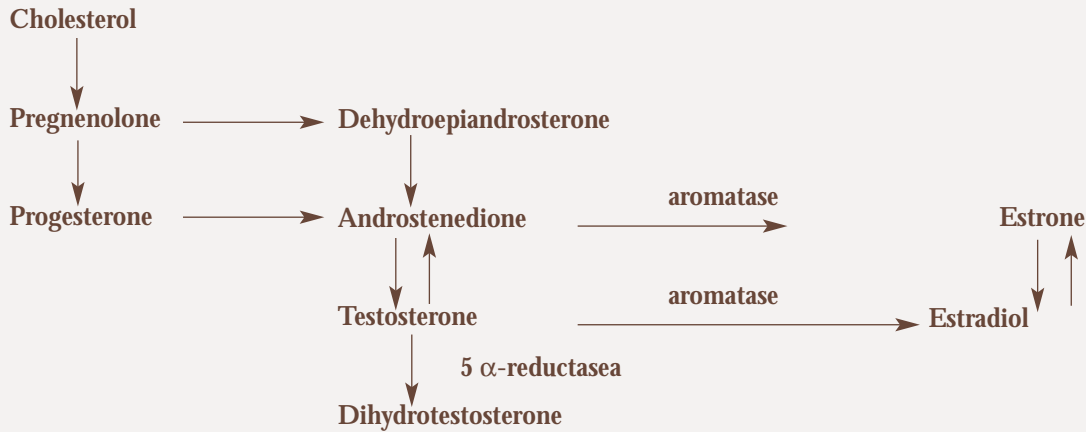
Testosterone is a steroid hormone made from cholesterol predominantly in the Leydig cells of the testis via the androgen biosynthetic pathway (Figure 2). Testosterone is the major determinant of male sexual differentiation in the fetus and male secondary characteristics and function in boys and men. The amount of testosterone synthesized in the testis is determined largely by prevailing plasma concentrations of luteinizing hormone (LH), a gonadotropin secreted by the pituitary gland. Luteinizing hormone secretion in turn is controlled by feedback regulation by plasma levels of sex steroid hormones. Serum levels of total and free testosterone increase during puberty, reaching a maximum in the twenties and thirties, then generally decline steadily at about 1 percent per year with increasing age (Figure 1). In response to declining testosterone concentrations in blood and reduced negative feedback, serum luteinizing

hormone levels tend to increase with aging. However, luteinizing hormone concentrations usually remain within the normal range as a result of age-related reduction in the secretion of gonadotropin-releasing hormone by the hypothalamus and reduced gonadotropin releasing hormone stimulation of the pituitary gland. The age-related decline in serum testosterone is due primarily to reduced testicular production of testosterone, but inadequate luteinizing hormone stimulation also contributes to the decline. Metabolic clearance of testosterone also decreases with aging attenuating the effect of reduced testosterone production by the testis. Finally, serum testosterone levels are suppressed further by comorbid conditions such as illness, medication, and malnutrition that are often associated with aging.

A critical factor in evaluating the biologic effectiveness of testosterone is the circulating concentration of bioavailable testosterone. Bioavailable testosterone, the fraction of circulating testosterone that is not tightly bound to sex hormone binding globulin, is considered to be the biologically active component that actually enters cells, interacts with intracellular androgen receptors, and in that manner regulates gene expression and cellular function. Like estrogen, the androgen receptor activity is modulated by a number of intracellular coregulators that modify the response to androgen in a tissue-specific manner. This rather straightforward picture is complicated by the likely presence of cell membrane resident androgen receptors that are responsible for rapid, nongenomic effects of testosterone, and by studies showing that sex hormone binding globulin itself can initiate cellular signaling when bound to steroid hormones (Rosner et al. 1999). Sex hormone binding globulin levels increase with age but decrease in response to conditions such as moderate obesity. These and other changes in sex hormone binding globulin levels may affect

Figure 2

Androgen Biosynthetic Pathway From Cholesterol



All of these steroids are available either as dietary supplements (pregnenolone, dehydroepiandrosterone, androstenedione) or prescribed for hormone replacement therapy.

total testosterone levels and may complicate their interpretation in certain clinical situations, reinforcing the need to measure free or bioavailable testosterone levels using an accurate assay in order to diagnose hypogonadism.

Testosterone is actively metabolized to estradiol, a potent estrogen, by the enzyme aromatase and to dihydrotestosterone, a more potent androgen than testosterone, by the enzymes 5α -reductase types 1 and 2 (Figure 2). Therefore, the physiological actions of testosterone may be mediated by both testosterone and dihydrotestosterone that interact with the androgen receptor, which is encoded by a single gene, as far as we know now, and estradiol, which interacts with two distinct estrogen receptors (alpha and beta) that are the products of two separate genes. The conversion of testosterone to dihydrotestosterone in certain androgen target tissues acts to amplify the actions of testosterone and is essential for primary sexual differentiation and growth of the external genitalia and prostate in the fetus and is important in development of male hair pattern. Some other androgen actions, such as enhanced growth and

development of skeletal muscle and bone, appear to be less influenced by dihydrotestosterone. Conversion of testosterone to estradiol is thought to play an important role in mediating some of the effects of testosterone, e.g., on bone, brain function, and adipose tissue. Circulating levels of total estradiol and dihydrotestosterone do not change appreciably with age, but bioavailable fractions of these hormones decline because sex hormone binding globulin levels increase with aging (Khosla et al. 1998). The relative roles of testosterone, dihydrotestosterone, and estradiol in mediating the effects of circulating testosterone on target tissues and biological function, especially as a function of aging, are not well understood and represent areas of active research.

If testosterone treatment for aging men is promoted on a widespread basis, an area crucial for further research will be age-related changes in tissue-specific sensitivity and dose response to testosterone, both at the molecular and clinical level. A report using a rat model of male reproductive aging provides evidence that the aging prostate becomes more sensitive to

testosterone (Banerjee et al. 1998). In contrast, indirect evidence suggests that muscle, bone, and central nervous system mechanisms mediating male libido may actually become less sensitive to testosterone with increasing age in men (Tsitouras et al. 1982).

TESTOSTERONE REGULATION OF SKELETAL MUSCLE

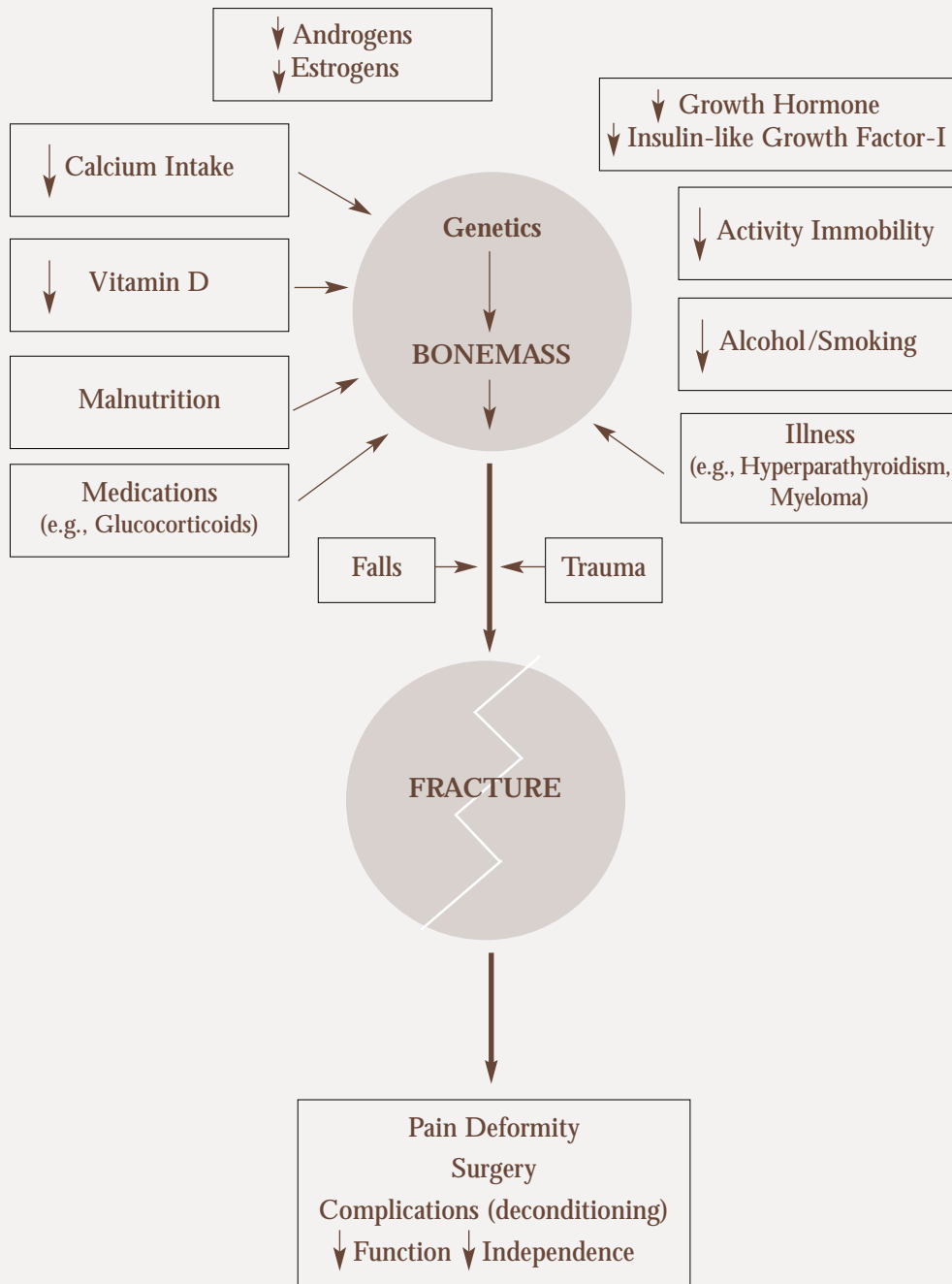
A common finding of studies of hypogonadal young men, as well as older men with age-related declines in testosterone, is reduced lean body mass. The observation that testosterone supplementation in both young and older men increases muscle mass suggests that testosterone may play an important role in the preservation of muscle mass although the underlying mechanism(s) is not well understood. In these studies, muscle strength frequently does not track with muscle mass, particularly in older subjects. Skeletal muscle is a very dynamic tissue, constantly undergoing muscle protein synthesis and breakdown. Studies have shown that androgens stimulate muscle protein synthesis in the short term (< six months), but chronic exposure shifts the effect to inhibition of protein breakdown. Androgens induce their specific response through the androgen receptor, which in turn regulates expression of androgen-regulated genes. A study in exercising rats (Inoue et al. 1994) showed that skeletal muscle growth depended on increased androgen receptor levels. Short-term exposure to a synthetic androgen in young men increased expression of the androgen receptor gene (Sheffield-Moore et al. 1999), while in older men testosterone administration increased androgen receptor levels at one month, but androgen receptor levels returned to baseline at six months (Ferrando et al. 2002). In this same study, insulin-like growth factor-I levels were increased by testosterone and remained elevated at six months while IGFBP-4 (insulin-like growth factor binding

protein) was decreased. Snyder et al. (1999a) showed an increase in insulin-like growth factor levels over three years while Wittert et al. (2002) failed to show such an increase.

A number of studies have shown an increase in muscle mass with testosterone treatment in older men (Tenover 1992; Katznelson et al. 1996; Snyder et al. 1999a; Bebb et al. 2001; Wittert et al. 2002); however, an increase in muscle strength has been reported less commonly (Morley et al. 1993; Sih et al. 1997; Urban et al. 1995; Tenover 1996; Clague et al. 1999; Bakhshi et al. 2000; Ferrando et al. 2002). A major reason for this is that many studies failed to treat persons who were clearly hypogonadal. Wittert et al. (2002) demonstrated that in persons who had borderline hypogonadism there was an increase in muscle mass but not in muscle strength. In addition, different doses of testosterone, i.e., injection versus patch versus oral, have been used; and Hikim et al. (2002) showed that the effects of testosterone on muscle are sensitive to dose. It has also been suggested that upper-limb muscles may be more sensitive to testosterone effects than are lower-limb muscles. These discrepant results require carefully designed studies to resolve the differences in results.

The composition of muscle is another important variable in assessing muscle function. Human skeletal muscle is composed of three basic fiber types—I, IIa, and IIx. Fiber typing is determined by ATPase histochemical staining intensities and immunohistochemical analysis using antibodies that identify myosin heavy chains (Scott et al. 2001). Type I fibers display slower contraction rates and more oxidative physiology while type II fibers are faster and use anaerobic metabolism. The plasticity of muscle fibers as displayed by their ability to convert between fiber types depending upon the demand on the muscle is a unique physiologic mechanism that supports possible interventions to optimize fiber composition

Figure 3



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and muscle function (Baldwin and Haddad 2001). Examination of muscle fiber types during aging shows a primary loss of type II fibers (Lexell 1995; Scott et al. 2001). A similar pattern of loss of muscle mass occurs in human muscle during prolonged exposure to microgravity (Fitts et al. 2001). The loss of muscle fibers in

frail elders can be reversed by weight-lifting exercises (Singh et al. 1999). Regarding androgen effects on skeletal muscle fiber type, norandrolone administration to rats increased muscle diaphragm size by increasing type IIa and IIx muscle fibers (Lewis et al. 2002).

Finally, the primary site of testosterone action may not be the muscle fiber, but rather the satellite cell or muscle stem cell. It has recently been observed that the testosterone-induced increase in muscle size is associated with an increased number of satellite cells as well as hypertrophy of both type I and II fibers. Testosterone may promote differentiation of a primordial stem cell into the myogenic lineage rather than the adipocyte lineage (Sinha-Hikim et al. 2002). If so, this could explain the increased age-related deposition of fatty streaks into muscle as testosterone levels decline. Changes in protein synthesis seen in response to testosterone mentioned above may thus reflect effects on stem cell differentiation pathways.

EFFECT OF TESTOSTERONE ON BONE DENSITY

Hypogonadism is a well-known risk factor for osteoporosis in men (Leder et al. 2001), and both surgical and medical castration reduce bone mineral density rapidly in men (Stepan et al. 1989; Smith et al. 2001). However, the relative roles of androgens and estrogens in bone development and in the maintenance of bone mass in men are unclear. Several observations suggest that androgens have a direct role in maintaining the skeleton. First, osteoblasts have androgen receptors (Colvard et al. 1989). Second, bone mineral density increases dramatically during puberty in boys, and peak cortical bone density is higher in men than in women (Bonjour et al. 1991). Cortical thickness and bone formation rates are reduced in androgen-resistant rats (Vanderschueren et al. 1993). Finally, both aromatizable and nonaromatizable androgens stimulate osteoblast activity and prevent castration-induced bone loss (Kasperk et al. 1990; Van Kesteren et al. 1996).

Several observations, however, suggest that the effects of androgens are mediated, at least in part, by their conversion to estrogens. First, osteoblasts have estrogen receptors as well as the ability to convert testosterone to estrogen by the aromatase

enzyme (Eriksen et al. 1988; Tanaka et al. 1993). Second, serum estradiol levels correlate better with bone density than do serum testosterone levels (Khosla et al. 1998; Amin et al. 2000). Orchiectomy and aromatase inhibition reduce bone density similarly in rats (Vanderschueren et al. 1996), and estrogen alone can maintain bone mass in castrated male rats and people (Cruess and Hong, 1978; Van Kesteren et al. 1996). Perhaps the best evidence for an important role for estrogens in bone in male humans is the finding that men with inactivating mutations in either the estrogen receptor gene (Smith et al. 1994) or the aromatase gene (Morishima et al. 1995; Carani et al. 1997) develop osteoporosis. This strongly suggests that estrogen plays a vital role in achieving normal peak bone mineral density in men. In adult men, additional recent evidence suggests that both androgens and estrogens play important roles in maintaining bone homeostasis (Falahati-Nini et al. 2000; Leder et al. 2001).

As men age, both cortical and trabecular bone mineral density decline (Wishart et al. 1995; Riggs et al. 1981; Zmuda et al. 2000). It is unclear whether this decline is due to age-related declines in either serum testosterone or estradiol, or to other bone-regulating factors such as parathyroid hormone, vitamin D, growth hormone, and insulin-like growth factor (Feldman et al. 2002; Ferrini and Barrett-Connor 1998; Denti et al. 2000; van den Beld et al. 2000) (Figure 3). When Snyder et al. (1999b) randomly administered transdermal testosterone or placebo to men over age 65 with serum testosterone levels below 475 ng/dL (mean 367 ng/dL), testosterone administration increased mean serum testosterone levels to 625 ng/dL, but changes in spine bone density were similar in testosterone-treated and placebo-treated men. Only in men whose serum testosterone levels were particularly low before treatment (i.e., < 200 ng/dL), did it appear that testosterone therapy improved spine bone mineral

density. Kenny et al. (2001) have also shown that transdermal testosterone prevented femoral neck bone loss, decreased body fat, and increased lean body mass and lower-extremity muscle strength in healthy older men with low bioavailable testosterone levels. Although these findings suggest that testosterone replacement may benefit some elderly men, further studies, particularly studies that examine fracture rates as an endpoint, are needed.

TESTOSTERONE, BRAIN FUNCTION AND COGNITION

Similar to the situation with bone, most studies of the effects of sex steroid hormones on brain function have centered on estrogen rather than testosterone, and few of those have focused on cognition. Testosterone, which crosses the blood-brain barrier easily, affects brain function via androgen receptor selectively distributed throughout the brain (Simerly et al. 1990). Additionally, androgens are probably synthesized in the brain and play an important role in its development, growth, maturation, and differentiation (Stoffel-Wagner 2001). Steroid biosynthetic and metabolic enzymes, in particular estrogen synthetase (aromatase), 5 α -reductase, and P450scc, are found in brain regions closely associated with memory and related functions (Lephart et al. 2001). Specific neurobiological effects of testosterone with direct relevance to cognition include increasing serotonergic activity in cerebral cortex and amygdala (Fink et al. 1999), choline acetyl transferase activity in the hippocampus (Nakamura et al. 2002), and neurokinin and cholecystokinin in amygdala and hypothalamus, and decreasing dopamine release in mesolimbic tract (Rubinow and Schmidt, 1996). Testosterone also attenuates β -amyloid-induced toxicity in cultured hippocampal neurons (Pike 2001), reduces neuronal secretion of A β peptide in cultured primary cortical neurons

(Gouras et al. 2000), and promotes α -cleavage processing of amyloid precursor protein, resulting in the formation of soluble, nontoxic fragments (Goodenough et al. 2000). Additionally, testosterone improves memory in the senescence-accelerated SAMP8 mouse, an animal model of β -amyloid overproduction, and decreases levels of amyloid precursor protein in this mouse (Flood et al. 1995). Finally, testosterone is aromatized to estradiol in the brain, which reportedly enhances the activity of several neurobiological systems closely associated with cognition (Cholerton et al. 2002).

To date the results of basic science investigations are nicely corroborated with those from clinical trials and epidemiological studies. Although not universally confirmed, administration of testosterone has been shown to enhance cognitive function in the majority of clinical studies. Of note, the cognition-enhancing efficacy of testosterone is not generalized but confined to specific domains. For example, weekly injections of testosterone enanthate for four to six weeks in two independent studies significantly enhanced spatial memory of healthy older men (Cherrier et al. 2001; Janowsky et al. 1998). Likewise, results from another study suggested that a three-month administration of testosterone via scrotal patch produced significant enhancement in spatial memory (Janowsky et al. 1994). In addition to spatial memory, findings from clinical studies indicated that treatment with testosterone enhanced working memory and verbal fluency as well (Janowsky et al. 2000; O'Connor et al. 2001).

Data from epidemiological studies also support the cognition-enhancing efficacy of testosterone. Moffat et al. (2002) have shown that, in men in the Baltimore Longitudinal Study of Aging, higher free testosterone levels are associated with better maintained cognition with age for some, but not all, of the cognitive domains. Cross-sectional studies have also suggested that higher

concentrations of endogenous testosterone are associated with enhanced cognitive function in older men (Morley et al. 1997b; Barrett-Connor et al. 1999). Further support for a direct relationship between testosterone and cognition is provided by the reported gender-related differences in performance on neuropsychological tests. Men reportedly outperform women on tests of visuospatial memory while women do better on tests of verbal fluency and perceptual speed (Linn and Petersen 1985; Halpern 1992).

The cognition-enhancing efficacy of testosterone, however, is not uniformly supported by findings from all clinical studies. For example, in one study biweekly injections of 200 mg of testosterone cypionate for 12 months did not improve performance on several tests of cognition for older hypogonadal men (Sih et al. 1997). Similarly, a single-dose injection of testosterone enanthate in another study blocked the practice effects in verbal fluency and did not enhance performance on any other cognitive test (Wolf et al. 2000). Finally, data from an epidemiological study showed no relationship between plasma levels of testosterone and spatial function of healthy men (Kampen and Sherwin 1996).

Overall, there is increasing evidence from both basic science and human studies to indicate that men with higher levels of serum testosterone maintain specific domains of cognitive function, and that administration of testosterone can enhance selective domains of cognition in men with lower levels of testosterone. Thus, supplementation could be a viable therapeutic option for cognitive deficits generally associated with healthy aging and neurodegenerative diseases. However, findings of prior clinical studies are preliminary and need to be systematically confirmed in larger clinical studies before the therapeutic potential of testosterone can be firmly established.

TESTOSTERONE AND PROSTATE

One of the greatest fears of supplementing older men with testosterone is an increased risk for benign prostate hyperplasia and/or prostate cancer (Jeyaraj et al. 2000; Guay et al. 2000), two diseases with high incidence and prevalence in older men. Prostate tissue contains large quantities of androgen receptor, and the presence of testosterone appears to be permissive for development and progression of both prostate diseases, although prostate cancer is also found in hypogonadal men (Morgentaler et al. 1996) with rates comparable to those of the general population. While prostate cancer is a common diagnosis and its incidence is increasing (Levi et al. 1998; La Rosa et al. 2000; Majeed et al. 2000; Brewster et al. 2000), mortality rates have remained stable over the years. The 10–15-year survival rates for localized disease are very high but do not seem to be affected by treatment (Chodak et al. 1994; Johansson et al. 1997). It appears that with the widespread screening for prostate-specific antigen, we are detecting many prostate cancers that would otherwise have remained clinically irrelevant. Latent prostate cancer is even more common (Suen et al. 1974; Rullis et al. 1975), as autopsy series of all ages around the globe give a 12 percent to 38 percent range (Breslow et al. 1977; Yatani et al. 1982).

Several studies have compared testosterone levels in prostate cancer patients at the time of diagnosis with those of age-matched controls (Hulka et al. 1987; Haapiainen et al. 1988; Gustafsson et al. 1996; Schatzl et al. 2000). In all studies, testosterone in prostate cancer patients was the same or lower than that of controls. There are numerous longitudinal studies on the association of testosterone levels with the future risk for prostate cancer development (Nomura et al. 1988; Barrett-Connor et al. 1990; Carter et al. 1995; Vatten et al. 1997; Heikkila et al. 1999), with

surveillance periods of up to 25 years. All studies except one (Gann et al. 1996) failed to detect any association. In contrast, an association between insulin-like growth factor and prostate cancer has been reported by most studies published recently (Mantzoros et al. 1997; Shaneyfelt et al. 2000; Harman et al. 2000). In a rodent model of age-dependent prostatic hyperplastic growth, the susceptible lobes of the prostate showed decreased rates of cell death and increased proliferation in conjunction with increased androgen receptor levels in old rats relative to young (Banerjee et al. 2000; Banerjee et al. 2001). In apparent contrast to these results, testosterone repressed tumor growth when a human prostate cell line was grown in immunodeficient male mice (Umekita et al. 1996; Joly-Pharaboz et al. 2000), although in one of those studies the tumor eventually did regrow even in the presence of androgen.

There are dozens of reports on prospective testosterone replacement studies over the last 20 years, some of which have surveillance periods of up to 6.5 years. No increase in prostate cancer has been reported in response to testosterone supplementation. The prostate-specific antigen may rise initially, appears to plateau later, and generally stays within normal limits; and the same is true for prostate volume. Furthermore, in some studies prostate volume, prostate-specific antigen, and urinary tract symptoms actually decreased (Tenover 1992; Holmang et al. 1993; Wallace et al. 1993; Douglas et al. 1995; Svetec et al. 1997; Nieschlag et al. 1999; Snyder et al. 2000; Jin et al. 2001; De Rosa et al. 2001; Pechersky et al. 2002). The mode of testosterone replacement may affect the results. The higher increases of prostate-specific antigen and volume were reported with parenteral testosterone and appear less pronounced or nonexistent in studies utilizing patch, gel, or oral testosterone undecanoate. However, no definitive conclusions can be drawn yet because of methodological shortcomings

of the studies available to date, including (a) short duration of follow-up in the vast majority of them, (b) the highly variable selection of patients (considering the effects of age, race, and ethnicity on prostate cancer incidence, trials controlling for these factors are needed), and (c) lack of standardized method of outcome reporting, e.g., different methods are used for prostate volume estimation, and only a few studies used transrectal ultrasound and/or biopsies of the prostate for assessment.

TESTOSTERONE AND ERECTILE FUNCTION

Testosterone clearly improves libido when administered to older men (Morales et al. 1997). Testosterone is also required for male genital differentiation and development, manifestation of male secondary sexual characteristics, and the initiation and maintenance of spermatogenesis. Nocturnal penile tumescence and ejaculatory volume is also dependent on testosterone. Male-type libido appears to require more than a minimum amount of serum testosterone (Bagatell et al. 1994). Erectile dysfunction, on the other hand, appears to be affected by many factors, including psychological factors, vascular and intrinsic penile disease, and autonomic neuropathy, in addition to hypogonadism. Thus, although no direct relationship between hypogonadism and human erectile dysfunction has been established, they are both common manifestations of aging (Korenman et al. 1990).

Explorations of biologic mechanisms underlying testosterone effects on erectile function come primarily from rodent studies. In rats, testosterone appears to enhance the erectile responses through regulation of the enzyme nitric oxide synthase. Because nitric oxide synthase is important for stimulating dilation of blood sinuses in erectile tissues, this action of testosterone could have an important positive local effect on erectile capability. Castration reduces erectile response

and nitric oxide synthase activity and gene expression, and either testosterone or dihydrotestosterone restores both to normal (Park et al. 1999; Chamness et al. 1995). The restoration of nitric oxide synthase activity by testosterone occurs in penile neurons (Baba et al. 2000) and pelvic ganglia, for which 40 percent of nitric oxide synthase-containing neurons also contain androgen receptors (Schirar et al. 1997). A single study has reported improved responses to sildenafil (Viagra) when testosterone is replaced (Tariq et al. 2003). In comparing erectile responses to testosterone or dihydrotestosterone, one study provided evidence that dihydrotestosterone is the more potent steroid (Park et al. 1999).

TESTOSTERONE, INSULIN SENSITIVITY AND THE CARDIOVASCULAR SYSTEM

There are few animal studies focused on the effect of testosterone on insulin sensitivity and cardiovascular function. In one study, insulin sensitivity in selected muscles was decreased by castration and restored by testosterone replacement at physiologic levels, but not by superphysiologic levels of testosterone (Holmang and Bjorntorp 1992). This study did not control for conversion of testosterone into estradiol, so it is not clear whether the effect is attributable entirely to androgenic (i.e., androgen receptor-mediated) effects of testosterone. Regarding the cardiovascular system, one study reported that either testosterone or estradiol treatment restored maximal serotonin-induced vasodilation in hearts isolated from castrated male rats (Moyses et al. 2001). The testosterone effect was probably mediated via conversion to estrogen because the estrogen level in these rats was similar to that seen in naïve or estrogen-treated castrated females. In a low-density lipoprotein receptor-deficient mouse model of atherogenesis, surgical castration accelerates and subsequent testosterone or estradiol

administration retards progression of atherosclerosis (Nathan et al. 2001). The effect of testosterone is antagonized by concomitant use of an aromatase inhibitor, suggesting this effect of testosterone is also mediated at least in part by conversion to estradiol in the vessel wall. In exploring the mechanism of this effect, Mukherjee et al. (2002) reported that, like estradiol, an aromatizable androgen such as testosterone, but not the nonaromatizable androgen dihydrotestosterone, inhibits TNF alpha-induced vascular cell adhesion molecule-1 expression in human umbilical vein endothelial cells. Vascular cell adhesion molecule expression is an early event in atherogenesis. Testosterone was less effective in the presence of an inhibitor of aromatase or the estrogen receptor blockers, suggesting that estradiol is the active steroid.

Morley (2003) has recently reviewed and summarized the effects of testosterone supplementation on a wide variety of physiological systems in older men. In addition to the effects already documented above, both testosterone and dihydrotestosterone generally raise insulin-like growth factor levels and lean body mass while decreasing fat mass. They also lower serum lipids, including total cholesterol, high-density lipoprotein and low-density lipoprotein. Coronary artery disease is associated with low testosterone levels in men (English et al. 2000) and short-term supplementation with testosterone has been used to treat angina, but long-term studies are needed to determine whether there are any deleterious effects on the cardiovascular system.

AGING-RELATED CHANGES IN TESTOSTERONE FUNCTION

Most large studies measuring testosterone and various indices of free or bioavailable testosterone have concluded that testosterone serum level declines progressively and monotonically with age at the rate of about 1 percent per year beginning

in the fourth decade of life (Figure 1). Observers agree that by the seventh to eighth decade of life, a significant number of otherwise healthy men have levels of free or bioavailable testosterone that, if observed in men under the age of 45, would undoubtedly lead to their classification as “hypogonadal.” Whether the fraction qualifying is 40 percent of these men (Morley et al. 2000) or 65 percent (Harman et al. 2001), the fact remains that the number of such men is substantial and growing. The extent to which this observed reduction in testosterone levels contributes to loss of bone, lean body/skeletal muscle mass, gain in body fat, and frailty remains to be determined. There are relatively few published studies about this issue. As reviewed above, preliminary evidence suggests that testosterone replacement has some potential to reduce these concomitants of aging in men, but the interactions of testosterone with diet, exercise, and other hormone deficiencies or excesses characteristic of aging are largely unexplored.

THE NEED FOR A LARGE CLINICAL STUDY

To date, a number of small-scale randomized trials of testosterone replacement therapy in older men have been conducted with reports of positive effects on bone mineral density, muscle strength, and body composition; i.e., increase in lean body mass and a decrease in fat mass (Wang et al. 2001; Snyder et al. 2000; Snyder et al. 2001; Blackman et al. 2002). Improvement in certain aspects of cognition and sense of well-being has also been reported (Wang et al. 2000). Results have been variable, and this may well be related to differences in dosage, route of administration, and serum concentrations of testosterone achieved, as well as in the initial degree of hypogonadism of the subjects studied. One study found that the men with the lowest serum testosterone levels showed the largest improvement in bone mineral density. None of the trials

has included a sufficient number of subjects to adequately assess possible effects on the incidence of prostate cancer and cardiovascular events. Given the increasing use of testosterone by the public, it is crucial to establish the risk/benefit ratio of testosterone replacement therapy so that patients and doctors can make informed choices. A large-scale study with approximately 6,000 subjects (3,000 taking testosterone with an equal number taking placebo) has been estimated to be necessary to ascertain changes in the incidence of prostate cancer and coronary events. This number of subjects, based on the need to define possible risks, should be enough to firmly establish the possible benefits of testosterone replacement therapy.

The need to conduct a large-scale clinical trial is underscored by the history of hormone replacement therapy (estrogen plus progesterone) in women. Decades of epidemiologic research led to wide-spread use of this treatment for postmenopausal women. Only recently, as a result of randomized placebo-controlled, large-scale clinical trials have we come to believe that the prior interpretation based on limited epidemiologic data was misleading, and the total morbidity attendant to treatment with hormone replacement therapy is increased, not decreased, with greater likelihood of cardiovascular events and development of breast cancer [see JAMA 288: 321-333 (2002)]. These data, which could only be attained from a large-scale clinical trial, are causing millions of women and their physicians to reassess the wisdom of continuing on hormone replacement therapy. Similarly, a large-scale clinical trial of testosterone replacement therapy for older men is required to inform men and their physicians about the risks and benefits of treatment with testosterone. The small numbers of older men who have participated in prior studies are not sufficient to determine the clinical value of

this treatment. The study should focus on the response of older hypogonadal men to an extended period of testosterone replacement therapy (five to six years). Ideally, desirable endpoints to measure include muscle mass and strength; bone mineral density and incidence of bone fractures; body composition; insulin sensitivity, glucose tolerance, and incidence of diabetes mellitus; cognitive function and incidence of dementia; sense of well-being and incidence of dysthymia; polycythemia; sleep apnea; progression of atherosclerosis; and, most important, the incidence of cardiovascular events, e.g., myocardial infarction, stroke, and cardiac death; the development of benign prostatic hypertrophy requiring invasive therapy; and the development of clinical prostate cancer. Some of the major questions about how to conduct such a trial have been addressed in some detail earlier (Bhasin et al. 1998).

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RESEARCH AGENDA

Beyond the need for a large clinical study to determine whether testosterone supplementation is both safe and efficacious, a number of other questions need to be addressed as well. These questions are briefly discussed below.

Assays for testosterone

Better technology is needed for assaying circulating levels of testosterone, particularly for clinical laboratories. Because testosterone occurs both free and bound to serum proteins, it is important to be able to accurately assay how much is in each fraction, i.e., free, weakly bound to protein and tightly bound to specific sex hormone binding globulin. Current estimates are that about 44 percent of circulating testosterone is bound to sex hormone binding globulin, and the other 56 percent is either free or loosely bound to albumin (Dunn et al. 1981). However, these estimates are controversial because assays are

variable and levels are subject to diurnal variation, leading to some confusion about what the normal ranges are and when an individual could be considered to be hypogonadal.

An important aspect of this problem is that commonly employed assays for “free testosterone” in commercial laboratories that depend on competitive binding of testosterone to ion exchange resins or glass beads are poorly reproducible and do not correlate well with carefully conducted measurements of free testosterone by dialysis or of bioavailable testosterone by ammonium sulfate precipitation; even standard radioimmunoassay or enzyme-linked immunosorbent assay measurement of total testosterone in various laboratories has been shown to result in significant variation in results obtained on replicate samples (Rosner 1997; Winters et al. 1998; Vermeulin et al. 1999; Rosner 2001; Morley et al. 2002). In the absence of reliable, well-standardized methodologies for determining blood levels of testosterone, little progress can be made in defining age-related hypogonadism chemically and functionally. If we cannot accurately determine which men have low biological action of testosterone based on serum measurements, it will be impossible to select appropriate populations to study for risk/benefit ratios of testosterone replacement in older men because baseline testosterone will undoubtedly be a major determinant of who is likely to benefit.

Screening tests for hypogonadism

Although at least three screening questionnaires are currently in use to determine whether men are functionally hypogonadal, independent epidemiological validation of these questionnaires is lacking. A screening questionnaire based more on quantifiable symptoms of hypogonadism is needed. Testosterone measured in saliva shows that testosterone declines with increasing age

(Ben-Aryeh et al. 1989; Read et al. 1981). While salivary testosterone is a proxy for free or weakly bound testosterone and it may be adequate as a screening test, it is not recommended as a diagnostic test.

Clinical trials

Many earlier clinical trials have suffered from a variety of methodological shortcomings, including insufficient numbers of subjects; short duration of follow-up; lack of adequate control for effects of age, race, ethnicity; medication use and illness; and lack of standardized methods of reporting. Care must be taken to address all of these issues in any new clinical trials undertaken. The source of the androgen also requires careful consideration. Use of a testosterone gel rather than an injection is recommended both to avoid large swings in testosterone levels leading to nonphysiological levels and because a gel is the form most likely to be used by the public if a trial indicates safety and efficacy.

Biological studies

Additional research is needed to:

- Identify levels of testosterone that better define physiological or functional hypogonadism for target tissues and organs
- Better understand the relative roles of testosterone, dihydrotestosterone, and E2 in mediating the effects of bioavailable testosterone on these target tissues and organs
- Determine the number and location of androgen receptors in target tissues and organs and whether these change with age

- Improve our knowledge of age-related changes in tissue-specific sensitivity and dose response to testosterone at both the molecular and clinical level.

In general, research is needed to understand the molecular mechanisms for the effects of testosterone on bone mineral density, regional fat distribution and metabolism, muscle mass and strength; physical performance and function, cognitive function and mood, libido and sexual activity; cardiovascular performance, and immune function, if any. Studies in the frail elderly population are particularly needed.

POLICY ISSUES

In the August 19, 2002, issue of the *New York Times*, Gina Kolata (2002) reported that two agencies of the U.S. government, the Department of Veterans Affairs and the National Institute on Aging, had recently announced it would not go ahead with a planned 6,000-man clinical trial to study testosterone replacement therapy in aging men. This was apparently due to concerns about whether a clinical trial could be designed that would protect the study's subjects from potential health risks such as prostate cancer, heart attacks, and strokes. Such concerns are consistent with the recent report that estrogen plus progesterone replacement therapy is not as safe as originally had been assumed [see *JAMA* 288: 321–333 (2002)]. However, this raises the obvious question: How can the medical community obtain this information without conducting a long-term trial?

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Glossary

ANDROGEN—a generic term for a hormone that stimulates the activity of the accessory sex organs of the male and encourages the development of male sex characteristics.

ANDROGEN RECEPTOR—a protein, usually found in either the cell membrane or in the nucleus, that binds androgens, thereby stimulating a variety of cellular responses.

ANDROPAUSE—hormonal changes that occur in some men as they age, varying widely in intensity and age of onset.

AROMATASE—the enzyme that converts androgens directly into estrogens.

β-AMYLOID—a small protein normally found in brain tissue; increased concentrations are associated with Alzheimer's disease.

BENIGN PROSTATE HYPERPLASIA—a nonmalignant enlargement of the prostate gland.

DIHYDROTESTOSTERONE—a more potent form of androgen produced from testosterone.

DYSTHYMIA—form of chronic depression.

ESTRADIOL—the most potent naturally occurring estrogen in mammals, generated from testosterone by the enzyme aromatase.

ESTROGEN—a generic term for a hormone that stimulates the activity of accessory sex organs of the female and encourages the development of female sex characteristics.

GONADOTROPIN—a hormone capable of promoting growth of the gonads, i.e., sex organs, produced in the pituitary gland.

GONADOTROPIN RELEASING HORMONE—a hormone produced in the hypothalamus that stimulates production of gonadotropins by the pituitary gland.

HIPPOCAMPUS—a region of the brain associated with memory.

HYPERLIPIDEMIA—an elevated concentration of lipids in blood.

HYPERTROPHY—overgrowth of a particular tissue or organ.

HYPOGONADAL—inadequate function of the gonads, resulting in low androgen levels in blood.

HYPOTHALAMUS—a region of the brain involved in function of the autonomic nervous system.

INSULIN-LIKE GROWTH FACTOR—small protein resembling insulin that stimulates cell growth.

LUTEINIZING HORMONE—a specific form of gonadotropin that increases testosterone production from the testes.

ORCHIECTOMY—removal of one or both testes.

OSTEOBLAST—bone cells whose function is to make new bone.

OSTEOPOROSIS—disease resulting from the reduction in bone density, occurring primarily in postmenopausal women and elderly men, increasing the risk of bone fracture.

POLYCYTHEMIA—an elevated concentration of red blood cells.

SATELLITE CELLS—stem cells found in skeletal muscle.

SEX HORMONE BINDING GLOBULIN—a protein circulating in blood that strongly binds sex steroid hormones.

SLEEP APNEA—absence of breathing during sleep.

TESTOSTERONE—a naturally occurring androgen in mammals produced primarily in the testes but also produced in the ovary in females.

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