The New England Journal of Medicine

VOLUME 335 JULY 4, 1996 NUMBER 1

THE EFFECTS OF SUPRAPHYSIOLOGIC DOSES OF TESTOSTERONE ON MUSCLE SIZE AND STRENGTH IN NORMAL MEN

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ABSTRACT

Background Athletes often take androgenic steroids in an attempt to increase their strength. The efficacy of these substances for this purpose is unsubstantiated, however.

Methods We randomly assigned 43 normal men to one of four groups: placebo with no exercise, testosterone with no exercise, placebo plus exercise, and testosterone plus exercise. The men received injections of 600 mg of testosterone enanthate or placebo weekly for 10 weeks. The men in the exercise groups performed standardized weight-lifting exercises three times weekly. Before and after the treatment period, fat-free mass was determined by underwater weighing, muscle size was measured by magnetic resonance imaging, and the strength of the arms and legs was assessed by bench-press and squatting exercises, respectively.

Results Among the men in the no-exercise groups, those given testosterone had greater increases than those given placebo in muscle size in their arms (mean [±SE] change in triceps area, 424±104 vs. −81±109 mm²; $P<0.05$) and legs (change in quadriceps area, 607±123 vs. −131±111 mm²; $P<0.05$) and greater increases in strength in the bench-press (9±4 vs. −1±1 kg, $P<0.05$) and squatting exercises (16±4 vs. 3±1 kg, $P<0.05$). The men assigned to testosterone and exercise had greater increases in fat-free mass (6.1±0.6 kg) and muscle size (triceps area, 501±104 mm²; quadriceps area, 1174±91 mm²) than those assigned to either no-exercise group, and greater increases in muscle strength (bench-press strength, 22±2 kg; squatting-exercise capacity, 38±4 kg) than either no-exercise group. Neither mood nor behavior was altered in any group.

Conclusions Supraphysiologic doses of testosterone, especially when combined with strength training, increase fat-free mass and muscle size and strength in normal men. (N Engl J Med 1996;335:1-7.)

ANABOLIC–ANDROGENIC steroids are widely abused by athletes and recreational bodybuilders because of the perception that these substances increase muscle mass and strength,[1-9] but this premise is unsubstantiated. Testosterone replacement increases nitrogen retention and fat-free mass in castrated animals and hypogonadal men,[10-15] but whether supraphysiologic doses of testosterone or other anabolic–androgenic steroids augment muscle mass and strength in normal men is unknown.[1-9] Studies of the effects of such steroids on muscle strength have been inconclusive,[16-33] and several reviews have emphasized the shortcomings of the studies.[1-5,8-10] Some of the studies were not randomized; most did not control for intake of energy and protein; the exercise stimulus was often not standardized; and some studies included competitive athletes whose motivation to win may have kept them from complying with a standardized regimen of diet and exercise.

We sought to determine whether supraphysiologic doses of testosterone, administered alone or in conjunction with a standardized program of strength-training exercise, increase fat-free mass and muscle size and strength in normal men. To overcome the pitfalls of previous studies, the intake of energy and protein and the exercise stimulus were standardized. Because some previous studies had demonstrated significant increases in muscle strength and hyper-

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trophy in experienced athletes but not in sedentary subjects, we studied men who had weight-lifting experience.

METHODS

Study Design

This study was approved by the institutional review boards of the Harbor–UCLA Research and Education Institute and the Charles R. Drew University of Medicine and Science. All the study subjects gave informed written consent. The subjects were normal men weighing 90 to 115 percent of their ideal body weights; they were 19 to 40 years of age and had experience with weight lifting. They were recruited through advertisements in local newspapers and community colleges. None had participated in competitive sports in the preceding 12 months. Men who had ever taken anabolic agents or recreational drugs or had had a psychiatric or behavioral disorder were excluded from the study.

Of 50 men who were recruited, 7 dropped out during the control period because of problems with scheduling or compliance. The remaining 43 men were randomly assigned to one of four groups: placebo with no exercise, testosterone with no exercise, placebo plus exercise, and testosterone plus exercise. The study was divided into a 4-week control period, a 10-week treatment period, and a 16-week recovery period. During the four-week control period, the men were asked not to lift any weights or engage in strenuous aerobic exercise.

Of the 43 men, 3 dropped out during the treatment phase: 1 because of problems with compliance, 1 because illicit-drug use was detected by routine drug screening, and 1 because of an automobile accident. Forty men completed the study: 10 in the placebo, no-exercise group; 10 in the testosterone, no-exercise group; 9 in the placebo-plus-exercise group; and 11 in the testosterone-plus-exercise group.

Standardization of Protein and Energy Intake

Two weeks before day 1, the men were instructed to begin following a standardized daily diet containing 36 kcal per kilogram of body weight, 1.5 g of protein per kilogram, and 100 percent of the recommended daily allowance of vitamins, minerals, and trace elements. Compliance with the diet was verified every four weeks by three-day records of food consumption. The dietary intake was adjusted every two weeks on the basis of changes in body weight.

Treatment

The men received either 600 mg of testosterone enanthate in sesame oil or placebo intramuscularly each week for 10 weeks in the Clinical Research Center. This dose is six times higher than the dose usually given as replacement therapy in men with hypogonadism and is therefore supraphysiologic. Doses as high as 300 mg per week have been given to normal men for 16 to 24 weeks without major toxic effects.[34]

Training Stimulus

The men in the exercise groups received controlled, supervised strength training three days per week during the treatment period. All the men trained at equivalent intensities in relation to their strength scores before the training. The training consisted of a cycle of weight lifting at heavy intensity (90 percent of the maximal weight the man lifted for one repetition before the start of training), light intensity (70 percent of the pretraining one-repetition maximal weight), and medium intensity (80 percent of this maximal weight) on three nonconsecutive days each week.[35] Regardless of the actual weights lifted, the training was held constant at four sets with six repetitions per set (a set is the number of complete repetitions of an exercise followed by rest). Because previous research had demonstrated increases in strength of approximately 7 percent for the bench-press exercise and 12 percent for the squatting exercise after four to five weeks of training,[35] the weights were increased correspondingly during the final five weeks of training in relation to the initial intensity. The number of sets was also increased from four to five, but the number of repetitions per set remained constant. The men were advised not to undertake any resistance exercise or moderate-to-heavy endurance exercise in addition to the prescribed regimen.

Evaluation and Outcome Measures

The primary end points were fat-free mass, muscle size as measured by magnetic resonance imaging (MRI), and muscle strength as based on the one-repetition maximal weight lifted during the bench-press and squatting exercises before and after the 10-week treatment period. Serum concentrations of total and free testosterone, luteinizing hormone, follicle-stimulating hormone, and sex hormone–binding globulin were measured on days 14 and 28 of the control period and days 2, 3, 7, 14, 28, 42, 56, and 70 of the treatment period. Blood counts, blood chemistry (including serum aminotransferases), serum concentrations of prostate-specific antigen, and plasma concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured at the start of the control period and on day 4; on days 28, 56, and 70 of the treatment period; and four months after the discontinuation of treatment. Periodic evaluations to identify adverse effects were performed by examiners unaware of the study-group assignments on days 1 and 28 of the control period; days 28, 56, and 70 of the treatment period; and four months after the discontinuation of treatment. Mood and behavior were evaluated during the first week of the control period and after 6 and 10 weeks of treatment. Sexual function and semen characteristics were not assessed.

Assessment of Muscle Size

Muscle size was measured by MRI of the arms and legs at the humeral or femoral mid-diaphyseal level, the junction of the upper third and middle third of the bone, and the junction of the middle third and lower third. The cross-sectional areas of the arms and legs, the subcutaneous tissue, the muscle compartment, and the quadriceps and triceps muscles were computed, and the areas at the three levels were averaged.

Analysis of Body Composition

Fat-free mass was estimated on the basis of measurements of body density obtained by underwater weighing. During weighing, the men were asked to exhale to the residual volume, as measured by helium dilution.

Measures of Muscle Strength

The effort-dependent performance of muscle was assessed on the basis of the maximal weight lifted for one repetition during the bench-press and squatting exercises.[36] Each man completed increasingly more difficult lifts with the same weights and bars that he used during training; in each exercise, the maximal weight lifted (the one-repetition maximum) was recorded as a measure of muscle strength.

Hormone Measurements

Serum concentrations of luteinizing hormone and follicle-stimulating hormone were measured by immunofluorometric assays,[36] each with a sensitivity of 0.05 IU per liter. Serum testosterone was measured by immunoassay,[37] and free testosterone was measured by equilibrium dialysis.[37] Serum concentrations of sex hormone–binding globulin and prostate-specific antigen were measured by immunoassays using reagents purchased from Delphia–Wallac (Turku, Finland) and Hybritech (San Diego, Calif.), respectively.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY SUBJECTS.*

GROUP	AGE	WEIGHT	HEIGHT	BODY-MASS INDEX†
	yr	kg	cm	
No exercise				
Placebo	27±5	79.5±13.6	177.5±7.7	25.1±2.9
Testosterone	26±6	82.2±6.0	177.1±7.2	26.4±3.1
Exercise				
Placebo	26±6	85.5±9.7	181.0±5.8	26.2±3.2
Testosterone	30±7	76.0±10.0	175.6±6.4	24.6±2.9

*Plus–minus values are means ±SD.

†Calculated as the weight in kilograms divided by the square of the height in meters.

Assessment of Mood and Behavior

A standardized Multidimensional Anger Inventory[38] that includes 38 questions to measure the frequency, duration, magnitude, and mode of expression of anger, arousal of anger, hostile outlook, and anger-eliciting situations and a Mood Inventory that includes questions pertaining to general mood, emotional stability, and angry behavior were administered before, during (week 6), and after the treatment (unpublished data). For each man a live-in partner, spouse, or parent answered the same questions about the man's mood and behavior.

Statistical Analysis

The Shapiro and Wilk test was used to test whether the outcome variables had a normal distribution. Changes were computed for each subject as the difference between the values for each variable at the beginning and end of the treatment period (from day 0 to day 70). These values were averaged among the subjects in each group to obtain the group means. Analysis of variance was used to determine whether there were base-line differences among the four groups. Two-tailed, paired t-tests were used to test for changes in each outcome variable in each group. If there was a change, an analysis of variance was used to test for differences between groups in the amount of change, and then Scheffé's test was used to assess pairwise differences. This test adjusts for multiple comparisons, but it does not yield exact P values for pairwise comparisons between groups.

RESULTS

The four groups were similar with respect to age and weight, height, and body-mass index before treatment (Table 1). Acne developed in three men receiving testosterone and one receiving placebo, and two men receiving testosterone reported breast tenderness, but no other side effects were noted. The serum liver-enzyme concentrations, hemoglobin concentrations, hematocrits, and red-cell counts did not change in any study group (Table 2). Serum creatinine concentrations did not change, except in the testosterone-plus-exercise group, in which the mean (±SE) serum creatinine concentration increased from 1.0 mg per deciliter (88 μmol per liter) to 1.1 mg per deciliter (97 μmol per liter) (P=0.02). Plasma concentrations of total and LDL cholesterol and triglycerides did not change in any study group; plasma HDL cholesterol decreased significantly in the placebo-plus-exercise group. There was no change in the serum concentration of prostate-specific antigen in any group.

Endocrine Responses

The base-line serum concentrations of total and free testosterone in the four groups were similar. The serum concentrations of total and free testosterone increased significantly in the two testosterone

TABLE 2. HEMOGLOBIN AND PLASMA LIPID CONCENTRATIONS BEFORE AND AFTER THE 10 WEEKS OF TREATMENT.*

VARIABLE	NO EXERCISE		EXERCISE	
	PLACEBO	TESTOSTERONE	PLACEBO	TESTOSTERONE
Hemoglobin (g/dl)				
Base line	14.9±0.2	15.1±0.2	14.5±0.3	15.3±0.4
10 wk	15.0±0.3	15.5±0.2	14.3±0.4	15.7±0.2
HDL cholesterol (mg/dl)				
Base line	39±2	37±3	42±3	40±2
10 wk	36±3	34±3	37±3†	36±3
LDL cholesterol (mg/dl)				
Base line	113±10	133±7	117±6	128±12
10 wk	116±11	133±9	115±7	121±10
Triglycerides (mg/dl)				
Base line	155±36	147±25	105±14	146±15
10 wk	139±27	111±13	104±21	125±15

*Plasma lipid concentrations were measured in 9 men assigned to placebo with no exercise, 8 men assigned to testosterone with no exercise, 8 men assigned to placebo plus exercise, and 10 men assigned to testosterone plus exercise. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein. To convert values for hemoglobin to millimoles per liter, multiply by 0.62; to convert values for cholesterol to millimoles per liter, multiply by 0.02586; and to convert values for triglycerides to millimoles per liter, multiply by 0.0113. Plus–minus values are means ±SE.

†P=0.04 for the comparison with the base-line value.

TABLE 3. SERUM CONCENTRATIONS OF ENDOCRINE HORMONES IN THE STUDY SUBJECTS BEFORE AND AFTER THE 10 WEEKS OF TREATMENT.*

HORMONE	NO EXERCISE		EXERCISE	
	PLACEBO	TESTOSTERONE	PLACEBO	TESTOSTERONE
Total testosterone (ng/dl)				
Base line	516±58	502±63	557±45	431±38
10 wk	453±35	2828±417†‡	667±117	3244±305†‡
Free testosterone (pg/ml)				
Base line	74±7	79±7	83±7	90±6
10 wk	74±13	497±62†‡	81±9	572±53†‡
Luteinizing hormone (mIU/ml)				
Base line	3.3±0.4	3.8±0.6	4.0±0.7	3.3±0.5
10 wk	4.3±0.9	0.4±0.2†‡	4.4±1.1	0.4±0.2†‡
Follicle-stimulating hormone (mIU/ml)				
Base line	3.1±0.3	3.1±0.4	3.2±0.6	3.0±0.6
10 wk	2.7±0.3	0.3±0.2†‡	4.4±1.1	0.10±0.03†‡
Sex hormone–binding globulin (ng/dl)				
Base line	224±33	256±34	353±41	271±43
10 wk	244±53	176±24‡§	320±31	201±34‡¶

*Values at 10 weeks were obtained 1 week after the final injection. To convert values for total testosterone to nanomoles per liter, multiply by 0.0347; to convert values for free testosterone to picomoles per liter, multiply by 3.47; to convert values for sex hormone–binding globulin to nanomoles per liter, multiply by 0.12. Plus–minus values are means ±SE.

†$P<0.001$ for the comparison with the corresponding base-line value.

‡$P<0.05$ for the comparison of the difference between this value and the base-line value with the corresponding difference in either placebo group.

§$P=0.008$ for the comparison with the corresponding base-line value.

¶$P=0.05$ for the comparison with the corresponding base-line value.

groups, but not in the placebo groups (Table 3). The base-line serum concentrations of luteinizing hormone, follicle-stimulating hormone, and sex hormone–binding globulin were similar in the four groups, and the concentrations decreased significantly in the two testosterone groups.

Body Weight and Composition

Body weight did not change significantly in the men in either placebo group (Table 4). The men given testosterone without exercise had a significant mean increase in total body weight, and those in the testosterone-plus-exercise group had an average increase of 6.1 kg in body weight — a greater increase than in the other three groups.

Fat-free mass did not change significantly in the group assigned to placebo but no exercise (Table 4 and Fig. 1). The men treated with testosterone but no exercise had an increase of 3.2 kg in fat-free mass, and those in the placebo-plus-exercise group had an increase of 1.9 kg. The increase in the testosterone-plus-exercise group was substantially greater (averaging 6.1 kg). The percentage of body fat did not change significantly in any group (data not shown).

Muscle Size

The mean cross-sectional areas of the arm and leg muscles did not change significantly in the placebo groups, whether the men had exercise or not (Table 4 and Fig. 1). The men in the testosterone groups had significant increases in the cross-sectional areas of the triceps and the quadriceps (Table 4); the group assigned to testosterone without exercise had a significantly greater increase in the cross-sectional area of the quadriceps than the placebo-alone group, and the testosterone-plus-exercise group had greater increases in quadriceps and triceps area than either the testosterone-alone or the placebo-plus-exercise group ($P<0.05$).

Muscle Strength

Muscle strength in the bench-press and the squatting exercises did not change significantly over the 10-week period in the group assigned to placebo with no exercise. The men in the testosterone-alone and placebo-plus-exercise groups had significant increases in the one-repetition maximal weights lifted in the squatting exercises, averaging 19 percent and 21 percent, respectively (Table 4 and Fig. 1). Similarly, mean bench-press strength increased in these two groups by 10 percent and 11 percent, respectively. In the testosterone-plus-exercise group, the increase in muscle strength in the squatting exercise (38 percent) was greater than that in any other group, as was the increase in bench-press strength (22 percent).

TABLE 4. BODY WEIGHT, FAT-FREE MASS, AND MUSCLE SIZE AND STRENGTH BEFORE AND AFTER THE 10 WEEKS OF TREATMENT.*

VARIABLE	NO EXERCISE		EXERCISE	
	PLACEBO	TESTOSTERONE	PLACEBO	TESTOSTERONE
Body weight (kg)				
Base line	79.5±4.3	82.2±1.9	85.5±3.3	76.0±3.0
10 wk	80.8±4.4	85.7±1.5	86.4±2.9	82.0±2.8†
P value	—	0.004	—	<0.001
Fat-free mass (kg)				
Base line	65.1±2.5	69.9±1.3	72.1±2.3	65.3±1.8
10 wk	65.9±2.7	73.1±2.2	74.1±2.2	71.4±1.8‡
P value	—	—	0.017	<0.001
Triceps area (mm^2)				
Base line	3621±213	3579±260	4,052±262	3483±217
10 wk	3539±226	4003±229§	4,109±230	3984±239§
P value	—	0.003	—	<0.001
Quadriceps area (mm^2)				
Base line	8796±561	9067±398	9,920±569	8550±353
10 wk	8665±481	9674±472§	10,454±474§	9724±348¶
P value	—	<0.001	—	<0.001
Bench-press exercise (kg lifted)				
Base line	88±5	96±8	109±12	97±6
10 wk	88±5	105±8§	119±11§	119±6‡
P value	—	—	0.005	<0.001
Squatting exercise (kg lifted)				
Base line	102±6	103±8	126±13	102±5
10 wk	105±6	116±5	151±13§	140±5¶
P value	—	0.004	<0.001	<0.001

*P values are shown for the comparison of the 10-week values with the base-line values when $P \leq 0.05$. Plus–minus values are means ±SE.

†$P<0.05$ for the comparison of the change from base line with that in either placebo group.

‡$P<0.05$ for the comparison of the change from base line with that in either no-exercise group.

§$P<0.05$ for the comparison of the change from base line with that in the group assigned to placebo with no exercise.

¶$P<0.05$ for the comparison of the change from base line with that in the other three groups.

Mood and Behavior

No differences were found between the exercise groups and the no-exercise groups or between the placebo groups and the testosterone groups in any of the five subcategories of anger assessed by the Multidimensional Anger Inventory. No significant changes in mood or behavior were reported by the men on the Mood Inventory or by their live-in partners, spouses, or parents on the Observer Mood Inventory.

DISCUSSION

Our results show that supraphysiologic doses of testosterone, especially when combined with strength training, increase fat-free mass, muscle size, and strength in normal men when potentially confounding variables, such as nutritional intake and exercise stimulus, are standardized. The combination of strength training and testosterone produced greater increases in muscle size and strength than were achieved with either intervention alone. The combined regimen of testosterone and exercise led to an increase of 6.1 kg in fat-free mass over the course of 10 weeks; this increase entirely accounted for the changes in body weight.

The exercise was standardized in all the men, and therefore the effects of testosterone on muscle size and strength cannot be attributed to more intense training in the groups receiving the treatment. Careful selection of experienced weight lifters, the exclusion of competitive athletes, and close follow-up ensured a high degree of compliance with the regimens of exercise, treatment, and diet, which was verified by three-day food records (data not shown) and the values obtained for serum testosterone, luteinizing hormone, and follicle-stimulating hormone. Except for one man who missed one injection, all the men received all their scheduled injections. It has been argued that studies in which large doses of androgens are used cannot be truly blinded because of the occurrence of acne or other side effects. In this study, neither the investigators nor the personnel performing the measurements knew the study-group assignments. Three men receiving testosterone and one man receiving placebo had acneiform eruptions; these men may have assumed themselves to be receiving testosterone. Thus, it cannot be stated with certainty

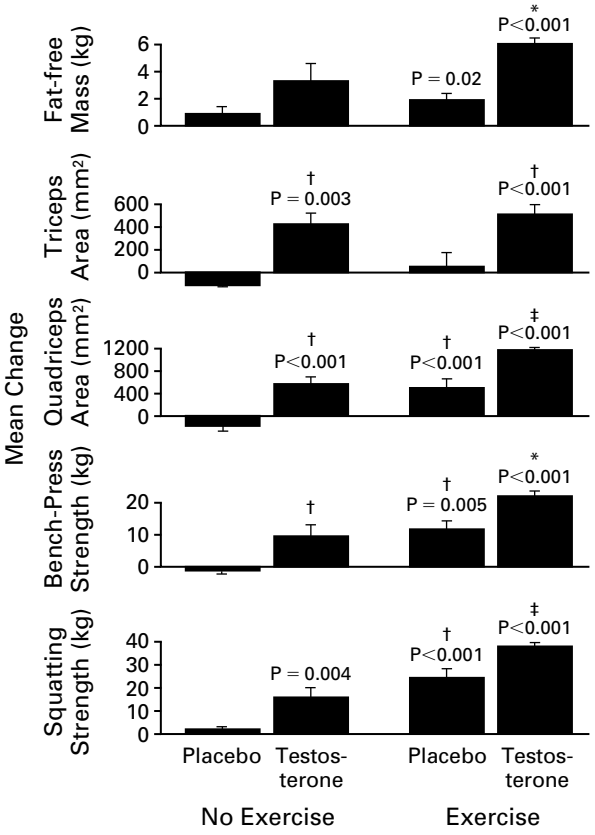

Figure 1. Changes from Base Line in Mean (±SE) Fat-free Mass, Triceps and Quadriceps Cross-Sectional Areas, and Muscle Strength in the Bench-Press and Squatting Exercises over the 10 Weeks of Treatment.

The P values shown are for the comparison between the change indicated and a change of zero. The asterisks indicate $P<0.05$ for the comparison between the change indicated and that in either no-exercise group; the daggers, $P<0.05$ for the comparison between the change indicated and that in the group assigned to placebo with no exercise; and the double daggers, $P<0.05$ for the comparison between the change indicated and the changes in all three other groups.

that the men were completely unaware of the nature of their treatments.

The doses of androgenic steroids used in previous studies were low,[1-5,11,12] mostly because of concern about potential toxic effects. In contrast, to our knowledge the dose of testosterone enanthate administered in this study (600 mg per week) is the highest administered in any study of athletic performance. Undoubtedly, some athletes and bodybuilders take even higher doses than those we gave. Furthermore, athletes often "stack" androgenic and anabolic steroids, taking multiple forms simultaneously. We do not know whether still higher doses of testosterone or the simultaneous administration of several steroids would have more pronounced effects. The absence of systemic toxicity during testosterone treatment was consistent with the results of studies of the contraceptive efficacy of that hormone.[34]

The method used in this study to evaluate muscle performance on the basis of the one-repetition maximal weight lifted is dependent on effort. Although the men receiving testosterone did have increases in muscle size, some of the gains in strength may have resulted from the behavioral effects of testosterone.

The dose dependency of the action of testosterone on fat-free mass and protein synthesis has not been well studied. Forbes[39] proposed a single dose–response curve extending from the hypogonadal to the supraphysiologic range. Others have suggested that there may be two dose–response curves: one in the hypogonadal range, with maximal responses corresponding to the serum testosterone concentrations at the lower end of the range in normal men, and the second in the supraphysiologic range, presumably representing a separate mechanism of action — that is, a pathway of independent androgen receptors.[1,40]

Supraphysiologic doses of testosterone, with or without exercise, did not increase the occurrence of angry behavior by these carefully selected men in the controlled setting of this experiment. Our results, however, do not preclude the possibility that still higher doses of multiple steroids may provoke angry behavior in men with preexisting psychiatric or behavioral problems.

Our results in no way justify the use of anabolic–androgenic steroids in sports, because, with extended use, such drugs have potentially serious adverse effects on the cardiovascular system, prostate, lipid metabolism, and insulin sensitivity. Moreover, the use of any performance-enhancing agent in sports raises serious ethical issues. Our findings do, however, raise the possibility that the short-term administration of androgens may have beneficial effects in immobilized patients, during space travel, and in patients with cancer-related cachexia, disease caused by the human immunodeficiency virus, or other chronic wasting disorders.

Supported by a grant (1 RO1 DK 45211) from the National Institutes of Health, by a General Clinical Research Center grant (MO-00543), and by grants (P20RR11145-01, a Clinical Research Infrastructure Initiative; and G12RR03026) from the Research Centers for Minority Institutions.

We are indebted to Dr. Indrani Sinha-Hikim for the serum hormone assays, to Dr. Paul Fu for the plasma lipid measurements, to the staff of the General Clinical Research Center for conducting the studies, and to BioTechnology General Corporation, Iselin, New Jersey, for providing testosterone enanthate.

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