Annu. Rev. Med. 2005. 56:117–37
doi: 10.1146/annurev.med.56.082103.104518

First published online as a Review in Advance on Aug. 20, 2004

ANDROPAUSE: Is Androgen Replacement Therapy Indicated for the Aging Male?*

Rabih A. Hijazi[1] and Glenn R. Cunningham[1,2]
Departments of [1]Medicine and [2]Molecular and Cellular Biology, Baylor College of Medicine and VA Medical Center, Houston, Texas; email: rhijazi@bcm.tmc.edu; glennc@bcm.tmc.edu

Key Words hypogonadism, testosterone deficiency, testosterone replacement therapy

■ **Abstract** The number of men in the United States ≥65 years of age is projected to increase from 14,452,000 in 2000 to 31,343,000 in 2030. Approximately 30% of men 60–70 years of age and 70% of men 70–80 years of age have low bioavailable or free testosterone levels. Symptoms and findings of testosterone deficiency are similar to those associated with aging. They include loss of energy, depressed mood, decreased libido, erectile dysfunction, decreased muscle mass and strength, increased fat mass, frailty, osteopenia, and osteoporosis. Several small clinical trials indicate that testosterone replacement therapy can improve many of these findings; however, the studies have not been powered to assess potential risks, such as the need for invasive treatment of benign prostatic hyperplasia, development of a clinical prostate cancer, or cardiovascular events. Thus, the benefit/risk ratio of testosterone replacement therapy in aging men is not known.

INTRODUCTION

The United States and world populations are aging. The number of individuals in the United States aged 65 years and older is expected to rise from 35 million in 2000 to ∼71 million in 2030. Men are projected to comprise 43% of the population ≥65 years of age in 2030 (1).

Testosterone (T) is the most important circulating androgen in men. Twenty percent of healthy ambulatory men in their sixties and 30% of men in their seventies have lower T levels than 97.5% of healthy 20–45-year-old men (2) (Figure 1). Approximately 40%–50% of circulating T in men is bound with high affinity to sex hormone binding globulin (SHBG) (3). This portion of the circulating total T is not readily available to target tissues, whereas T bound to albumin and free T (1%–3%) are available to target tissues (4). The albumin-bound and free T are

*The U.S. Government has the right to retain a nonexclusive, royalty-free license in and to any copyright covering this paper.

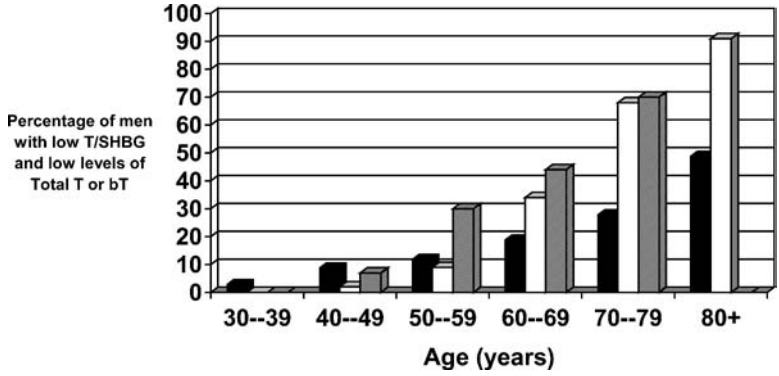

Figure 1 Prevalence of hypogonadism based on low levels of total testosterone, free testosterone index (T/SHBG), and bioavailable testosterone. The graph shows the percentage of the population with total testosterone levels <325 ng/dl (*black*), the percentage of the population with T/SHBG <0.153 nmol/nmol (*white*), and the percentage of the population with bioavailable testosterone (bT) levels <70 ng/dl (*grey*). Bioavailable testosterone was not measured in some age groups (2, 8).

referred to as the bioavailable or weakly bound T. The number of aging men with subnormal bioavailable or free T is considerably greater than the number of men with only low total T because SHBG levels increase with aging (5).

Symptoms and findings of T deficiency are similar to those associated with aging. They include loss of energy, depressed mood, decreased libido, erectile dysfunction, decreased muscle mass and strength, increased fat mass, frailty, osteopenia, and osteoporosis. Limited studies in men ≥65 years of age indicate that T replacement therapy (TRT) can improve many of these parameters. However, the studies have not been powered to assess the effects of TRT on potential risks, such as needing invasive treatment of benign prostatic hyperplasia, developing a clinical prostate cancer, or having a cardiovascular event. Thus, the benefit/risk ratio of TRT in aging men is not known. There is considerable evidence that TRT is effective in younger men with T deficiency. Because the benefits are known in younger men and the risks are low, the benefit/risk ratio is good.

TESTOSTERONE AND AGING

T Levels and Aging

Multiple cross-sectional and a few longitudinal studies have shown that serum T levels in men decrease with age (2, 5–7). Measures of age-related changes in total T underestimate changes in T available to target tissues. Several cross-sectional studies have shown an increase of SHBG with aging as well as a decrease in T and free T levels independent of body mass index (5–7). Longitudinal studies have confirmed these findings (2, 8, 9). Feldman et al. found that total T levels

decreased by 0.8% per year while bioavailable T fell by 2% per year and SHBG levels increased by 1.6% per year (9). These changes are due in part to a reduction in the number of Leydig cells in the testes that produce T (10).

The decline in T levels with aging, when associated with symptoms and signs of androgen deficiency, has been called andropause. This association has also been called androgen deficiency in the aging male (ADAM), partial androgen deficiency in the aging male (PADAM), or aging-associated androgen deficiency (AAAD). The term andropause is inaccurate because men do not have menses and because androgen secretion does not cease; it gradually decreases but usually continues at some level. However, "andropause" is widely used by the lay press and laymen as well as clinicians.

LH Levels and Aging

Luteinizing hormone (LH) levels increase slightly with aging (8, 11, 12). Tenover et al. studied older men and noted that pituitary secretion of LH was intact, but testicular secretion of T was impaired in some older men (13). The normal diurnal variation in T levels is blunted in aging men (13).

However, the majority of hypogonadal men over age 60 have low or inappropriately normal LH levels (14). Older men with low T levels typically have abnormal LH pulse frequency and reduced pulse amplitude, suggesting hypothalamic dysfunction (15, 16). Luboshitzky et al. found that less pulsatile T and more LH were secreted in healthy middle-aged men at night than in healthy young men (17). The association between T rhythm and REM sleep also was disrupted. Most investigators have concluded that the decline in nocturnal T with aging results from combined testicular and pituitary hypogonadism.

SHBG Levels and Aging

SHBG levels are affected by several conditions. SHBG levels are inversely correlated with increased total body fat and with subcutaneous and visceral adiposity (18, 19). Levels also vary inversely with hyperinsulinism in nondiabetic subjects (20). They seem to be an indicator of general adiposity rather than an index of altered insulin/glucose homeostasis in morbidly obese subjects. Hyperinsulinism also decreases SHBG synthesis by cultured hepatic cells (21). These observations have been interpreted to show that obesity causes insulin resistance and hyperinsulinism, and hyperinsulinism decreases SHBG levels. Hypothyroidism and the nephrotic syndrome also reduce SHBG levels. Estrogen (22), hyperthyroidism (23), some anticonvulsants (24), a high-phytoestrogen diet (25), hepatic cirrhosis (26), and aging increase SHBG levels.

Androgen Action and Metabolism of T

Androgen action appears to be mostly maintained with aging, though this has not been studied extensively. However, androgen binding sites in the hippocampus, penile tissues, and genital skin are decreased in aging men and animals (27, 28). It

is recognized that shortening of the CAG repeat in the androgen receptor increases androgen action, but it is not likely that this, per se, changes with aging (29). It will be important to determine if there are age-related changes in coactivators and corepressors that are important in mediating androgen action at the cellular level.

T is metabolized to dihydrotestosterone (DHT) and to estradiol in tissues that have 5α-reductase activity and/or aromatase activity. DHT is a very potent androgen at the tissue level. It contributes most of the androgenic effects in genital tissues, accessory sex organs and hair follicles. Five-alpha-reductase activity also is present in some areas of the brain and in bone (30). Aromatase activity is primarily present in adipose tissue, so most of the circulating estradiol and estrone in males comes from peripheral conversion of T and androstenedione (31). T production rates in young adult males range between 4 and 10 mg/d with an average of 6.6 mg/d (32). In men over age 65, the mean production rate decreases to 4.2 mg/d. Plasma levels of T reflect an age-related decrease in both secretion and the metabolic clearance rate.

POTENTIAL BENEFITS OF TESTOSTERONE REPLACEMENT THERAPY

Bone

Bone strength decreases with aging. Men undergo a gradual loss in bone mass beginning in their thirties. It is estimated that 2 million men in the United States have osteoporosis and that 1 in 8 men over age 50 will have an osteoporosis-related fracture (33). Risk factors for osteoporosis include family history of osteoporosis, smoking, excessive alcohol intake, physical inactivity, poor nutrition, vitamin D deficiency, inadequate calcium intake, hypogonadism, and use of some medications (e.g., glucocorticoids, anticonvulsants) (34). Osteopenia and osteoporosis are common in males with congenital causes of hypogonadism. It is clear that severe T deficiency occurring later in life also results in bone loss. For example, androgen deprivation therapy for prostate cancer has been shown to result in rapid bone loss, osteopenia, and osteoporosis (35, 36). Although less severe T deficiency in aging men appears to increase osteopenia and osteoporosis, population-based studies suggest that estrogen levels are better correlated with loss of bone mineral density in men (37–40).

Estrogen is very important in bone development in males, as illustrated by individuals with aromatase deficiency. Males with inactivating mutations of the aromatase gene develop osteopenia and osteoporosis that improve with estradiol therapy (41, 42). Estrogen also plays a major role in bone metabolism of older males (43). In aging men treated with a gonadotropin-releasing hormone (GnRH) agonist, a model of severe hypogonadism, estrogen decreases bone resorption markers and increases markers of bone formation. The investigators in these studies have estimated that two thirds of the effect of TRT is due to an estrogen effect (43, 44). Most of the estrogen in men is derived from the aromatization of T to estradiol and

androstenedione to estrone. Estradiol is more potent, but accurate measurement in males is difficult because assay sensitivity and accuracy are marginal at the low levels that are normal in men. Total estradiol levels are also affected by SHBG levels, so accurate measurements of free estradiol or bioavailable estradiol are most informative. Males have larger bones and greater bone mass than females, so androgen as well as estrogen is critical for the development of a normal male skeletal mass. T also may act directly on androgen receptors in bone cells or indirectly by modulating the action of cytokines or growth factor metabolism (45). In summary, both androgens and estrogens affect bone metabolism in men, and both may be reduced with aging and hypogonadism.

At least five published placebo-controlled trials have reported the effects of TRT on bone turnover markers and bone density in older men with low or low-normal baseline T levels (46–50). These trials included 13–108 men treated for 3–36 months. No trial examined the effects of TRT on fracture rates. Snyder et al. (49) included many men with low-normal total T levels. They found that TRT increased bone mineral density only when the baseline T level was low (<300 ng/dl). In contrast, Amory et al. (50) observed very significant changes in bone mineral density in men 65 and older with baseline T levels <350 ng/dl when treated for 3 y with T enanthate (∼150 mg/2 weeks). Because TRT increases estradiol levels as well as T levels, it is likely that some, if not most, of the effect is mediated by estrogen receptors.

Cognitive Function

Cognitive function decreases with aging. Most of the age-related changes in cognition are associated with vascular and/or degenerative diseases that cause anatomic changes in the central nervous system. The possibility that an age-related fall in T causes functional changes in cognition is of great interest. In a study involving 407 men aged 50–91 years at baseline and followed for an average of 10 years, Moffat et al. showed that higher free T indices were associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning, and a reduced rate of decline in visual memory (51). Men classified as hypogonadal had significantly lower scores on measures of memory and visuospatial performance and a faster decline in visual memory. In another study, low estradiol and high total and bioavailable T levels predicted better performance on several tests of cognitive function in older men (52).

T could exert its actions through androgen receptors that could modulate serotonin, dopamine, calcium, and acetylcholine signaling pathways. Androgen also increases neurite arborization to facilitate intercellular communication (53, 54). T can be aromatized in the brain to estrogen, and thus some of the effects of T may be mediated through its conversion to estradiol. Most of the effects of androgen on cognitive function are thought to be domain-specific. For example, observations that men outperform women in a variety of visuospatial skills suggest that androgens might enhance these skills (54). Results from five placebo-controlled

trials that have examined the effect of T on cognitive function were mixed (55–59). Some, but not all, of the trials found better verbal memory and spatial cognition in the T-treated men than in placebo-treated men, but no significant differences in other cognitive domains. Sih et al. (55) found no effect of T administration on cognition. Limitations of these trials include small sample sizes with heterogeneous patient characteristics, the use of a variety of neuropsychological tests (some that lack prior validation), and the use of different treatment protocols.

Body Composition, Strength, and Function

Aging is associated with an increase in fat mass, even if total body weight is maintained at a level achieved in the early twenties, and a decrease in lean body mass and strength. It is estimated that skeletal muscle mass decreases 35% between the ages of 20 and 80 (53). This sarcopenia associated with loss of strength leads to impairment of physical function, such as ability to arise from a chair, climb stairs, maintain balance, and generate gait speed. This impairment can result in loss of mobility, falls and fractures, loss of independence, and depression (60).

The cellular and molecular mechanisms by which androgens affect changes in fat-free mass, muscle mass, and strength are only partially understood. Androgen administration to sexually immature boys increased nitrogen retention. Other studies have observed increased protein synthesis and muscle hypertrophy. Multiple placebo-controlled trials in both younger and aging men with T deficiency have assessed changes in muscle strength and body composition measures in response to exogenous T. Most noted increases in fat-free mass and decreases in fat mass. Some, but not all, found significant improvements in leg and arm strength (50, 61–66). Bhasin et al. clearly demonstrated dose-related increases in skeletal muscle mass in young males (67). In other studies, the Bhasin group also demonstrated a dose-dependent increase in muscle mass and strength in younger men made hypogonadal with a GnRH agonist (68, 69). More recent studies have demonstrated that T caused dose-dependent increases in skeletal muscle mass in aging men (S. Bhasin, personal communication). Urban et al. investigated the effect of T supplementation on skeletal muscle in six healthy older men with serum T levels of 480 ng/dl or less. T injections were given for 4 weeks to produce serum levels equal to those of younger males (63). Raising T concentrations in elderly men increased skeletal muscle protein synthesis and strength in both right and left hamstring and quadriceps muscles. This increase may have been mediated by stimulation of the intramuscular IGF-I (insulin-like growth factor 1) system. Bakhshi et al. reported improvement in rehabilitation outcomes that included functional independence score and grip strength in older men treated with T (70). Androgen responsiveness appears to be maintained, at least in skeletal muscle, in aging men.

The effects of androgen on fat mass are interesting and incompletely understood. Males typically have more abdominal fat (visceral and subcutaneous) than females; hypogonadal males have increased fat mass with greater distribution to the buttocks and thighs, similar to what is seen in females. When hypogonadal males have

increased fat mass, TRT usually reduces it somewhat (typically by 2–3 kg). These changes have been noted in both younger and aging males (50, 65). Woodhouse et al. established a dose-responsive effect of T on fat mass (71). The mechanisms for these changes are thought to include stimulation of lipoprotein lipase and perhaps a reduction in stem cells that differentiate into adipose cells (72).

Mood and Depression

It is estimated that 2 million older Americans are depressed (73). Depression increases with aging. Although depression is not a part of the aging process, medical diseases associated with aging such as stroke, diabetes, and heart disease reduce physical activity and contribute to depression. It is estimated that 80% of older adults with depression improve when they receive an antidepressant medication, psychotherapy, or both (73). T may have a beneficial effect on mood and depression, as it is known to modulate the serotonin and dopamine pathways.

Administration of androgens appears to improve positive aspects of mood and reduce negative aspects of mood such as irritability in young, hypogonadal men (74), and improvements in mood are usually observed in clinical trials involving mostly middle-aged men (75). In several small, uncontrolled studies of depressed hypogonadal men, T was effective in reducing depressive symptoms (76). T supplementation was more effective than placebo in restoring libido and energy and alleviating depressed mood in men infected with HIV (77). In another study of 19 men with low baseline T levels being treated for refractory depression with standard antidepressive therapy, Pope et al. found that patients using T gel had greater improvements than placebo controls in measures of mental health as assessed by Hamilton Depression Index scores (78).

The relationship between the age-related decline in endogenous T levels and changes in mood has not been studied extensively, and findings have been inconsistent. In cross-sectional studies, Barrett-Connor et al. reported increased scores on the Hamilton Depression Index with increasing age, and they also observed that increased scores in these aging men correlated inversely with bioavailable T levels (52). Only limited TRT studies in T-deficient men have been reported. There are also some indications from other placebo-controlled trials that men likely to show an improvement are those who are already depressed or who are ill or frail. However, most of the studies were small and of short duration (3 months or less).

Sexual Function

T and its metabolite, DHT, are critical for development of the external genitalia, prostate, seminal vesicles, vas deferens, and spermatogenesis. They also appear to be essential for development and maintenance of libido or sexual desire, and they probably have a direct effect on penile erections. Jain et al. conducted a meta-analysis evaluating the effects of T supplementation on erectile dysfunction (79). They found an overall response rate of 57%, but some of the men were not hypogonadal. TRT affects nocturnal erections and penile rigidity in hypogonadal males

(80, 81). Although erections can be induced in hypogonadal men in response to sexually explicit visual stimuli, TRT improves penile rigidity (82). These clinical observations are consistent with findings in lower animal models (83). TRT normalizes cavernous-nerve-stimulated erections in castrated rats. This effect is reduced by concomitant treatment with a 5α-reductase inhibitor, indicating that the effect is mediated by DHT. T or DHT increases neuronal and endothelial nitric oxide synthase activity, and this is thought to increase nitric oxide, the most potent relaxor of corpora cavernosal smooth muscle. In the rat, neurons responsible for penile vascular smooth muscle relaxation possess both androgen receptors and nitric oxide synthase. In a recent study in humans (84), T appears to have a direct vascular effect in the corpora cavernosa, mediating the ability of nitric oxide to relax corporal tissue and allow increased penile blood flow. The T concentrations needed to maintain normal sexual activity appear to be in the low-normal range, or possibly slightly less than 300 ng/dl in healthy young men.

At least 10 placebo-controlled trials have evaluated sexual function with T therapy. The study populations were often relatively young; in four trials, the mean age was 52 or less. Overall, T may be beneficial to men with low baseline T levels (85, 86). Studies in men with normal baseline T levels usually show no effect on erection and inconsistent effects on libido (87, 88). Thus, T appears to potentiate libido by a central effect and erections by central and peripheral effects.

Aging is associated with a reduction in sexual activity (89). How much T deficiency contributes to this decline is unclear. Aging men also have multiple vascular and neurological conditions that can reduce sexual drive and penile erections. Furthermore, sexual activity can persist in some men for more than a year following medical or surgical castration. Thus, comorbid medical conditions in an aging population are common, and they may affect the response to TRT. Studies assessing the effects of TRT on sexual function in aging, T-deficient men are very limited. Few studies have been conducted in a placebo-controlled manner using validated questionnaires or objective measurements of penile tumescence.

POTENTIAL RISKS OF TESTOSTERONE REPLACEMENT THERAPY

Cardiovascular

Cardiovascular disease remains the number one killer for men in the United States. It is twice as common in men as in women at any age during the reproductive years (90). Whether this is due to protective effects of estrogen, harmful effects of T, or other factors has been the subject of many studies. In one study, estrogen therapy in men with cardiovascular disease increased cardiovascular events (91). Furthermore, estrogen therapy in postmenopausal women also appears to cause some increase in cardiovascular events (92, 93). Epidemiological studies in men show a neutral or a negative correlation between T levels and cardiovascular disease (90). Most studies have examined the effects of T on individual factors that contribute to

cardiovascular disease, such as lipids, apoproteins, insulin sensitivity, endothelin levels, platelet function, clotting parameters, vascular reactivity, arterial intimal thickening, and hematocrit. The correlations vary depending on the specific endpoint. Most of these trials were of short duration (4 weeks to 36 months) and involved a relatively small number of men. TRT tends to lower the levels of total, LDL, and HDL cholesterol (94). A meta-analysis concluded that the effects of T enanthate on total, HDL, and LDL cholesterol were small but significant (95). It will require a large clinical trial with hard endpoints to determine if TRT affects cardiovascular disease and events.

Red Blood Cells

Prior to puberty, boys and girls have similar hemoglobin levels and hematocrits. However, boys' hematocrits rise 3–4 percentage points by the end of puberty, and this difference is maintained during adulthood in the absence of disease. T stimulates erythropoietin secretion by the kidney and has a direct effect on the bone marrow to stimulate red blood cell precursors (96).

Most studies of the effect of T on red blood cells in hypogonadal males have reported an increase in hematocrit and hemoglobin levels. In men under age 50, it is rare to see the hematocrit rise above 50% in the absence of underlying pulmonary or cardiac disease. By contrast, among men over 60, hematocrits of $>52\%$ in response to TRT are not unusual. The cause(s) for the excessive rise in hematocrit is not fully known, but it occurs more frequently in men who are treated with larger doses of parenteral T esters than in those receiving transdermal TRT (97).

Prostate

Prostate cancer is the most common nonskin cancer in males (98). The greatest risk factor is age, with $>75\%$ of new diagnoses occurring in men over 65. The autopsy prevalence of microscopic or occult prostate cancers is low in men who were in their forties, but $\sim$40%–50% of men in their sixties have occult prostate cancer and 80% by age 80 (99). The prevalence of prostate cancer has been reported for the 2950 men (age 62–91 years) who were assigned to the placebo group in the Prostate Cancer Prevention Trial. Men who never had a prostate-specific antigen (PSA) level of >4.0 ng/ml or an abnormal digital rectal examination underwent a prostate biopsy after being in the study for seven years (100). Prostate cancer was diagnosed in 15.2% of the men, and 14.9% had a Gleason score of 7 or higher. The prevalence of prostate cancer for men with PSA levels of <0.5 ng/ml was 6.6%, 10.1% for values of 0.6–1.0 ng/ml, 17% for values of 1.1–2.0 ng/ml, 23.9% for values of 2.1–3.0 ng/ml, and 26.9% for values of 3.1–4.0 ng/ml. High-grade cancers (7 or greater) increased from 12.5% with the lowest PSA levels to 25% in the group with PSA of 3.1–4.0 ng/ml. Most of the occult cancers never become clinical cancers. However, it is not known whether TRT will increase this risk.

Two prospective cohort studies and 10 nested case-control studies have correlated T levels with future development of prostate cancer (101). None of these

studies found a positive correlation between total T or bioavailable T (four studies) levels and future prostate cancer; however, the nested case-control study reported by Gann et al. found a positive relationship after T was adjusted for the SHBG level (101a). Although it is reasonable to adjust for SHBG, this study found that high total T levels and low SHBG levels were correlated with future prostate cancer. One usually sees total T levels increase with increasing SHBG. As suggested by Hsing, it is desirable to correlate prostate cancer with measures of androgen action, rather than a single blood level at some point in the past (101b), but such studies are lacking.

The influence of T on prostate carcinogenesis and other prostate outcomes remains poorly defined. Some animal studies suggest that T may be a weak carcinogen in susceptible animals. Most studies indicate that T can act as a tumor promoter at normal physiological levels (102–104). The direct relevance of these studies to humans is uncertain (105). Despite the lack of evidence implicating androgens in carcinogenesis, it is clear that prostate cancer rarely, if ever, develops in an environment devoid of androgens, and the majority of prostate carcinomas require androgens for growth. Androgen ablation causes regression of metastatic prostate carcinoma, but cancer cells that survive androgen deprivation ultimately proliferate, causing relapse and androgen-independent disease.

Assessments of the risks of TRT have focused primarily on the potential for increasing the incidence of clinical prostate cancer and/or increasing the need for invasive treatment of benign prostatic hyperplasia. Clinical trials of TRT in men $\geq$65 years of age are limited in sample size and treatment duration. They have not been powered to address the issue of prostate cancer risk. Most of the randomized trials excluded men with prostate abnormalities and were conducted in healthy older men. There usually is some increase in the mean PSA level in the treatment arm as compared with either the placebo group or baseline values. The largest randomized trial in older men, which was also one of the longest, evaluated PSA levels in 108 men at 3 and 6 months and then every 6 months for the 3 years of the study (65). PSA increased significantly in the T-treated group by 6 months and then leveled off. One prostate cancer case was diagnosed in the T group. A meta-analysis of placebo-controlled trials (S. Bhasin, personal communication) found somewhat more prostate cancer diagnoses among men treated with T, but these men were also more likely to have prostate biopsies. Given the prevalence of occult prostate cancer in this age group, the usefulness of this analysis is limited. Rhoden & Morgentaler evaluated hypogonadal men prior to and during 12 months of TRT (106). Of the 75 men, 55 had benign prostate biopsies [i.e., without prostatic intraepithelial neoplasia (PIN–)] and 20 had prostatic intraepithelial neoplasia without frank cancer (PIN+) prior to initiating therapy. Biopsy was repeated if digital rectal examination findings changed or PSA increased by 1 ng/ml or greater. PSA levels were similar at baseline and after one year of TRT in men with or without PIN. Only one man in the PIN+ group had cancer on repeat biopsy. The authors conclude that after one year of TRT, men with PIN do not have a greater increase in PSA or a significantly increased risk of cancer than men without PIN lesions. Definitive

resolution of this issue will require a large clinical trial that insures equal numbers of men in both arms (T and placebo) undergo prostate biopsies. It is estimated that such a trial will require 6000 men be randomized to TRT or placebo and treated for an average of 5 years.

Another approach to reducing the risk of developing prostate cancer is to combine TRT with a chemopreventive agent. The Tenover group did utilize the 5α-reductase inhibitor, finasteride, in combination with TRT, but the number of men in each group was too small to permit any conclusions regarding the ability of finasteride to prevent prostate cancer (50). The large Prostate Cancer Prevention Trial (PCPT) was powered to examine the effects of finasteride on the development of prostate cancer (107). The PCPT found that finasteride reduced biopsy-diagnosed prostate cancer by 25% (18.4% versus 24.8%), but overall, some 5.1% of men in the placebo group and 6.4% of those in the finasteride group had a cancer with a Gleason score of 7 or higher (relative risk, 1.27; 95% confidence interval, 1.07 to 1.50).

T treatment of T-deficient men does increase prostate volume to that seen in eugonadal age-matched men (108). When men with mild to moderate bladder outlet symptoms are selected for clinical trials with T, significant worsening of lower urinary tract symptoms is rarely a problem.

Benign prostatic hyperplasia (BPH) is a noncancerous enlargement of the prostate that can obstruct urine flow. Around 90% of males 70 and older have some symptoms of lower urinary tract obstruction (109), but nonprostatic factors commonly contribute to lower urinary tract symptoms in men and women. Treatment with a 5α-reductase inhibitor reduces prostate volume by only 15%–20%, but longer studies indicate that finasteride significantly reduces progression of BPH, urinary retention, and need for invasive treatment (110). It may be that combining TRT with a 5α-reductase inhibitor will reduce the risk of progression of BPH and need for invasive treatment of BPH. Long-term use of a 5α-reductase inhibitor to prevent BPH progression or prostate cancer is not routinely advised at present, but this could change as we learn more about the long-term effects of these inhibitors on development of prostate cancer and progression of BPH.

TESTOSTERONE DELIVERY SYSTEMS

Overview

The goals of TRT are to reduce symptoms and prevent morbidity. The serum T levels that will achieve these goals are likely to vary depending on the target organs. For example, most of the benefits of T on libido and erectile function can be achieved when T levels are in the low-normal range. In contrast, T has dose-dependent effects on skeletal muscle. Ideally, therapy should restore or maintain libido and erectile function; improve or maintain virilization, muscle mass and strength, and bone density; and alleviate other symptoms related to hypogonadism. Absolute contraindications to TRT include prostate or breast cancer.

TABLE 1 Testosterone delivery systems

Oral	Subcutaneous	Intramuscular	Transdermal
fluoxymesterone	testosterone cypionate	testosterone pellets	testosterone patch
methyl testosterone	testosterone enanthate		testosterone gel
testosterone undecanoate	testosterone propionate		
buccal testosterone	testosterone undecanoate*		
SARM*			

*Experimental.

Oral

The U.S. Food and Drug Administration (FDA) has approved several T delivery systems (Table 1). Soon after the synthesis of T, chemists sought to inhibit its rapid metabolism by the liver when T was given orally. Addition of a 17-alpha alkyl group to T caused some reduction in first-pass catabolism by the liver. However, oral alkylated androgens should not be used in men for TRT because of poor efficacy unless given in divided doses of 40–50 mg/d. At these doses, side effects include cholestasis, cystic disease of the liver, and hepatoma (111, 112). Oral T undecanoate is available in Canada and Europe. When T undecanoate is suspended in oil, it is taken up by the intestinal lymphatics, and ultimately enters the superior vena cava. Even though hepatic first-pass metabolism is prevented, a daily dose of 180–240 mg must be given in divided doses to be effective (113). In 2003, the FDA approved an oral bioadhesive T tablet (114). The tablet adheres to the gum. As it becomes hydrated, T is released into the oral cavity where it is absorbed into the systemic circulation. Tablets must be replaced every 12–14 h. In the phase III study, some men dropped out within the first two weeks because they could not tolerate having a foreign substance in the mouth or because dentures tended to dislodge the tablet. However, ~85% of men who completed the study achieved T levels within the physiological range most of the 24 h.

Parenteral

The lipophilic esters (T propionate, enanthate, and cypionate) are suspended in oil, producing a depot with slow release when injected intramuscularly. The pharmacokinetics are suboptimal. Peak levels usually are supernormal and nadir values may be subnormal. The variation in serum T levels may cause mood changes. There is evidence that this delivery system causes excessive erythrocytosis more frequently than transdermal therapy (115). T propionate is too short-acting to be used for chronic replacement therapy. Peak levels occur 48–72 h after administration of either T cypionate or T enanthate (116). Although intramuscular administration of T cypionate or enanthate is biologically effective, these treatments can be associated with symptoms, especially when the interval between injections is longer than 2 weeks. Injection of 50–200 mg of T enanthate every 1 or 2 weeks, respectively, provides the most physiological serum levels of T (116). One goal is

midnormal serum level of T midway between injections. As a general guide, the level of T at the nadir should be somewhat above the lower limit of normal. This form of TRT costs ~$300–600/year. Some patients can self-inject an androgen, and others have a spouse or friend do this for them. A return to the physician's office for T injections significantly increases the cost.

T Pellets

T pellets are effective but have not been very popular in the United States. The need for a small incision and use of a retention suture to keep them in place limits their acceptance (117). The ability of pellets to maintain T levels within the normal range for 3–4 months is desirable in younger men, but this feature carries risk in aging men.

Transdermal Patches

Transdermal administration of T was introduced in the United States in 1994 as a scrotal patch. The patch was available in a 40 or 60 cm^2 size, which delivered 4 and 6 mg of T daily, respectively (118). Serum levels peaked 3–5 h after application (119). The patch was applied daily after bathing and worn for 24 h. Subsequently, nonscrotal T patches were developed (120). Delivery of 5 mg of T/day requires a permeation enhancer to increase transdermal absorption of T. The patch is applied daily to the arm, hip, or abdomen, and serum levels peak 3–8 h later. The FDA has approved two torso patches, but only one patch currently is marketed. Skin rash is common with this patch, and the annual cost ranges from $800 to $2280.

Transdermal Gels

The FDA approved the first T gel in 2000 and a second gel in 2003 (121, 122). The gels are applied daily to nongenital skin. One gel is available in packets of 2.5 g (25 mg of T) and 5 g (50 mg of T), and the other comes in a dispenser that delivers approximately 2.5 or 5 g of the gel. Serum levels plateau within a few days and are relatively stable when the gel is applied daily. Skin rashes are uncommon. The gels dry quickly but, theoretically, skin contact can transfer T to a female or a child. Patients are thus advised to apply the gel to the upper arm or abdomen, where it can be covered. The published pharmacokinetics indicate that there may be some differences between the two T gels, but limited comparative data are available in the same patients. The annual cost is approximately $2400.

INVESTIGATIONAL ANDROGENS

Several other androgens are under investigation, including a long-acting intramuscular form of T undecanoate (123). Several pharmaceutical companies have programs to develop nonsteroidal selective androgen receptor modulators (SARMs). As with selective estrogen receptor modulators (SERMs), the goal is to stimulate some tissues that normally are androgen-responsive and to avoid others. This is

particularly beneficial in older men, in whom it is desirable to stimulate skeletal muscle, bone, external genitalia, and the brain but to avoid stimulation of the prostate. It is not clear, however, whether any single compound can have all of the beneficial effects and also spare the prostate. A particular challenge is to have a positive effect on bone and perhaps the brain, since estradiol, a metabolite of T, is responsible for some of the T effect in these tissues. It is not likely that nonsteroidal SARMs or their metabolites will stimulate both androgen and estrogen receptors.

MONITORING

Documentation that TRT achieves adequate serum levels is essential. This monitoring should be done 1–3 months after starting therapy. Ideally, therapy should provide physiological serum T levels (400–600 ng/dl) and physiological DHT and estradiol levels. Periodic follow-up of patients on TRT is essential, especially in men over age 50. The clinical response and potential side effects should be monitored at 3, 6, and 12 months and then annually. Some side effects of therapy can be attributed to T itself and others to the delivery system. They include acne, worsening of lower urinary tract symptoms, exacerbation of erythrocytosis, and worsening sleep apnea. Lipid disturbances usually are not significant, so lipid monitoring frequency is similar to that in eugonadal men. Gynecomastia may result from aromatization of T to estradiol. It is also possible that androgens might cause an occult prostate cancer to increase in size and to become clinically detectable. The care provider should inquire about obstructive urinary symptoms and obstructive sleep apnea before and after initiation of therapy in men aged >40. A postvoid residual urine volume, urinary flow rate, or sleep study may be warranted. As noted, 17-α alkylated androgens can cause liver toxicity. T injections are more likely than other modes of delivery to cause fluctuations in mood and excessive erythrocytosis. T patches frequently cause skin reactivity and dermatitis. A hematocrit, PSA, digital rectal examination, and breast examination should be performed at baseline, at 3, 6, and 12 months, and then annually in men aged >50. African Americans or men who have a first-degree relative with prostate cancer should have annual measurements of PSA and a digital rectal examination of the

TABLE 2 Comparison of the dose, peak, and frequency of administration of commonly prescribed testosterone delivery systems

Delivery system	Route	Dose	Peak (hours)	Frequency
T enanthate/cypionate	intramuscular	50–200 mg	48–72	every 1–2 weeks
patch (Androderm®)	transdermal	5 mg	3–8	Daily
gel (Androgel®)	transdermal	2.5–10 g	Flat	Daily
gel (Testim®)	transdermal	2.5–10 g	3–10	Daily
buccal (Striant®)	oral	30 mg	10–12	Q 12 h

prostate starting at age 40. Referral to an urologist is indicated for PSA >4.0 ng/ml or if PSA changes by >0.45 ng/ml per year over 2 years (124).

CONCLUSION

Endogenous T levels decline with aging, and they may be responsible for some of the symptoms and findings associated with aging. Several studies suggest that some symptoms and signs may be improved by TRT, but neither potential benefits nor potential risks are fully known. A large-scale trial is needed to determine the benefits and risks of TRT in aging men. At this time it is premature to make a general recommendation about T supplementation in older men.

There currently are several T delivery systems. These systems can provide physiological blood levels of T in most aging men, but they differ significantly in their pharmacokinetic properties (Table 2). If TRT is provided to an aging man, it is essential that hematocrit and PSA be monitored and digital rectal examination of the prostate performed on a prescribed basis. Bone mineral density should be assessed at baseline and every 1–2 years in men with T scores below –2 (i.e., bone mineral density 2 standard deviations below the mean value in young adults of the same sex and race).

The *Annual Review of Medicine* is online at http://med.annualreviews.org

LITERATURE CITED

1. U.S. Census Bureau. 2004. http://www.census.gov/ipc/www/usinterimproj/natprojtab02a.xls
2. Harman SM, Metter EJ, Tobin JD, et al. 2001. Longitudinal effects of aging on serum total and free T levels in healthy men. Baltimore Longitudinal Study of Aging. *J. Clin. Endocrinol. Metab.* 86:724–31
3. Dunn JF, Nisula BC, Rodbard D. 1981. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. *J. Clin. Endocrinol. Metab.* 53:58–68
4. Pardridge WM. 1981. Transport of protein-bound hormones into tissues in vivo. *Endocrine Rev.* 2:103–23
5. Deslypere JP, Vermeulen A. 1984. Leydig cell function in normal men: effect of age, life-style, residence, diet, and activity. *J. Clin. Endocrinol. Metab.* 59:955–62
6. Gray A, Feldman HA, McKinlay JB. 1991. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *J. Clin. Endocrinol. Metab.* 73:1016–25
7. Morley JE, Charlton E, Patrick P, et al. 2000. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism* 49:1239–42
8. Morley JE, Kaiser FE, Perry HM III, et al. 1997. Longitudinal changes in T, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism* 46:410–13
9. Feldman HA, Longcope C, Derby CA, et al. 2002. Age trends in the level of serum T and other hormones in

middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J. Clin. Endocrinol. Metab.* 87: 589–98

10. Neaves WB, Johnson L, Porter JC, et al. 1984. Leydig cell numbers, daily sperm production, and serum gonadotropin levels in aging men. *J. Clin. Endocrinol. Metab.* 49:756–73
11. Baker HW, Burger HG, de Kretser DM, et al. 1976. Changes in the pituitary-testicular system with age. *Clin. Endocrinol.* 5:349–72
12. Harman SM, Tsitouras PD. 1980. Reproductive hormones in aging men. I. Measurement of sex steroids, basal luteinizing hormone, and Leydig cell response to human chorionic gonadotropin. *J. Clin. Endocrinol. Metab.* 51:35–40
13. Tenover JS, Matsumoto AM, Plymate SR, et al. 1987. The effects of aging in normal men on bioavailable T and luteinizing hormone secretion: response to clomiphene citrate. *J. Clin. Endocrinol. Metab.* 65:1118–26
14. Korenman SG, Morley JE, Mooradian AD, et al. 1990. Secondary hypogonadism in older men: its relation to impotence. *J. Clin. Endocrinol. Metab.* 71:963–69
15. Deslypere JP, Kaufman JM, Vermeulen T, et al. 1987. Influence of age on pulsatile luteinizing hormone release and responsiveness of the gonadotrophs to sex hormone feedback in men. *J. Clin. Endocrinol. Metab.* 64:68–73
16. Tenover JS, Matsumoto AM, Clifton DK, et al. 1988. Age-related alterations in the circadian rhythms of pulsatile luteinizing hormone and T secretion in healthy men. *J. Gerontol. Med. Sci.* 43: M163–69
17. Luboshitzky R, Shen-Orr Z, Herer P. 2003. Middle-aged men secrete less T at night than young healthy men. *J. Clin. Endocrinol. Metab.* 88:3160–66
18. Couillard C, Gagnon J, Bergeron J, et al. 2000. Contribution of body fatness and adipose tissue distribution to the age variation in plasma steroid hormone concentrations in men: the HERITAGE Family Study. *J. Clin. Endocrinol. Metab.* 85:1026–31
19. Abate N, Haffner M, Garg A, et al. 2002. Sex steroid-hormones, upper body obesity and insulin resistance. *J. Clin. Endocrinol. Metab.* 87:4522–27
20. Phillips GB, Jing T, Heymsfield SB. 2003. Relationships in men of sex hormones, insulin, adiposity, and risk factors for myocardial infarction. *Metabolism* 52:784–90
21. Plymate SR, Jones RE, Matej LA, et al. 1988. Regulation of sex hormone binding globulin (SHBG) production in Hep G2 cells by insulin. *Steroids* 52:339–40
22. Anderson DC. 1974. Sex-hormone-binding globulin. *Clin. Endocrinol.* 3: 69–96
23. Lovejoy JC, Smith SR, Bray GA, et al. 1997. Effects of experimentally induced mild hyperthyroidism on growth hormone and insulin secretion and sex steroid levels in healthy young men. *Metabolism* 46:1424–28
24. Motta E. 2000. Epilepsy and hormones. *Neurol. Neurochir. Pol.* 33(Suppl. 1):31–36
25. Adlercreutz H, Hockerstedt K, Bannwart C, et al. 1987. Effect of dietary components, including lignans and phytoestrogens, on enterohepatic circulation and liver metabolism of estrogens and on sex hormone binding globulin (SHBG). *J. Steroid Biochem.* 27:1135–44
26. Selby C. 1990. Sex hormone binding globulin: origin, function and clinical significance. *Ann. Clin. Biochem.* 27:532–41
27. Tohgi H, Utsugisawa K, Yamagata M, et al. 1995. Effects of age on messenger RNA expression of glucocorticoid, thyroid hormone, androgen and estrogen receptors in postmortem human hippocampus. *Brain Res.* 700:245–53
28. Roehrborn CG, Lange JL, George FW,

et al. 1987. Changes in amount and intracellular distribution of androgen receptor in human foreskin as a function of age. *J. Clin. Invest.* 79:44–47

29. Lamb DJ, Weigel NL, Marcelli M. 2001. Androgen receptors and their biology. *Vitam. Horm.* 62:199–30
30. Russell DW, Wilson JD. 1994. Steroid alpha-reductase: two gene/two enzymes. *Annu. Rev. Biochem.* 63:25–61
31. Simpson ER, Zhao Y, Agarwal VR, et al. 1997. Aromatase expression in health and disease. *Recent Prog. Horm. Res.* 52:185–13
32. Vermeulen A. 1976. Plasma levels and secretion rate of steroids with anabolic activity in man. *Environ. Qual. Saf.* Suppl. 5:171–80
33. NIH Osteoporosis and Related Bone Diseases National Resource Center. 2003. *Fast facts on osteoporosis.* http://www.osteo.org/osteolinks.asp
34. National Institute of Arthritis and Musculoskeletal and Skin Diseases. 2003. *Osteoporosis: progress and promise.* http://www.niams.nih.gov/hi/topics/osteoporosis/opbkgr.htm
35. Dawson NA. 2003. Therapeutic benefit of bisphosphonates in the management of prostate cancer-related bone disease. *Exp. Opin. Pharmacother.* 4:705–16
36. Smith MR. 2003. Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. *Cancer* 97:789–95
37. Greendale GA, Edelstein S, Barrett-Connor E. 1997. Endogenous sex steroids and bone mineral density in older women and men: the Rancho Bernardo Study. *J. Bone Miner. Res.* 12: 1833–43
38. Slemenda CW, Longcope C, Zhou L, et al. 1997. Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. *J. Clin. Invest.* 100:1755–59
39. van den Beld AW, de Jong FH, Grobbee DE, et al. 2000. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density and body composition in elderly men. *J. Clin. Endocrinol. Metab.* 85:3276–82
40. Szule P, Munoz F, Claustrat B, et al. 2001. Bioavailable estradiol may be an important determinant of osteoporosis in men: the MINOS study. *J. Clin. Endocrinol. Metab.* 86192–99
41. Herrmann BL, Saller B, Janssen OE, et al. 2002. Impact of estrogen replacement therapy in a male with congenital aromatase deficiency caused by a novel mutation in the CYP19 gene. *J. Clin. Endocrinol. Metab.* 87:5476–84
42. Maffei L, Murata Y, Rochira V, et al. 2004. Dysmetabolic syndrome in a man with a novel mutation of the aromatase gene: effects of testosterone, alendronate, and estradiol treatment. *J. Clin. Endocrinol. Metab.* 89:61–70
43. Khosla S, Melton LJ 3rd, Atkinson EJ, et al. 1998. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *J. Clin. Endocrinol. Metab.* 83: 2266–74
44. Leder BZ, LeBlanc KM, Schoenfeld DA, et al. 2003. Differential effects of androgens and estrogens on bone turnover in normal men. *J. Clin. Endocrinol. Metab.* 88:204–10
45. Wergdal JE, Baylink DJ. 1996. Mechanism of action of androgens on bone cells. In *Pharmacology, Biology, and Clinical Applications of Androgens: Current Status and Future Prospects*, ed. S Bhasin, HL Gabelnick, JM Spieler, et al., pp. 259–64. New York: Wiley-Liss
46. Christmas C, O'Connor KG, Harman SM, et al. 2002. Growth hormone and sex steroid effects on bone metabolism and bone mineral density in healthy aged women and men. *J. Gerontol. A Biol. Sci. Med. Sci.* 57:M12–18

47. Tenover JS. 1992. Effects of T supplementation in the aging male. *J. Clin. Endocrinol. Metab.* 75:1092–98
48. Kenny AM, Prestwood KM, Gruman CA, et al. 2001. Effects of transdermal T on bone and muscle in older men with low bioavailable T levels. *J. Gerontol. A Biol. Sci. Med. Sci.* 56:M266–72
49. Snyder PJ, Peachey H, Hannoush P. 1999. Effect of T treatment on bone mineral density in men over 65 years of age. *J. Clin. Endocrinol. Metab.* 84:1966–72
50. Amory JK, Watts NB, Easley KA, et al. 2004. Exogenous T or T with finasteride increases bone mineral density in older men with low serum T. *J. Clin. Endocrinol. Metab.* 89:503–10
51. Moffat SD, Zonderman AB, Metter EJ, et al. 2002. Longitudinal assessment of serum free T concentration predicts memory performance and cognitive status in elderly men. *J. Clin. Encrinol. Metab.* 87:5001–7
52. Barrett-Connor E, Goodman-Gruen D, Patay BL. 1999. Endogenous sex hormones and cognitive function in older men. *J. Clin. Endocrinol. Metab.* 84:3681–85
53. Bhasin S, Buckwalter JG. 2001. T supplementation in older men: a rational idea whose time has not yet come. *J. Androl.* 22:718–31
54. Maccoby EE, Kaclin CN. 1974. *The Psychology of Sex Differences.* Stanford, CA: Stanford Univ. Press
55. Sih R, Morley JE, Kaiser FE, et al. 1997. T replacement in older hypogonadal men: a 12-month randomized controlled trial. *J. Clin. Endocrinol. Metab.* 82:1661–67
56. Janowsky JS, Oviatt SK, Orwoll ES. 2000. Sex steroids modify working memory. *J. Cogn. Neurosci.* 12:407–14
57. Cherrier MM, Asthana S, Plymate S, et al. 2001. T supplementation improves spatial and verbal memory in healthy older men. *Neurology* 10:57:80–88
58. Kenny AM, Bellantonio S, Gruman CA, et al. 2002. Effects of transdermal T on cognitive function and health perception in older men with low bioavailable T levels. *J. Gerontol. A Biol. Sci. Med. Sci.* 57:M321–25
59. Janowsky JS, Oviatt SK, Orwoll ES. 1994. T influences spatial cognition in older men. *Behav. Neurosci.* 108:325–32
60. Roubenoff R, Hughes VA. 2000. Sarcopenia: current concepts. *J. Gerontol. A. Biol. Sci. Med. Sci.* 55:M716–24
61. Bhasin S, Bross R, Storrer TW, et al. 1998. Androgens and muscles. In *T: Action, Deficiency, Substitution*, ed. E Nieschlag, HM Behre, pp. 210–27. Berlin: Springer-Verlag
62. Griggs RC, Kingston W, Jozefowicz RF, et al. 1989. Effect of T on muscle mass and muscle protein synthesis. *J. Appl. Physiol.* 66:498–503
63. Urban RJ, Bodenburg YH, Gilkison C, et al. 1995. T administration to elderly men increases skeletal muscle strength and protein synthesis. *Am. J. Physiol.* 269:E820–26
64. Field AE, Colditz GA, Willett WC, et al. 1994. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. *J. Clin. Endocrinol. Metab.* 79:1310–16
65. Snyder PJ, Peachey H, Hannoush P, et al. 1999. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J. Clin. Endocrinol. Metab.* 84:2647–53
66. Ferrando AA, Sheffield-Moore M, Paddon-Jones D, et al. 2003. Differential anabolic effects of T and amino acid feeding in older men. *J. Clin. Endocrinol. Metab.* 88:358–62
67. Bhasin S, Storer TW, Berman N, et al. 1996. The effects of supraphysiologic doses of T on muscle size and strength in normal men. *N. Engl. J. Med.* 335:1–7
68. Sinha-Hikim I, Artaza J, Woodhouse L, et al. 2002. Testosterone-induced

increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. *Am. J. Physiol. Endocrinol. Metab.* 283:E154–64

69. Storer TW, Magliano L, Woodhouse L, et al. 2003. Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. *J. Clin. Endocrinol. Metab.* 88:1478–85
70. Bakhshi V, Elliott M, Gentili A, et al. 2000. T improves rehabilitation outcomes in ill older men. *J. Am. Geriatr. Soc.* 48:550–53
71. Woodhouse LJ, Gupta N, Bhasin M, et al. 2004. Dose-dependent effects of testosterone on regional adipose tissue distribution in healthy young men. *J. Clin. Endocrinol. Metab.* 89:718–26
72. Sinha-Hikim I, Roth SM, Lee MI, et al. 2003. Testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number in healthy, young men. *Am. J. Physiol. Endocrinol. Metab.* 285:E197–205
73. National Institute of Mental Health. 2003. *Men and depression.* http://menanddepression.nimh.nih.gov/infopage.asp?id=l0#men
74. Margolese HC. 2000. The male menopause and mood: T decline and depression in the aging male—Is there a link? *J. Geriatr. Psychol. Neurol.* 13: 93–101
75. Wang C, Alexander G, Berman N, et al. 1996. T replacement improves mood in hypogonadal men—a clinical research study. *J. Clin. Endocrinol. Metab.* 81:3578–83
76. Wang C, Swedloff RS, Iranmanesh A, et al. 2000. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. *J. Clin. Endocrinol. Metab.* 85:2839–53
77. Grinspoon S, Corcoran C, Stanley T, et al. 2000. Effects of hypogonadism and T administration on depression indices in HIV-infected men. *J. Clin. Endocrinol. Metab.* 85:60–65
78. Pope HG Jr., Cohane GH, Kanayama G, et al. 2003. T gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am. J. Psychiatry* 160:105–11
79. Jain P, Rademaker AW, McVary KT. 2000. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J. Urol.* 164:371–75
80. Cunningham GR, Hirshkowitz M, Korenman SG, et al. 1990. Testosterone replacement therapy and sleep-related erections in hypogonadal men. *J. Clin. Endocrinol. Metab.* 70:792–97
81. Arver S, Dobs AS, Meikle AW, et al. 1996. Improvement of sexual function in T deficient men treated for 1 year with a permeation enhanced testosterone transdermal system. *J. Urol.* 155:1604–8
82. Carani C, Granata AR, Bancroft J, et al. 1995. The effects of T replacement on nocturnal penile tumescence and rigidity and erectile response to visual erotic stimuli in hypogonadal men. *Psychoneuroendocrinology* 20:743–53
83. Mills TM, Lewis RW. 1999. The role of androgens in the erectile response: a 1999 perspective. *Mol. Urol.* 3:75–86
84. Aversa A, Isidori AM, Spera G, et al. 2003. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. *Clin. Endocrinol. (Oxf.)* 58:632–38
85. Davidson JM, Camargo CA, Smith ER. 1979. Effects of androgen on sexual behavior in hypogonadal men. *J. Clin. Endocrinol. Metab.* 48:955–58
86. Skakkebaek NE, Bancroft J, Davidson DW, et al. 1981. Androgen replacement with oral T undecanoate in hypogonadal men: a double blind controlled study. *Clin. Endocrinol.* (*Oxf.*) 14:49–61
87. Schiavi RC, White D, Mandeli J, et al. 1997. Effect of T administration on

sexual behavior and mood in men with erectile dysfunction. *Arch. Sex. Behav.* 26:231–41
88. Benkert O, Witt W, Adam W, et al. 1979. Effects of T undecanoate on sexual potency and the hypothalamic-pituitary-gonadal axis of impotent males. *Arch. Sex. Behav.* 8:471–79
89. Davidson JM, Chen JJ, Crapo L, et al. 1983. Hormonal changes and sexual function in aging men. *J. Clin. Endocrinol. Metab.* 57:71–77
90. Wu FC, von Eckardstein A. 2003. Androgens and coronary artery disease. *Endocr. Rev.* 24:183–17
91. The Coronary Drug Project Research Group. 1973. The Coronary Drug Project. Findings leading to discontinuation of the 2.5-mg day estrogen group. *JAMA* 226:652–57
92. Grady D, Herrington D, Bittner V, et al. 2002. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 288:49–57
93. Anderson GL, Limacher M, Assaf AR, et al. 2004. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 291:1701–12
94. Kenny AM, Prestwood KM, Gruman CA, et al. 2002. Effects of transdermal T on lipids and vascular reactivity in older men with low bioavailable T levels. *J. Gerontol. A Biol. Sci. Med. Sci.* 57:M460–65
95. Whitsel EA, Boyko EJ, Matsumoto AM, et al. 2001. Intramuscular T esters and plasma lipids in hypogonadal men: a meta-analysis. *Am. J. Med.* 111:261–69
96. Shahidi NT. 1973. Androgens and erythropoiesis. *N. Engl. J. Med.* 289:72–80
97. Dobs AS, Meikle AW, Arver S, et al. 1999. Pharmacokinetics, efficacy, and safety of a permeation-enhanced T transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J. Clin. Endocrinol. Metab.* 84:3469–78
98. American Cancer Society. 2003. *What are the key statistics about prostate cancer?* http://www.cancer.org/docroot/STT/stt_0_2003
99. Sakr WA, Grignon DJ, Crissman JD, et al. 1994. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20–69: an autopsy study of 249 cases. *In Vivo* 8:439–43
100. Thompson IM, Pauler DK, Goodman PJ, et al. 2004. Prevalence of prostate cancer among men with a prostate-specific antigen level $<$ or $=$ 4.0 ng per milliliter. *N. Engl. J. Med.* 350:2239–46
101. Rhoden EL, Morgentaler A. 2004. Risks of T-replacement therapy and recommendations for monitoring. *N. Engl. J. Med.* 350:482–92
101a. Gann PH, Hennekens CH, Ma J, et al. 1996. Prospective study of sex hormone levels and risk of prostate cancer. *J. Natl. Cancer Inst.* 21(88):1118–26
101b. Hsing AW. 1996. Hormones and prostate cancer: Where do we go from here? *J. Natl. Cancer Inst.* 88:1093–95
102. Noble RL. 1977. The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration. *Cancer Res.* 37:1929–33
103. Bosland MC. 2000. The role of steroid hormones in prostate carcinogenesis. *J. Natl. Cancer Inst. Monogr.* 27:39–66
104. Stanbrough M, Leav I, Kwan PW, et al. 2001. Prostatic intraepithelial neoplasia in mice expressing an androgen receptor transgene in prostate epithelium. *Proc. Natl. Acad. Sci. USA.* 98:10823–28
105. Marcelli M, Cunningham GR. 1999. Hormonal signaling in prostatic hyperplasia and neoplasia. *J. Clin. Endocrinol. Metab.* 84:3463–68
106. Rhoden EL, Morgentaler A. 2003. T replacement therapy in hypogonadal men

at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *J. Urol.* 170:2348–51

107. Thompson IM, Goodman PJ, Tangen CM, et al. 2003. The influence of finasteride on the development of prostate cancer. *N. Engl. J. Med.* 349:215–24
108. Behre HM, Bohmeyer J, Nieschlag E. 1994. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin. Endocrinol. (Oxf.)* 40: 341–49
109. National Institute of Diabetes and Digestive and Kidney Diseases. 2003. *Prostate enlargement: benign prostatic hyperplasia*. http://kidney.niddk.nih.gov/kudiseases/pubs/prostateenlargement/index.htm
110. McConnell JD, Roehrborn CG, Bautista OM, et al. 2003. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N. Engl. J. Med.* 349:2387–98
111. Westaby D, et al. 1977. Liver damage from long-term ethyl T. *Lancet* 2:262–63
112. Overly WL, Dankoff JA, Wang BK, et al. 1984. Androgens and hepatocellular carcinoma in an athlete. *Ann. Intern. Med.* 100:158–59
113. Gooren LJ. 1994. A ten-year safety study of the oral androgen T undecanoate. *J. Androl.* 15:212–15
114. Wang C, Swerdloff R, Kipnes M, et al. 2004. New T buccal system (Striant®) delivers physiologic T levels: pharmacokinetics study in hypogonadal men. *J. Clin. Endocrinol. Metab.* 89:3821–29
115. Snyder PJ, Lawrence DA. 1980. Treatment of male hypogonadism with T enanthate. *J. Clin. Endocrinol. Metab.* 51:1335–39
116. Handelsman DJ, Conway AJ, Boylan LM. 1990. Pharmacokinetics and pharmacodynamics of T pellets in man. *J. Clin. Endocrinol. Metab.* 71:216–22
117. Korenman SG, Viosca S, Garza D, et al. 1987. Androgen therapy of hypogonadal men with transscrotal T systems. *Am. J. Med.* 83:471–78
118. Cunningham GR, Cordero E, Thornby JI. 1989. T replacement with transdermal therapeutic systems. Physiological serum T and elevated dihydro T levels. *JAMA* 261:2525–30
119. Meikle AW, Mazer NA, Moellmer JF, et al. 1992. Enhanced transdermal delivery of T across nonscrotal skin produces physiological concentrations of T and its metabolites in hypogonadal men. *J. Clin. Endocrinol. Metab.* 74:623–28
120. Swerdloff RS, Wang C, Cunningham G, et al. 2000. Long-term pharmacokinetics of transdermal T gel in hypogonadal men. *J. Clin. Endocrinol. Metab.* 85:4500–10
121. Steidle C, Schwartz S, Jacoby K, et al. 2003. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J. Clin. Endocrinol. Metab.* 88:2673–81
122. von Eckardstein S, Nieschlag E. 2002. Treatment of male hypogonadism with T undecanoate injected at extended intervals of 12 weeks: a phase II study. *J. Androl.* 23:419–25
123. Bhasin S, Singh AB, Mac RP, et al. 2003. Managing the risks of prostate disease during T replacement therapy in older men: recommendations for a standardized monitoring plan. *J. Androl.* 24:299–11

Annual Review of Medicine
Volume 56, 2005

CONTENTS