

Metabolic and Behavioral Effects of High-Dose, Exogenous Testosterone in Healthy Men*

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ABSTRACT

In addition to their use as replacement therapy for hypogonadal males, androgens, particularly testosterone (T), are being explored as potential hormonal male contraceptive agents, alone or in combination with other compounds. Androgens have regulatory effects on a variety of physiological systems in addition to gonadotropin secretion and spermatogenesis. Therefore, as hormonal contraceptive regimens that alter serum T levels are explored, it is important to evaluate their effects on these aspects of normal male physiology.

The effects of exogenous T on suppression of spermatogenesis in 19 healthy men were recently compared, using a T dosage of 200 mg im/week for 20 weeks. Before treatment, the men were evaluated during a 3-month pretreatment period, and after treatment, they were followed for 4–6 months or until their sperm counts normalized. Because of the lack of information regarding the effects of exogenous T on nonreproductive physiology, we examined the effects of high-dose T on plasma lipids, calcium metabolism, and sexual behavior in our subjects.

Mean serum T and estradiol levels increased significantly during the treatment period. Plasma high-density lipoprotein (HDL) cholesterol levels decreased significantly within the first month and remained suppressed during the duration of T administration. At the end of the treatment period, mean plasma HDL cholesterol had decreased by $13 \pm 2\%$ ($P < 0.05$); plasma levels of HDL₂, HDL₃, and apoprotein AI also decreased significantly; mean levels of low density lipoprotein cholesterol and triglycerides were unchanged. After 1 month of the recovery

period, plasma HDL levels had returned to the baseline range.

Serum calcium levels decreased slightly during treatment; this decrease was statistically significant. Urinary calcium excretion did not change. Mean levels of serum intact PTH increased by $84 \pm 17\%$ ($P < 0.05$) during T administration; in contrast, 25-hydroxyvitamin D levels decreased by $16 \pm 4\%$ ($P < 0.05$), and 1,25-dihydroxyvitamin D levels did not change significantly. All markers of calcium metabolism returned to baseline during the posttreatment period.

Little change was found in self-reported sexual and aggressive behaviors during the study. There was a trend toward increased arousal and spontaneous erections during T administration, but this did not reach statistical significance. Frequency of sexual intercourse, masturbation, and kissing and fondling did not change, nor was the subjects' satisfaction in their relationships affected by T administration.

Mean body weight increased by 4.0 ± 0.5 kg. Approximately half the men noted mild acne. Body weight and acne symptoms returned to baseline during the recovery period.

These data demonstrate that the serum levels of T produced by administration of T enanthate, 200 mg im weekly, lead to suppressed levels of plasma HDL cholesterol, alterations in calcium metabolism, increased body weight, and in some men, mild acne. These results imply that T enanthate at this dosage is moderately supraphysiological and may be inappropriately high for long-term administration to large groups of normal men for the purpose of contraception. (*J Clin Endocrinol Metab* 79: 561–567, 1994)

IN addition to their use as replacement therapy for hypogonadal males, androgens, particularly testosterone (T), are being explored as potential hormonal male contraceptive agents, alone (1–5) or in combination with other compounds (2, 5–7). An optimal contraceptive regimen for men will effectively suppress spermatogenesis, resulting in azoospermia in a high percentage of men who use it properly. The regimen should be completely reversible; in addition, it should have no adverse effects on other physiological processes. Androgens are known to have effects on a variety of physiological systems in addition to spermatogenesis, including body composition, lipids, sexual function and behavior,

bone metabolism, and erythropoiesis (7–9). Therefore, as hormonal contraceptive regimens that alter serum T levels are explored, it is important to evaluate their effects on these aspects of normal male physiology.

Most studies of T effects on nonreproductive systems have used the paradigm of T replacement to androgen-deficient men. Less is known about the effects of exogenous T in healthy men. In one very recent study (10), administration of T enanthate to healthy men for 3 weeks resulted in significant suppression of plasma high-density lipoprotein (HDL) cholesterol, but in two other studies of slightly longer duration (11, 12), high-dose, exogenous T administration had no significant effects on plasma lipids in healthy men. However, the effects of long-term T administration have not been well studied. Although T deficiency is well known to cause osteopenia in men (13, 14), little is known about the effects of exogenous T on bone metabolism in healthy young males. Similarly, although several investigators have studied the effects of T replacement on sexual behavior in hypogonadal men (15, 16), in only a few recent studies have the effects of

Received January 13, 1994. Accepted April 28, 1994.

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* This work was supported by NIH Grants P50-HD-12629, HD-13527, and K0800890-01, Veterans Affairs Medical Research Funds, The Andrew W. Mellon Foundation, and the Clinical Research Center of the University of Washington (supported by NIH Grant RR-37).

high-dose T (17) or methyltestosterone (18) been examined in normal young men.

We have recently compared the effects of two regimens, both containing high-dose, exogenous T on spermatogenesis in healthy men (5). In that study, we administered T for 20 weeks at a dose of 200 mg im/week to 19 healthy young men. Because of the lack of information regarding the effects of exogenous T on nonreproductive physiology, we report now the effects of high-dose T on plasma lipids, calcium metabolism, and sexual behavior in our subjects.

Subjects and Methods

Subjects

Nineteen healthy men, ages 19–42, completed the study. These men were participating in a study of two potential male contraceptive regimens that use exogenous T (5). All of the men had normal medical histories, physical examinations, and screening laboratory studies. None of the men smoked, and none abused alcohol. None of the men was an elite athlete, although several men exercised regularly. Eight were married. Four of the other nine were not sexually active at the beginning of the study. All of the men signed informed consents, which were approved by the Human Subjects Committee of the University of Washington.

Clinical protocol

The study consisted of a 3- to 4-month baseline period, a 20-week treatment period, during which each subject received T enanthate, 200 mg im, weekly. Ten men were assigned randomly to receive the GnRH antagonist Nal-Glu, ([Ac-D2Nal¹, D4Cl Phe², D3Pal³, Arg⁵, DGLu⁶(AA), DAla¹⁰] GnRH), 100 µg/kg·day sc, as well; the other nine men received a saline placebo, 0.6–1.0 mL sc, instead of Nal-Glu. The study included a posttreatment period, which lasted 4–6 months for most of the men. Three men chose to end their participation after 16 weeks of hormone administration. Two of the men had made plans to leave the area for vacation; the other man chose not to continue because of local side effects from Nal-Glu. None of the men discontinued participation because of problems relating to T administration.

The pretreatment phase began in September–November; the treatment phase began in November–January; and the posttreatment phase began in April–June. During each phase of the study, fasting blood samples were drawn monthly for analysis of hormones, plasma lipids, and chemistry parameters. During the third month of the pretreatment, treatment, and posttreatment periods, an additional sample was collected for measurement of calcium-related parameters. At the time of this blood sample, subjects were also asked to collect a 24-h urine specimen during the next 2–3 weeks. During the treatment period, all monthly blood samples were drawn on day 7 after the preceding T injection, before any additional injections were administered; T levels therefore reflect the nadir (day 7) values. A single blood sample was also collected 2 days after T injection during the fourth month of the study to give an estimate of the highest T levels attained during the week.

Subjects attended a volunteer clinic each month. At these clinics, they were interviewed and examined by a physician, and they were asked to complete the behavioral questionnaire. Although subjects were not specifically required to maintain stable diet and exercise patterns during the study, they were requested to do so to the extent possible. At each visit, an investigator asked each subject about any changes in diet or exercise habits during the preceding month.

Three men left the area during the posttreatment period, and several other men became noncompliant with the protocol after the first few months of the posttreatment period. Data from the last few months of the posttreatment period are therefore incomplete.

Drug preparation and administration

Testosterone enanthate (Bristol-Myers-Squibb Inc., Princeton, NJ) was administered in a dosage of 200 mg (1 mL) weekly by nursing staff at the Clinical Research Center at the University of Washington or Pacific Medical Center. The Nal-Glu GnRH antagonist was provided by the NICHD Contraceptive Development Branch (Bethesda, MD). The antagonist was dissolved in bacteriostatic water containing 4% mannitol, diluted to a concentration of 10 mg/mL, and then, under sterile conditions, passed through a 0.2-µm filter into sterile vials and stored at –20 °C until used. All of the subjects were taught to self-administer their injections. Subjects received new vials of antagonist each month and refrigerated each vial between injections. To ensure compliance, subjects returned their empty vials each month.

Hormone assays

Serum T levels were measured by RIA using reagents from the World Health Organization Matched Reagent Program by methods previously described (19). Serum T was separated from serum by ether extraction; bound and free hormone were separated by dextran-coated charcoal. The assay sensitivity was 0.35 nmol/L; the intra- and interassay variabilities were 4.1% and 8.1%, respectively. Estradiol (E₂) was measured by RIA using a kit purchased from ICN Biomedicals, Inc., Diagnostics Division (Carson, CA). In our laboratory, the limit of detectability of the assay is 18.3 pmol/L.

Lipid assays

HDL cholesterol and HDL subclasses were measured by dextran sulfate-magnesium precipitation using the method of Warnick *et al.* (20). Total cholesterol and triglycerides were measured enzymatically (21) using an ABA 200 biochromatic instrument (Abbott Laboratories, North Chicago, IL). Low-density lipoprotein (LDL) cholesterol was calculated indirectly, using the formula, LDL cholesterol = total cholesterol – (HDL cholesterol + triglycerides/5) (22). These calculations were made before the data were converted to Système International units. Apoprotein AI was measured by nephelometry using a Behring Nephelometer Analyzer (Behring Diagnostics, Marburg, Germany).

Calcium metabolism

Serum and urinary calcium assays were performed in the University of Washington Medical Center's clinical laboratory using standard methodology. Serum intact PTH (iPTH) was measured with the Nichols Institute (San Juan Capistrano, CA) immunoradiometric iPTH(1–84) assay. The capture antibody is absorbed onto a polystyrene bead and is specific for the C-terminal 39–84 fragment of PTH. The ¹²⁵I-labeled signal antibody is specific for the 1–34 N-terminal fragment of PTH. The sensitivity of the assay is 3 ng/L.

The 1,25-dihydroxyvitamin D [1,25-(OH)₂-D] levels were determined with the Nichols Institute kit. Solid-phase extraction on C18-hydroxy columns was used to separate the 1,25-(OH)₂-D from other vitamin D isomers. The concentration of 1,25-(OH)₂-D is determined by competitive protein assay using calf thymus receptor. Dextran-coated charcoal is used to separate bound and free ligand. The sensitivity of the assay is 40 pmol/L. Twenty-five-hydroxyvitamin D [25-(OH)-D] was measured using a competitive protein binding assay using vitamin D₃ binding protein from vitamin D-deficient rats as the binder (23). The assay was performed after extraction of serum samples with ethanol and subsequent chromatography on silicic acid columns. The sensitivity of the assay is less than 2.5 nmol/L; interassay coefficients of variation are 31.3% and 14.7% at concentrations of 79 and 170 nmol/L, respectively.

Behavioral questionnaires

The behavioral questionnaire consisted of 12 questions concerning sexual function, 2 questions regarding satisfaction with an ongoing relationship, and 6 questions assessing aggressive behavior. We included questions from several sources, including the Spanier Dyadic Adjustment Scale (24), the Buss Durkee Hostility Index (25), and standard sexual

history forms (26). Each of these forms has been widely used in prior research and on clinical and nonclinical samples, as well as to measure the results of clinical interventions (27). Their psychometric reliability and validity properties have been shown to be adequate; we selected questions from each document to ensure a workable questionnaire length for the study. There were 9 possible responses to questions relating to the frequency of sexual activities. A response of 1 corresponded to not at all; 2 corresponded to less than once per month; 3 corresponded to once per month; 4 corresponded to once every 2 weeks; 5 corresponded to once per week; 6 corresponded to twice per week; 7 corresponded to 3–4 times per week; 8 corresponded to once per day; and 9 corresponded to more than once per day. Subjects were also given an opportunity to comment on any aspect of their physical or emotional well being not addressed by the questionnaire.

Statistical analysis

The mean serum levels of T in the two groups of men were not different during the control period or during the treatment period at either the peak or nadir time points (Table 1). Therefore, for the analysis of the metabolic and behavioral data, the two subjects were combined into one group containing 19 men. For each lipid and hormone parameter, each man's pretreatment data were meaned; these values were then meaned to give the group mean value. Similarly, the data from the fourth and fifth treatment months and the last 2 months of the recovery period were meaned for each man. In the three men who did not complete 20 weeks of treatment, the value from the fourth treatment month was used in computing group means. Differences across time were determined using analysis of variance with repeated measures.

Results

Serum hormone levels

Mean serum T and E_2 levels before treatment were similar in men who received Nal-Glu plus T or T alone (Table 1). During the treatment period, mean serum T levels (both the nadir and high values) were significantly elevated above the pretreatment range ($P < 0.05$; Table 1). E_2 levels also increased significantly during the treatment period. By the end of the recovery period, serum T and E_2 values had returned to the baseline state.

Plasma lipoproteins

During the pretreatment period, mean plasma HDL cholesterol in the subjects was 1.34 ± 0.08 mmol/L. After T administration began, HDL cholesterol levels decreased by $13 \pm 2\%$ (Fig. 1; $P < 0.05$). The rate of decrease was greatest during the first month of treatment; a plateau was reached after the third month. Within 1 month after T administration ended, plasma HDL levels returned to the baseline range and remained there throughout the posttreatment period. Both HDL₂ and HDL₃ cholesterol levels were suppressed significantly during T administration, decreasing by $19 \pm 4\%$

and $10 \pm 2\%$, respectively ($P < 0.05$ for both parameters; Table 2). Mean plasma levels of apoprotein AI also decreased significantly (Table 2).

Total cholesterol decreased significantly during the treatment period, primarily as a result of the decrease in HDL cholesterol levels. LDL cholesterol levels decreased slightly, and the mean triglyceride level increased slightly during T administration, but these changes were not clinically or statistically significant (Table 2).

Calcium metabolism

During T administration, there was a small but significant decrease in serum calcium, whereas urinary calcium excretion did not change (Table 3). At the same time, serum iPTH levels increased by $84 \pm 17\%$ (Table 3, $P < 0.05$). This increase occurred in 18 of the 19 men. Serum iPTH levels returned to baseline during the posttreatment period. Mean serum 25-(OH)-D levels decreased by $16 \pm 4\%$ (Table 3; $P < 0.05$) during T administration; during the posttreatment period, which corresponded to the summer months, mean 25-(OH)-D levels increased significantly compared to baseline. Mean 1,25-(OH)₂-D levels increased slightly during the treatment period (Table 3), although this increase was not significant. There was no significant relationship between changes in 25-(OH)-D, 1,25-(OH)₂-D, or iPTH levels in the men.

Behavior

The mean frequency of sexual intercourse, kissing and fondling, and masturbation did not change during the study (Table 4). There was a small trend toward increased desire and arousal (spontaneous erections) during T administration, but these increases were not statistically significant (Table 4). Measures of aggressive behavior did not change during T administration, although some subjects did complain of increased irritability. Measures of the subjects' satisfaction with their relationships did not change during the treatment period (Table 4).

Body weight and skin changes

During T treatment, all of the men gained weight; the mean weight gain was 4.0 ± 0.5 kg (range, 0.1–kg). Most of the weight gain occurred during the first 2 months of treatment, but small increases in body weight occurred during months 3–5. During the recovery period, body weights returned to baseline in 2–3 months. There was no relationship between pretreatment body weight and the amount of weight

TABLE 1. Mean \pm SE serum T and E_2 levels in men who received Nal-Glu plus T, T alone, and in the combined group of men

	Serum T (nmol/L)				Serum E_2 (pmol/L)		
	Pretreatment	Nadir value	High value	Posttreatment	Pretreatment	Treatment	Posttreatment
Nal-Glu + T (n = 10)	17.2 ± 1.3	$26.8 \pm 1.8^*$	$32.9 \pm 3.3^*$	16.0 ± 1.1 (n = 8)	0.16 ± 0.01	$0.31 \pm 0.04^*$	0.16 ± 0.04 (n = 8)
T alone (n = 9)	16.4 ± 1.4	$25.5 \pm 1.3^*$	$34.5 \pm 4.0^*$	17.9 ± 2.0 (n = 7)	$0.15 \pm .01$	$0.31 \pm 0.03^*$	0.16 ± 0.02 (n = 7)
All men (n = 19)	16.8 ± 0.9	$26.1 \pm 1.1^*$	$33.5 \pm 2.5^*$	16.7 ± 1.0 (n = 15)	0.15 ± 0.01	$0.31 \pm 0.03^*$	0.16 ± 0.01 (n = 15)

* $P < 0.05$ compared with pretreatment and posttreatment values.

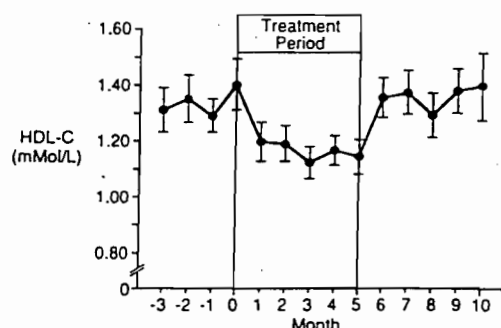


FIG. 1. Mean \pm SE plasma HDL cholesterol levels in the subjects during the course of the study ($n = 19$ during months 3–7; $n = 8–15$ thereafter). All data points during the treatment period were significantly decreased ($P < 0.05$) compared with the baseline and posttreatment values.

TABLE 2. Mean \pm SE plasma levels of HDL₂ cholesterol, HDL₃ cholesterol, apoprotein AI, total cholesterol, LDL cholesterol, and triglycerides in the subjects before treatment, at the end of the treatment period, and during the posttreatment period

	Pre-treatment	Treatment	Post-treatment
HDL ₂ cholesterol (mmol/L)	0.29 \pm 0.04	0.21 \pm 0.02*	0.35 \pm 0.05 (n = 8)
HDL ₃ cholesterol (mmol/L)	1.08 \pm 0.04	0.96 \pm 0.04*	1.04 \pm 0.05 (n = 8)
Apoprotein AI (mg/dL)	132 \pm 5	121 \pm 4*	142 \pm 7 (n = 8)
Total cholesterol (mmol/L)	4.86 \pm 0.21	4.53 \pm 0.19*	4.91 \pm 0.27 (n = 15)
LDL cholesterol (mmol/L)	3.02 \pm 0.18	2.84 \pm 0.17	3.04 \pm 0.24 (n = 15)
Triglycerides (mmol/L)	1.11 \pm 0.09	1.17 \pm 0.13	1.06 \pm 0.17 (n = 15)

* $P < 0.05$ compared with pretreatment and posttreatment values.

gained during T administration. Approximately half the men in each group noted mild acne, which resolved during the posttreatment period. The men who developed acne tended to be younger or had a history of severe acne during adolescence. None of the men discontinued the study because of weight gain or acne. All of the men who received Nal-Glu developed induration at the subcutaneous injection sites. The degree and extent of induration varied considerably among the individual men, as did the discomfort caused by injection of the antagonist. None of the men who received T alone developed local symptoms at the injection sites, although occasional bruising did occur.

Discussion

We administered T enanthate, 200 mg im weekly, to 19 healthy men for 16–20 weeks and assessed the resulting

effects on selected metabolic and behavioral endpoints. We found that the levels of T produced by this regimen have relatively few effects on sexual or aggressive behavior. In contrast, androgens seem to have a greater role in the regulation of plasma lipids, calcium homeostasis, body weight, and acne. These latter findings, particularly the suppressive effect of this dose of exogenous T on plasma HDL cholesterol, are of importance in the design of a hormonal contraceptive regimen for men.

In our study, HDL cholesterol levels decreased by $13 \pm 2\%$ by the end of the treatment period. Both the HDL₂ and HDL₃ subfractions were suppressed, although the suppression of HDL₂ was relatively greater. Zmuda *et al.* (10) showed similar suppressive effects of the same dosage of exogenous T after 3 weeks in healthy volunteers. In contrast, other investigators (11, 12) have found that parenteral T administration resulted in smaller decreases in HDL, and Byerley *et al.* (28) recently reported no change in total HDL or HDL₂ in five men treated with a GnRH agonist and replacement T administered by a long-acting microcapsule formulation. In those studies, the treatment periods were shorter in duration, and the serum T levels achieved were similar or slightly greater than we observed. Since the majority of the suppressive effect of T on plasma HDL in our study occurred during the first 4 weeks of our study, it is unlikely that the duration of the treatment period accounts for the differing results. However, it is possible that these investigators found smaller changes in HDL cholesterol because their subjects' mean pretreatment HDL levels were somewhat lower than in our subjects or those of Zmuda *et al.* (10).

We cannot predict accurately the potential health risks of long-term exogenous T administration on metabolic parameters in healthy men; however, if the decrease in HDL cholesterol we observed in our subjects were maintained over an extended period of time, the risk of coronary artery disease in some men could be increased. Jacobs *et al.* (29) found that cardiovascular mortality resulting from a decrease in HDL cholesterol of 0.26 mmol/L was approximately equal to an increase in LDL cholesterol of 0.78 mmol/L, and they calculated a hazard rate ratio for coronary artery disease (CAD) of 1.43 per 0.26-mmol/L decrease in HDL cholesterol. In other studies (30, 31), coronary risk decreased by 2–3% for each increment in plasma HDL of 0.026 mmol/L. By extrapolation, if T-induced suppression of HDL were maintained over a period of years, the risk of CAD in some men might increase approximately 20%. In men with high baseline HDL levels, this degree of increase might be clinically irrelevant, but in men with lower baselines, or in men with other risk factors for CAD, a 20% increase in risk might be unacceptable.

TABLE 3. Mean \pm SE plasma levels of serum and urinary calcium, serum iPTH, 25-OH-D, and 1,25-(OH)₂-D in the subjects before treatment, at the end of the treatment period, and during the posttreatment period

	Pretreatment	Treatment	Posttreatment
Serum calcium (mmol/L)	2.34 \pm 0.50	2.27 \pm 0.42*	2.30 \pm 0.57 (n = 15)
Urinary calcium (mmol/d)	4.61 \pm 0.42	4.49 \pm 0.62	5.32 \pm 0.57 (n = 8)
iPTH (ng/L)	24 \pm 2	41 \pm 3*	29 \pm 3 (n = 15)
25-OH-D (nmol/L)	71.9 \pm 5.0	60.9 \pm 4.2*	95.6 \pm 5.7 (n = 15)
1,25-(OH) ₂ -D (pmol/L)	84.5 \pm 5.9	93.2 \pm 6.7	74.6 \pm 6.1 (n = 15)

* $P < 0.05$ compared with pretreatment and posttreatment values.

TABLE 4. Mean \pm SE levels of subjects' satisfaction with their sexual relationships and happiness in relationships before, during, and after treatment with T enanthate

	Pretreatment	Treatment	Posttreatment (n = 11)
Satisfaction with sexual relationship ^a	4.9 \pm 0.3	5.0 \pm 0.2	4.2 \pm 0.3
Happiness in relationship ^b	3.8 \pm 0.3	4.1 \pm 0.3	4.0 \pm 0.3
Frequency of sexual intercourse ^a	4.5 \pm 0.5	4.4 \pm 0.4	4.6 \pm 0.5
Frequency of kissing ^c	6.0 \pm 0.6	6.3 \pm 0.6	6.0 \pm 0.7
Frequency of masturbation ^c	5.8 \pm 0.4	6.0 \pm 0.3	5.7 \pm 0.4
Frequency of desire ^c	7.8 \pm 0.3	8.1 \pm 0.2	8.1 \pm 0.2
Frequency of arousal or spontaneous erections ^c	7.9 \pm 0.3	8.1 \pm 0.2	8.0 \pm 0.3

^a Scores ranged from 1 (extremely unsatisfactory) to 6 (extremely satisfactory).

^b Scores ranged from 0 (extremely unhappy) to 6 (perfect).

^c Scores ranged from 1 (not at all) to 9 (more than once a day).

During the period of T administration, serum calcium and serum 25-(OH)-D levels decreased significantly; serum iPTH levels increased dramatically, and 1,25-(OH)₂-D levels did not change. These results must be interpreted in light of both season of the year and of previously reported effects of androgens on calcium metabolism. Seasonal variations in 25-(OH)-D and 24,25-(OH)₂-D have been well described (32, 33), with higher levels occurring in summer months, when most individuals have increased light exposure. However, serum levels of 1,25-(OH)₂-D lack this seasonal variation in nutritionally replete individuals (34). In one study (35), urinary calcium excretion was reported to be maximal during the summer and minimal during the winter; serum calcium levels were not reported. The effects of season on serum iPTH may depend on the vitamin D status of the population. Lips *et al.* (36) found that serum iPTH levels in an elderly population were highest in the winter months, but Krall *et al.* (37) showed that this relationship held only in postmenopausal women with low intakes of vitamin D. In our study, the treatment period occurred during the winter months, and this may explain the observed decrease in serum 25-(OH)-D levels. We did not request formal dietary histories from our subjects. However, in previous studies we have found that most healthy young men have vitamin D intakes greater than the recommended daily allowance (our unpublished data), and the lack of change in 1,25-(OH)₂-D levels supports the premise that our subjects were nutritionally replete. Thus, the observed increase in iPTH levels in these men during T administration is unlikely to have resulted from a deficiency in vitamin D intake or from the season.

Although the association between male hypogonadism and osteoporosis is well described, there are relatively few data regarding the effects of androgens on biochemical markers of bone metabolism. In some but not all studies, normalization of serum T levels in young, hypogonadal men also results in increased serum 1,25-(OH)₂-D levels (38–40). However, exogenous T administration to healthy men with mild hypogonadism does not produce a similar increase (41–43), nor are changes in serum calcium, iPTH, or osteocalcin observed. In agreement with our findings, Young *et al.* (44)

have recently reported significant increases in serum iPTH and osteocalcin, along with a small but significant decrease in serum calcium, in healthy, eugonadal men treated with exogenous T (200 mg/week for 6 months). It is possible that androgens exert some of their stimulatory effect on bone mass by inhibiting the action of PTH, decreasing bone resorption and also causing a compensatory elevation of serum PTH. This hypothesis is supported by *in vitro* data demonstrating that androgens decrease PTH-stimulated cAMP in human osteosarcoma cells (45).

We found that during the course of 16–20 weeks of treatment with exogenous T, the only measurable change in sexual or aggressive behavior was a small trend toward increased sexual desire and arousal; no change in self-reported sexual behaviors or in aggressive behaviors were observed in the monthly assessments. We did not use a daily rating system, nor did we incorporate partner observations, and it is therefore possible that subtle changes occurred that our methods were not sufficiently sensitive to detect. However, Anderson *et al.* (17) have demonstrated that in T-treated volunteers, a significant increase in psychosexual stimulation occurred during T administration, but there was no change in sexual activity or aggressive behavior in these men. In that study, a daily rating system as well as a monthly questionnaire were used. Thus it is likely that the relatively small behavioral changes that we observed in our volunteers were real and not a result of limitations in our questionnaire. Su *et al.* (18) reported recently that administration of high-dose methyltestosterone to normal subjects for 3 days resulted in increased sexual arousal and energy, as well as increased irritability, mood swings, and hostility. However, since the effects of 17-alkylated androgens on several physiological parameters differ from those of T itself on those parameters (46), their results are not directly comparable with ours.

Body weight changes varied considerably among the men. The factors contributing to the amount of weight gained by each man likely included each subject's dietary habits, stimulation of appetite during T administration, and physical activity. The mean weight gain we observed is similar to that observed by others under similar paradigms (44, 47, 48). We did not measure body composition in this study; however, androgens, including T enanthate, increase muscle mass in animals and in humans (44, 47–49), and it is likely that most of the men in our study also had increased fat-free mass during the period of T administration. The effects of androgens on skin and sebum production have been well described (8), and it is not surprising that some subjects developed acne during T administration. Although none of our subjects' symptoms limited their participation in the study, in other trials, a few subjects have developed acne of a degree of severity that caused them to discontinue T injections (1, 2, 4).

In summary, our data suggest that concerns of adverse effects of exogenous T on male sexual and aggressive behavior have perhaps been overstated. They also demonstrate that the serum levels of T produced by administration of this dosage of T enanthate lead to suppressed levels of plasma HDL cholesterol, alterations in calcium metabolism, increased body weight, and in some men, mild acne. These results imply that T enanthate at this dosage is moderately