

Effects of Supraphysiologic Doses of Testosterone on Mood and Aggression in Normal Men

A Randomized Controlled Trial

Harrison G. Pope, Jr, MD, MPH; Elena M. Kouri, PhD; James I. Hudson, MD, SM

Background: Field studies of illicit anabolic-androgenic steroid users suggest that some develop manic or aggressive reactions to these drugs—a potential public health problem. However, controlled laboratory evaluations of these effects remain limited.

Methods: In a randomized, placebo-controlled, crossover trial, we administered testosterone cypionate for 6 weeks in doses rising to 600 mg/wk and placebo for 6 weeks, separated by 6 weeks of no treatment, to 56 men aged 20 to 50 years. Psychiatric outcome measures included the Young Mania Rating Scale (YMRS), the Point Subtraction Aggression Paradigm (a computerized provocation test of aggression), the Aggression Questionnaire of Buss and Perry, the Symptom Checklist-90-R, daily diaries of manic and depressive symptoms, and similar weekly diaries completed by a “significant other” who knew the participant well.

Results: Testosterone treatment significantly increased manic scores on the YMRS ($P = .002$), manic scores

on daily diaries ($P = .003$), visual analog ratings of liking the drug effect ($P = .008$), and aggressive responses on the Point Subtraction Aggression Paradigm ($P = .03$). Drug response was highly variable: of 50 participants who received 600 mg/wk of testosterone cypionate, 42 (84%) exhibited minimal psychiatric effects (maximum YMRS score, <10), 6 (12%) became mildly hypomanic (YMRS score, 10-19), and 2 (4%) became markedly hypomanic (YMRS score, ≥ 20). The 8 “responders” and 42 “non-responders” did not differ significantly on baseline demographic, psychological, laboratory, or physiological measures.

Conclusions: Testosterone administration, 600 mg/wk increased ratings of manic symptoms in normal men. This effect, however, was not uniform across individuals; most showed little psychological change, whereas a few developed prominent effects. The mechanism of these variable reactions remains unclear.

Arch Gen Psychiatry. 2000;57:133-140

THE MALE hormone testosterone and its synthetic analogs compose the family of hormones called anabolic-androgenic steroids (AASs). Probably more than a million Americans, primarily young men—including 4% to 7% of male high school

See also pages 141, 149, and 155

students—have used these hormones illicitly to improve athletic performance or personal appearance.¹⁻⁴ During the past 10 years, results of a growing literature of field studies^{1,5-13} suggest that some illicit AAS users develop marked aggression, hypomania, and occasionally frank mania during AAS exposure, as well as depressive symptoms and even suicidality during AAS withdrawal. The euphoric effects of AAS use and the dysphoric effects of withdrawal may contribute to a syndrome of AAS dependence in some individu-

als.^{1,13-15} Several articles^{1,8,16-22} speculate that AAS use may precipitate criminal violence. These effects may be dose related, with frequent symptoms in individuals using the equivalent of more than 1000 mg of testosterone per week,⁵⁻⁷ occasional symptoms at intermediate dosages,^{6,8-13} and few symptoms at 300 mg per week or less.^{6,23} In one field study of 88 illicit AAS users,⁶ 25 (28%) reported using at least 1000 mg of testosterone or the equivalent per week, and another 51 (58%) had used between 300 and 1000 mg per week—often as “stacks” of oral and injectable AAS taken simultaneously. Thus, many illicit users may be at risk for psychiatric morbidity.

However, interpretation of these findings is limited by the problems common to observational studies. For example, selection bias may affect which users will present for study, and information bias may arise in participants recalling psychological effects experienced in the past while taking illicit drugs of uncertain potency or au-

From the Biological Psychiatry Laboratory, McLean Hospital, Belmont; and Department of Psychiatry, Harvard Medical School (Drs Pope, Kouri, and Hudson), and Department of Biostatistics, Harvard School of Public Health (Dr Hudson), Boston, Mass.

PARTICIPANTS AND METHODS

PARTICIPANTS

We advertised at several local colleges and 1 local gymnasium to recruit men aged 20 to 50 years from 3 groups: (1) men who did not lift weights regularly and never used AASs, (2) men who lifted weights regularly (at least 3 times per week for ≥ 2 years) and never used AASs, and (3) men who formerly used AASs illicitly. We required each participant to furnish a “significant other”—a spouse, sexual partner, or close friend—to rate his behavior in a weekly diary (see the “Study Procedures” subsection) and to alert the investigators if he displayed adverse behavioral changes. We informed each participant and significant other that we were investigating the psychological effects of receiving supraphysiologic doses of testosterone, and required both to sign informed consent forms approved by the institutional review board of McLean Hospital, Belmont, Mass.

At baseline evaluation, we obtained demographic information, psychiatric and substance abuse histories using the Axis I portion of the Structured Clinical Interview for DSM-III-R,³⁹ and medical histories. The evaluation also included a physical examination, determination of body fat using calipers,⁴⁰ an electrocardiogram, and laboratory tests (see the “Study Procedures” subsection). We excluded participants who (1) met DSM-III-R criteria⁴¹ for any substance abuse or dependence within the past year; (2) reported current or past major depression, active suicidal ideation, hypomania, mania, or psychotic symptoms; (3) had ever required use of any regular psychiatric medication; (4) exhibited a clinically significant medical condition; or (5) had used any AASs within the past 90 days, as determined by self-report and baseline urine testing.

STUDY PROCEDURES

Qualifying participants were then seen weekly for 25 weeks. They were randomized to receive intragluteal injections of testosterone or placebo under double-blind conditions for weeks 1 through 6 (the “first treatment period”), a washout for weeks 7 through 12, injections of the opposite treatment for weeks 13 through 18 (the “second treatment period”), and a second washout for weeks 19 through 25.

During the testosterone treatment period, participants received 150 mg each of the first 2 weeks, 300 mg the third and fourth weeks, and 600 mg each of the last 2 weeks. Placebo injections consisted of equivalent amounts of the sesame oil vehicle. We assessed psychiatric symptoms at each visit using the Young Mania Rating Scale (YMRS),⁴² 24-item Hamilton Depression Rating Scale,⁴³ Aggression Questionnaire of Buss and Perry (AQ),⁴⁴ and Symptom Checklist-90-R.⁴⁵ Weight, pulse, and blood pressure were also measured weekly. Laboratory tests—including standard chemistries, hematological measures, neuroendocrine measures (total testosterone, luteinizing hormone, follicle-stimulating hormone, and prolactin), urinalysis, and urine screening for drugs of abuse (including AASs^{46,47})—were administered every 3 weeks. Blood and urine samples for these tests were obtained within a few minutes before or after any intragluteal injections. To minimize the possible confounding effects of diet and weight training,²⁴ we asked participants to maintain a stable diet and exercise pattern throughout the 25 weeks, although this behavior was not formally monitored. Virtually all injections and investigator-administered ratings were performed by one of us (H.G.P.); in his absence, they were performed by another physician (J.I.H.). Thus, the raters were aware of when participants were receiving treatment but were unaware of the identity of that treatment.

At home, participants also completed a 17-item daily diary (available on request) covering 12 manic symptoms and 5 depressive symptoms experienced during the past 24 hours. The diaries generated a manic score of 0 to 48 and a depression score of 0 to 20. Participants also marked a 100-point visual analog “liking” scale with 3 anchors: “I dislike the way that I feel on this medication very much” (0 points), “neutral” (50 points), and “I like the way that I feel on this medication very much” (100 points). Total manic, depressive, and liking scores for each week represented the mean scores of all diaries submitted during the preceding 7 days. Significant others rated the participant’s behavior weekly in a virtually identical diary. Participants received approximately \$50 per week for study participation and significant others received \$5 per weekly diary.

In the second study year, we introduced a computerized measure of aggression, the Point Subtraction Aggression Paradigm (PSAP).⁴⁸ This test was administered to most participants at weeks 1, 5, 7, 13, 17, and 19. We presented

thenticity. The confounding effects of users’ premonitory personalities and expectations, concomitant abuse of other substances, and the physiological and psychological effects of weight training might also bias the findings.^{6,24-26}

Experimental treatment studies avoid such limitations but ethically cannot use highly supraphysiologic doses of AAS approaching those used illicitly. Endocrinologic,^{27,28} physiological,²⁹⁻³¹ and medical³²⁻³⁴ studies have typically used at most 300 mg/wk of testosterone²⁷⁻³⁴ or nandrolone²⁹ and have noted few psychiatric effects. However, 3 recent laboratory studies have used higher doses: 2 reported occasional manic or hypomanic reactions in participants administered methyltestosterone³⁵ or testosterone,³⁶ whereas a third study using testosterone did not.^{37,38}

To augment these limited data, we performed a randomized, placebo-controlled, double-blind crossover study

of the psychiatric effects of intramuscular testosterone cypionate treatment, at dosages rising to 600 mg/wk, in 56 normal men. We hypothesized that this supraphysiologic dosage of an AAS would increase hypomanic and aggressive symptoms. We also tested the hypothesis that such effects, if present, would be more prominent in men who had previously used AASs illicitly or who lifted weights regularly.

RESULTS

PARTICIPANT CHARACTERISTICS

Of 66 participants recruited, 56 were randomized, 55 were followed up in the first study period; 53 received at least 5 injections and were considered fully evaluable, as defined in the “Data Analysis” subsection of the “Participants and Methods” section (demographic characteris-

this technique in detail in a previous article,⁴⁹ together with preliminary data from 5 participants in the present study. Briefly, each participant was seated in a booth equipped with a monitor screen and was told that he was playing against an unseen male opponent, which was actually a computer. The participant could accumulate points on the screen—exchangeable for money—by pressing one button, or he could deprive his “opponent” of points by pressing another button. During the session, the opponent provoked the participant by randomly depriving him of points. The participant’s aggression score represented the total number of points that he subtracted from his opponent in retaliation to this provocation. In accordance with published scoring methods for this test,⁴⁸ we excluded participants who guessed that their opponent was a computer. Participants were judged to have guessed correctly if they both (1) failed to deprive their opponent of points during 1 or more sessions, and (2) responded on a post-study questionnaire⁴⁹ that their opponent had been a computer.

DATA ANALYSIS

For the primary analysis of each outcome measure, we compared the changes during the testosterone and placebo periods. We defined each period to begin on the day of the first injection and end 1 week after the last injection (when the effects of testosterone would be expected to be greatest). We considered participants to be “fully evaluable” for a given treatment period if they received at least the first 5 of 6 scheduled injections to ensure that all testosterone treatment periods included at least 1 injection of 600 mg of testosterone. In addition to the analysis of fully evaluable participants, we also analyzed participants’ responses after administration of 300 mg of testosterone, using as the end point the visit 1 week after the second injection of 300 mg (week 5 or week 17).

We used a model for the mean of the response variable derived from Senn⁵⁰ to analyze crossover studies. This model incorporates terms for treatment and period effects but not for carryover (or residual) effect. The decision to exclude such a term was based on the work of Freeman,⁵¹ who showed that models with a term for carryover effect are biased and possess poor power to detect a carryover effect. In any event, a carryover effect seemed unlikely with our design because

evidence from kinetic studies^{52,53} with testosterone cypionate suggests that a 6-week washout period after a 6-week treatment period allows neuroendocrine function to return to baseline. Thus, the model was as follows: $E(Y_i) = \beta_0 + \beta_1 \text{treatment} + \beta_2 \text{period}$, where $E(Y)$ is the expected value of the outcome variable for the i th subject; *treatment* is an indicator variable for testosterone treatment; and *period* is an indicator variable for the first treatment period.

To model the covariance, we wanted to allow for both dependence of repeated observations within the same individual and possible dependence of variance of the response variable on the mean. Therefore, we used PROC MIXED in SAS⁵⁴ to fit 3 models for the “working” covariance: one allowed variance to depend on treatment group, another allowed variance to depend on treatment period, and a third assumed equal variance (compound symmetry). We chose the best-fitting model in each analysis and computed SEs based on empirical variances.

We tested for effects of previous AAS use and/or regular weight lifting by putting terms in the model for the various participant categories (1 indicates no weight lifting, no previous AAS use; 2, regular weight lifting, no previous AAS use; and 3, previous AAS use). Because it was unclear whether this variable should be best treated as a nominal or an ordinal variable, we analyzed it both ways.

We also analyzed data from only the first treatment period using the Wilcoxon rank sum test, 2-tailed. This analysis was free of concern about carryover effect and distributional assumptions but ignored almost half of the data. Thus, it represented an unquestionably valid but overly conservative assessment of treatment effects.

In an a posteriori analysis, we classified participants’ responses to testosterone treatment as marked, moderate, or minimal on the basis of YMRS scores (see “Results” section), and then compared attributes of marked or moderate responders with those of minimal responders using the Fisher exact test, 2-tailed. In these and all other comparisons, we considered $P < .05$ to be statistically significant.

Because the outcome measures in this study are correlated to an unknown degree, it is difficult to calculate an appropriate correction for the effect of multiple comparisons. Results are therefore presented without correction. Thus, some findings, especially those of marginal significance and those that do not test a priori hypotheses, may represent chance associations.

tics of these 53 men are shown in **Table 1**). Forty-nine participants were followed up in the second study period; 47 were fully evaluable.

PSYCHIATRIC MEASURES

Manic scores on the YMRS increased significantly with testosterone treatment (**Table 2**). However, this effect was not uniform: most participants exhibited little change during testosterone treatment, whereas a few displayed marked symptoms (see the **Figure** and the “Comment” section). While taking testosterone, no participant reported actual violence (see definition in Table 1), but several described instances of uncharacteristic aggressiveness; we withdrew one participant from the study after the fifth week because he became alarmingly hypomanic and aggressive (**Figure**). Of 34 participants administered the PSAP

at baseline and after at least 1 treatment period, 1 was excluded because he misinterpreted the instructions and 6 because they guessed that their opponent was a computer (see “Study Procedures” subsection of the “Participants and Methods” section). Thus, 27 participants were evaluable for at least 1 study period. Because some participants were not given the PSAP at week 13 (the baseline for the second period), we analyzed this measure using the end-point value (week 7 or week 19) for testosterone vs placebo treatment, with the week 1 value as a covariate. Despite the smaller number of participants in this analysis, aggression scores on the PSAP increased significantly with testosterone treatment. Again, however, this effect was not uniform; most participants showed little change and a few showed marked changes. The manic and liking scores on participants’ daily diaries also showed a significant testosterone treatment effect. Diaries from significant oth-

Table 1. Demographic Characteristics of 53 Evaluable Study Participants

Characteristic*	Participants, No. (%)†
Age, y	
20-29	41 (77)
30-39	9 (17)
40-49	3 (6)
Ethnicity	
White	32 (60)
African American	9 (17)
Hispanic	8 (15)
Asian	3 (6)
American Indian	1 (2)
Weight lifting experience	
None or irregular	27 (51)
Regular weight lifting; no steroid use‡	13 (25)
Previous steroid use‡	13 (25)
Sexual orientation	
Heterosexual	47 (89)
Homosexual	6 (11)
Current alcohol consumption, drinks/wk§	
0-12	47 (89)
13-24	6 (11)
Current cigarette smoking, packs/wk	
0	45 (85)
<1	7 (13)
1	1 (2)
Illicit drug use in past year	
Marijuana	17 (32)
Cocaine	1 (2)
Psychiatric history	
Past DSM-III-R Axis I disorder	1 (2)
Past violence¶	13 (25)
First-degree relative with major mood disorder#	11 (21)
Height, mean ± SD, m	1.78 (.07)
Weight, mean ± SD, kg	80.0 (11.8)
Fat-free mass index, mean ± SD, kg/m ² **	21.5 (2.2)

* There were no significant differences between the 23 men who received testosterone cypionate first and the 30 men who received placebo first in any characteristics shown (using the Wilcoxon rank sum test, 2-tailed, for age, height, weight, and fat-free mass index and exact tests of 2 × N contingency tables for all other characteristics).

† Because of rounding, percentages may not all total 100.

‡ Regular weight lifting was defined as 2 years or more of weight lifting at least 3 times per week in a commercial or school weight training facility. Of 13 participants reporting past steroid use, 12 had engaged in regular weight lifting.

§ One drink was defined as 12 oz of beer, 4 oz of wine, or 1.5 oz of distilled spirits.

|| The single positive participant reported cannabis dependence and alcohol dependence while in college, in full remission for 6 years before entering study.

¶ Defined as having engaged in at least 1 physical fight causing injury to another individual or having caused more than \$100 of damage to objects (doors, windows, etc) during an episode of anger since age 13 years.

Nine relatives had major depression, 1 had bipolar disorder, and 1 had schizoaffective disorder, bipolar type.

** Fat-free mass index = [(lean body mass)/height²] + 6.1(1.8 - height), where height is measured in meters and lean body mass in kilograms. See Kouri et al⁵⁵ for the explanation of this formula.

ers did not show a significant testosterone effect, although manic scores on participants' and significant others' diaries correlated highly at the end of the testosterone treatment period (Spearman $Y = 0.59$; $P < .001$).

Self-rating scales showed few drug treatment effects. Only 1 of 4 AQ subscale scores, verbal hostility, increased significantly with testosterone therapy among

evaluative participants ($P = .03$), and this score displayed a significant period effect, with second-period increases greater than those of the first period ($P = .01$). Only 1 of 9 Symptom Checklist-90-R subscale scores, phobic anxiety, showed a significant increase with testosterone treatment ($P = .006$). Depression scores on both types of diaries and on the Hamilton Depression Rating Scale remained low, with no changes even approaching significance during testosterone administration or withdrawal. When we expanded our analysis to include the 55 participants who had received at least 1 injection, the effect of testosterone treatment and the levels of significance on all primary psychiatric measures remained virtually unchanged.

We examined whether the categories of weight lifting and previous AAS use (no regular weight lifting and no previous use, regular weight lifting without previous use, previous use, and both weight lifting and previous use groups combined) were associated with a significant effect on outcome measures. We found no significant effect or even tendency toward an effect ($P < .10$) on any outcome measure in Table 2, regardless of whether these categories were treated as ordered or unordered.

Next, by examining response to testosterone treatment at the 300-mg level, as discussed in the "Participants and Methods" section, we found only a slight effect. The effect of testosterone treatment (mean ± SE) was 1.1 ± 0.6 ($\chi^2_1 = 3.68$; $P = .06$) on the YMRS, 1.2 ± 0.6 ($\chi^2_1 = 4.20$; $P = .04$) on the daily diary manic score, and 3.4 ± 0.1 ($\chi^2_1 = 4.49$; $P = .03$) on the daily diary liking score. The effect did not approach significance on the PSAP at 47 ± 39 ($\chi^2_1 = 1.41$; $P = .23$), or on the other measures.

Looking at the first treatment period only, the changes on psychiatric measures were similar to those found in the primary analysis but yielded lower levels of statistical significance. Of the 4 measures showing a significant effect for testosterone treatment in the primary analysis, the change in YMRS scores was significantly greater with testosterone than with placebo treatment (median, 2 vs 0; $z = 2.96$; $P = .003$). All changes on the other 3 measures showed a tendency toward statistical significance in the same direction (PSAP: median, 99 vs 14; $z = 1.71$; $P = .09$; daily diary manic scores: median, 0.1 vs -1.0; $z = 1.66$; $P = .10$; liking scores: median, 0 vs 0; $z = 1.62$; $P = .11$). As with the primary analysis, the difference between testosterone and placebo treatment on the other 4 primary psychological measures was not significant.

Finally, in an a posteriori analysis, we divided the evaluative participants into 3 groups based on maximum YMRS score attained during each treatment: marked responders (YMRS score of ≥ 20 , indicating manic symptoms likely to impair social and occupational functioning), moderate responders (YMRS scores of 10-19, indicating milder hypomanic symptoms), and minimal responders (YMRS scores of < 10). Because there were no significant period effects in the analyses of YMRS data, we scored participants' responses to testosterone treatment, regardless of the period during which it was administered. This classification yielded 2 marked, 6 moderate, and 42 minimal responders to testosterone treatment (Figure). By comparison, the 50 placebo periods produced no marked, 1 moderate, and 49 minimal re-

Table 2. Psychiatric Measures at Baseline and End Point With Placebo and Testosterone Treatment in 53 Evaluable Participants*

Measure	Placebo Treatment		Testosterone Treatment		Effect of Testosterone Treatment†	χ^2	P
	Baseline	End Point	Baseline	End Point			
YMRS score	0.3 ± 0.8	1.1 ± 2.5	0.5 ± 1.0	3.9 ± 4.9	2.6 ± 0.8	9.83	.002
PSAP score‡	208 ± 235	222 ± 241	208 ± 235	362 ± 301	167 ± 75	4.93	.03
Daily diaries							
Manic score	7.9 ± 3.8	7.4 ± 4.4	7.5 ± 4.2	9.2 ± 4.9	1.9 ± 0.6	9.09	.003
Liking score	50 ± 2.8	50 ± 4.9	51 ± 2.9	55 ± 12.0	5.0 ± 1.8	7.11	.008
Significant other diaries, manic score§	9.6 ± 4.4	9.7 ± 5.2	9.9 ± 5.1	11.4 ± 7.4	0.8 ± 1.4	0.39	.53
Aggression Questionnaire total score	56.4 ± 15.0	56.9 ± 16.0	55.7 ± 13.5	56.2 ± 15.8	1.0 ± 1.0	0.88	.35
SCL-90-R global severity index	0.10 ± 0.16	0.07 ± 0.10	0.07 ± 0.13	0.08 ± 1.6	0.04 ± 0.03	1.84	.18
Hamilton Depression Rating Scale score	1.0 ± 1.6	0.8 ± 1.2	0.9 ± 1.6	0.8 ± 1.4	-0.06 ± 0.37	0.02	.88

*Values are expressed as mean ± SD at the beginning and end of each treatment period as defined in the text. YMRS indicates Young Mania Rating Scale; PSAP, Point Subtraction Aggression Paradigm; and SCL-90-R, Symptom Checklist-90-R.

†The effect of testosterone treatment represents the estimate of the mean ± SE value of change during the testosterone period minus the change during the placebo period.

‡N = 27.

§N = 51.

sponses. Diary scores seemed to be consistent with this classification: manic scores of the 8 moderate or marked responders increased significantly more than those of the 42 minimal responders (median, 6.9 vs 0.2; $z = 3.90$; $P < .001$ by Wilcoxon rank sum test, 2-tailed), as did liking scores (median, 6 vs 0; $z = 2.93$; $P = .003$) and manic scores on the significant other diaries (median, 8.9 vs -0.2; $z = 3.48$; $P < .001$). We then compared the 8 moderate or marked responders with the 42 minimal responders on all baseline variables in Table 1 and on all physiological and laboratory variables in Table 3. The latter were examined at baseline and at the end of the testosterone period. No comparison yielded a significant difference. Also, none of the 11 individuals reporting a first-degree relative with a major mood disorder were among the 8 testosterone responders.

PHYSIOLOGICAL MEASURES

Although diet, exercise, and times of blood drawing were not standardized across participants in this primarily psychiatric study, testosterone treatment produced expected changes on physiological and laboratory test results (Table 3).^{27,37,56} Measures differing significantly between testosterone and placebo treatment among the 53 fully evaluable participants are summarized in Table 3; all other measures on the standard chemistry, hematologic, and urinalysis battery produced no significant differences. No serious laboratory abnormalities or adverse medical events occurred during the study.

COMMENT

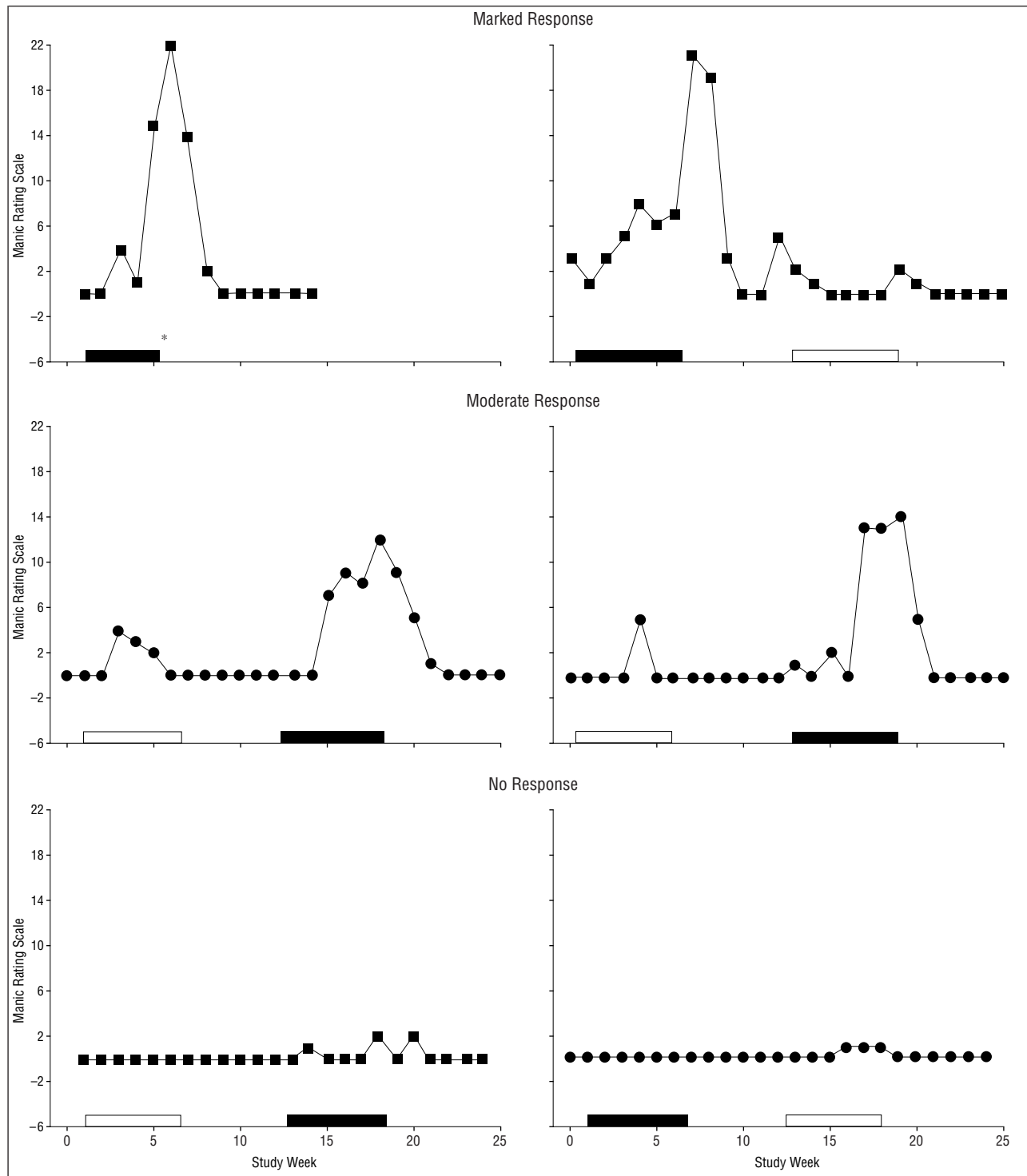
In a placebo-controlled, double-blind, crossover study of administration of supraphysiologic doses of testosterone cypionate to normal men, testosterone treatment significantly increased several measures of manic and aggressive symptoms; these effects seemed to be independent of whether the participant had engaged in regular weight lifting or had used AAS illicitly in the past. These effects were largely confined to a small group of “responders”—but this group proved indistinguishable from “non-

responders” on demographic, psychological, physiological, and laboratory measures. The small number of responders in this analysis raises the possibility of a type II error—failure to reject the null hypothesis when a true difference exists. Also, the laboratory measures included total but not free testosterone, leaving open the small possibility that responders might have differed on the latter measure. However, such responses may be idiosyncratic and presently unpredictable.

Several limitations of the study should be considered. First, the crossover design raises the question of a carryover effect.^{50,51} Although statistical methods have low power to detect a carryover effect, it seems unlikely: among participants who received testosterone in the first treatment period, all psychiatric measures returned to baseline at least 1 week before the beginning of the second treatment period (in other words, no significant differences were found between values at week 1 and at week 12 on any variable using paired *t* tests). Furthermore, in the analysis of the first treatment period only—which avoids the issue of a carryover effect—testosterone treatment differed significantly from placebo treatment on the YMRS, and showed trends in the same direction on the PSAP and on manic and liking scores on the daily diaries. Nevertheless, a carryover effect cannot be completely excluded in the primary analysis.

Second, study measures did not produce uniformly positive findings: the self-rating scales (AQ and Symptom Checklist-90-R) and diaries completed by the participants' significant others showed few differences, comparable to those found on the YMRS, PSAP, and daily diaries. However, neither the AQ nor the Symptom Checklist-90-R rates hypomania,^{44,45} and the AQ may also be less sensitive than other measures of aggression.⁵⁷ The significant others' ratings also seemed to be insensitive, likely as a result of carelessness or noncompliance. Therefore, the YMRS, PSAP, and daily diaries were probably better adapted to measuring effects of testosterone.

Another possible criticism is that some participants might have guessed when they were receiving testosterone and hence displayed bias because of expecta-



Responses of 6 participants to testosterone cypionate treatment on the Young Mania Rating Scale. Black bars represent testosterone treatment periods; white bars, placebo periods. Asterisk indicates discontinuation of testosterone treatment after week 5 for this participant because of rapidly escalating manic symptoms.

tional effects.³¹ However, several observations weigh against this possibility. First, individuals previously experienced with AAS use or with regular weight lifting would presumably be more sensitive to expectational effects than those with no such experience. Yet, as mentioned previously, neither previous AAS use nor regular weight lifting was significantly associated with manic or aggressive responses to testosterone. Second, expecta-

tional bias would not easily explain the testosterone treatment effect on the PSAP, in which the participant was not informed that he was being tested for aggression. Third, there was no significant correlation between change in lean body mass and changes on the 8 psychiatric measures shown in Table 2 ($P > .10$ in all cases by Spearman rank correlation), suggesting that increased size and strength were not associated with elevated mood and ag-

Table 3. Physiological and Laboratory Measures That Changed Significantly With Testosterone Treatment*

Measure	Placebo Treatment		Testosterone Treatment		Effect of Testosterone Treatment†	χ^2	P
	Baseline	End Point	Baseline	End Point			
Physiological							
Systolic blood pressure, mm Hg	123 ± 11	119 ± 12	124 ± 12	127 ± 12	7.5 ± 2.4	10.0	.002
Testicular length, mm	47.0 ± 5.0	48.0 ± 3.9	48.0 ± 4.6	44.0 ± 4.7	-3.8 ± 0.8	20.9	<.001
Lean body mass, kg	68.9 ± 9.2	69.5 ± 9.4	68.0 ± 9.6	71.5 ± 9.6	3.0 ± 0.4	59.0	<.001
Chemistry							
Aspartate aminotransferase, U/L	27 ± 12	27 ± 22	23 ± 6	29 ± 13	4.6 ± 1.9	6.1	.01
Albumin, g/L	48 ± 3	48 ± 3	47 ± 3	46 ± 2	-2.0 ± 0.4	14.5	<.001
HDL cholesterol, mmol/L	1.24 ± 0.41	1.22 ± 0.44	1.24 ± 0.41	0.96 ± 0.28	-0.27 ± .05	25.4	<.001
Cholesterol-HDL ratio	4.1 ± 1.6	4.0 ± 1.6	3.9 ± 1.5	4.7 ± 1.6	0.8 ± 0.2	23.4	<.001
Hematology							
White blood cell count × 10 ⁹ /L	6.6 ± 1.8	6.8 ± 1.6	6.7 ± 1.5	8.1 ± 2.1	1.1 ± 0.3	10.1	.001
Hematocrit	0.45 ± 0.03	0.44 ± 0.05	0.44 ± 0.03	0.46 ± 0.03	0.02 ± 0.01	10.7	.001
Hemoglobin, g/L	153 ± 10	150 ± 9	148 ± 9	152 ± 11	7 ± 2	12.8	<.001
Mean corpuscular hemoglobin, pg	30 ± 2	30 ± 2	30 ± 2	30 ± 2	0.7 ± 0.1	19.8	<.001‡
Urine							
Urine pH	5.7 ± 0.8	5.5 ± 0.6	5.7 ± 0.7	6.0 ± 0.7	0.5 ± 0.2	9.3	.004‡
Endocrine							
Testosterone, nmol/L§	16.3 ± 5.9	18.4 ± 11.4	17.4 ± 4.9	76.0 ± 21.9	56.9 ± 3.8	211.4	<.001
Luteinizing hormone, IU/L	53 ± 13	51 ± 12	52 ± 11	34 ± 8	-16 ± 2	45.4	<.001
Follicle-stimulating hormone, IU/L	232 ± 75	239 ± 76	239 ± 83	140 ± 40	-100 ± 13.2	57.9	<.001
Prolactin, µg/L	10.5 ± 5.8	11.4 ± 5.3	10.9 ± 5.4	19.0 ± 6.8	6.0 ± 1.1	28.7	<.001

*Values are expressed as mean ± SD at the beginning and end of each treatment period as defined in the text. HDL indicates high-density lipoprotein.

†The effect of testosterone treatment represents the estimate of the mean ± SE value of change during the testosterone period minus the change during the placebo period.

‡One participant was withdrawn from the study after 5 injections because of severely hypomanic symptoms (see text). Although he is included in the analysis of psychological measures (see text and Table 2), he was excluded from the laboratory measures. Therefore, N = 52 for all measures except for the neuroendocrine measures, where N = 51 because of missing data on 1 participant.

§To convert testosterone from nanomoles per liter to nanograms per deciliter, divide nanomoles per liter by 0.0347.

Table 4. Placebo-Controlled Studies Examining Psychiatric Effects of Administration of Testosterone, ≥500 mg/wk, or the Equivalent

Study	Drug and Dosage	Participants Receiving Full Dose, No.	Participants Exhibiting Manic or Hypomanic Reactions, No. (%)
Su et al ³⁵	Methyltestosterone, 240 mg/d	20	2 (10)
Bhasin et al ³⁷	Testosterone enanthate, 600 mg/wk	21	0 (0)
Yates et al ³⁶	Testosterone cypionate, 500 mg/wk	18	1 (6)
Present study	Testosterone cypionate, 600 mg/wk	50	2 (4)
Total	...	109	5 (5)*

*The 95% confidence interval for frequency of manic or hypomanic reactions, 1.4% to 10.4%.

gression scores. These reasons notwithstanding, we cannot exclude the possibility of expectational bias.

Conversely, several methodological limitations may have caused us to underestimate the psychiatric effects of testosterone treatment. First, the modest dose and duration of testosterone treatment in our study, chosen for considerations of safety, did not match the high doses of AAS, frequently comprising several agents taken simultaneously and often ingested, by illicit users.⁵⁻⁷ Second, we excluded prospective participants with a history of a major psychiatric disorder, but illicit users do not select themselves with similar care. Third, study participants were not permitted to use illicit drugs during the study, and none regularly consumed large amounts of alcohol. Illicit AAS users, lacking such restrictions, might be at higher risk for psychiatric effects than participants taking testosterone alone. Fourth, we withdrew 2 participants from testosterone treatment during the study because of adverse psychiatric effects; had these participants hypothetically con-

tinued through the full protocol, the effect of testosterone treatment might have been greater. For these reasons, the findings of the present investigation may represent a "lower bound" for the true rate of psychiatric effects exhibited by AAS users in the field.

In summary, our findings augment the evidence that administration of 300 mg per week of testosterone or the equivalent produces few psychiatric effects,^{6,23,27-34,36} whereas dosages of 500 per week or more produce occasional prominent manic or hypomanic reactions (**Table 4**). Such reactions are probably more frequent "in the field" than in the laboratory and may represent an underrecognized public health problem. To understand the biological or psychological contexts for these seemingly idiosyncratic reactions, future investigators should consider using larger sample sizes, more sophisticated batteries of neuroendocrine measures, and more detailed assessments of baseline psychological and neuropsychological indices.

Accepted for publication March 5, 1999.

This study was supported in part by grant RO1-DA06543 from the National Institute on Drug Abuse, Rockville, Md.

We are indebted to Alicja Skupny and Jack Mendelson, MD, for the performance and interpretation of the neuroendocrine measures; Don H. Catlin, MD, and Caroline K. Hatton, PhD, of the UCLA Olympic Analytical Laboratory, Los Angeles, Calif, for urinary anabolic-androgenic steroid testing; Pharmacia & Upjohn Co, Bridgewater, NJ, for supplying testosterone cypionate and matched placebo; David Katz, MD, for assistance with the design of the study and commentary on the manuscript; David Amato, PhD, and Garrett Fitzmaurice, PhD, for assistance with statistical analyses; and Paul Oliva and John Borowiecki for assistance with data collection and management.

Reprints: Harrison G. Pope, Jr, MD, MPH, Biological Psychiatry Laboratory, McLean Hospital, 115 Mill St, Belmont, MA 02178 (e-mail: pope@mclean.harvard.edu).

REFERENCES

1. Pope HG Jr, Katz DL. Psychiatric effects of exogenous anabolic-androgenic steroids. In: Wolkowitz OM, Rothschild AJ, eds. *Psychoneuroendocrinology for the Clinician*. Washington, DC: American Psychiatric Press. In press.
2. Yesalis CE, Kennedy NJ, Kopstein AN, Bahrke MS. Anabolic-androgenic steroid use in the United States. *JAMA*. 1993;270:1217-1221.
3. Buckley WA, Yesalis CE, Friedl KE, Anderson W, Streit A, Wright J. Estimated prevalence of anabolic steroid use among male high school seniors. *JAMA*. 1988; 260:3441-3445.
4. Durant RH, Rickert VI, Ashworth CS, Newman C, Slavens G. Use of multiple drugs among adolescents who use anabolic steroids. *N Engl J Med*. 1993;328:922-926.
5. Pope HG Jr, Katz DL. Affective and psychotic symptoms associated with anabolic steroid use. *Am J Psychiatry*. 1988;145:487-490.
6. Pope HG Jr, Katz DL. Psychiatric and medical effects of anabolic-androgenic steroid use. *Arch Gen Psychiatry*. 1994;51:375-382.
7. Parrott AC, Choi PYL, Davies M. Anabolic steroid use by amateur athletes: effects upon psychological mood states. *J Sports Med Phys Fitness*. 1994;34:292-298.
8. Choi PYL, Parrott AC, Cowan D. High-dose anabolic steroids in strength athletes: effects upon hostility and aggression. *Human Psychopharmacol*. 1990;5:349-356.
9. Lefavi RG, Reeve TG, Newland MC. Relationship between anabolic steroid use and selected psychological parameters in male bodybuilders. *J Sports Behav*. 1990;13:157-166.
10. Perry PJ, Yates WR, Andersen KH. Psychiatric symptoms associated with anabolic steroids: a controlled, retrospective study. *Ann Clin Psychiatry*. 1990;2:11-17.
11. Moss HB, Panzak GL, Tarter RE. Personality, mood, and psychiatric symptoms among anabolic steroid users. *Am J Addict*. 1992;1:315-324.
12. Burnett KF, Kleiman ME. Psychological characteristics of adolescent steroid users. *Adolescence*. 1994;29:81-89.
13. Malone DA Jr, Dimeff R, Lombardo JA, Sample BRH. Psychiatric effects and psychoactive substance use in anabolic-androgenic steroid users. *Clin J Sports Med*. 1995;5:25-31.
14. Kashkin KB, Kleber HD. Hooked on hormones? an anabolic steroid addiction hypothesis. *JAMA*. 1989;262:3166-3170.
15. Brower KJ, Blow FC, Young JP, Hill EM. Symptoms and correlates of anabolic-androgenic steroid dependence. *Br J Addict*. 1991;86:759-768.
16. Conacher GN, Workman DG. Violent crime possibly associated with anabolic steroid use [letter]. *Am J Psychiatry*. 1989;146:679.
17. Bidwell M, Katz DL. Injecting new life into an old defense: anabolic steroid-induced psychosis as a paradigm of involuntary intoxication. *Univ Miami Entertainment Sports Law Rev*. 1989;7:1-63.
18. Pope HG Jr, Katz DL. Homicide and near-homicide by anabolic steroid users. *J Clin Psychiatry*. 1990;51:28-31.
19. Dalby JT. Brief anabolic steroid use and sustained behavioral reaction. *Am J Psychiatry*. 1990;149:271-272.
20. Stanley A. Anabolic steroids—the drugs that give and take away manhood: case with an unusual physical sign. *Med Sci Law*. 1994;34:82-83.
21. Choi PYL, Pope HG Jr. Violence toward women and illicit androgenic-anabolic steroid use. *Ann Clin Psychiatry*. 1994;6:21-25.
22. Pope HG Jr, Kouri EM, Powell KF, Campbell C, Katz DL. Anabolic-androgenic steroid use among 133 prisoners. *Compr Psychiatry*. 1996;37:322-327.
23. Bahrke MS, Wright JE, Strauss RH, Catlin DH. Psychological moods and subjectively perceived behavioral and somatic changes accompanying anabolic-androgenic steroid use. *Am J Sports Med*. 1992;20:717-724.
24. Bahrke MS, Yesalis CE. Weight training: a potential confounding factor in examining the psychological and behavioral effects of anabolic-androgenic steroids. *Sports Med*. 1994;18:309-318.
25. Riem KE, Hursley KG. Using anabolic-androgenic steroids to enhance physique and performance: effects on moods and behavior. *Clin Psychol Rev*. 1995;15: 235-256.
26. Rubinow DR, Schmidt PJ. Androgens, brain, and behavior. *Am J Psychiatry*. 1996; 153:974-984.
27. Bagatell CJ, Heiman JR, Matsumoto AM, Rivier JE, Bremner WJ. Metabolic and behavioral effects of high-dose, exogenous testosterone in healthy men. *J Clin Endocrinol Metab*. 1994;79:561-567.
28. Anderson RA, Bancroft J, Wu FCW. The effects of exogenous testosterone on sexuality and mood of normal men. *J Clin Endocrinol Metab*. 1992;75:1503-1507.
29. Hannan CJ, Friedl KE, Zold A, Kettler TM, Plymate SR. Psychological and serum homovanillic acid changes in men administered androgenic steroids. *Psychoneuroendocrinology*. 1991;16:335-343.
30. Forbes GB, Porta CR, Herr BE, Griggs RC. Sequence of changes in body composition induced by testosterone and reversal of changes after drug is stopped. *JAMA*. 1992;267:397-399.
31. Björkqvist K, Nygren T, Björklund AC, Björkqvist SE. Testosterone intake and aggressiveness: real effect or anticipation? *Aggr Behav*. 1994;20:17-26.
32. Griggs RC, Pandya S, Florence JM, et al. Randomized controlled trial of testosterone in myotonic dystrophy. *Neurology*. 1989;39:219-222.
33. Skakkebaek NE, Bancroft J, Davidson DW, Warner PM. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double-blind controlled study. *Clin Endocrinol*. 1981;14:49-61.
34. O'Carroll R, Bancroft J. Testosterone therapy for low sexual interest and erectile dysfunction in men: a controlled study. *Br J Psychiatry*. 1984;145:146-151.
35. Su T-P, Pagliaro M, Schmidt PJ, Pickar D, Wolkowitz OM, Rubinow DR. Neuro-psychiatric effects of anabolic steroids in male normal volunteers. *JAMA*. 1993; 269:2760-2764.
36. Yates WR, Perry P, Macindoe J, Holman T, Ellingrad V. Psychosexual effects of three doses of testosterone cycling in normal men. *Biol Psychiatry*. 1999;45: 254-260.
37. Bhasin S, Storer TW, Berman N, et al. The effect of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med*. 1996; 335:1-7.
38. Tricker R, Casaburi R, Storer TW, et al. The effect of supraphysiological doses of testosterone on angry behavior in healthy eugonadal men. *J Clin Endocrinol Metab*. 1996;81:3754-3758.
39. Spitzer RL, Williams JBW, Gibbon M. *Structured Clinical Interview for DSM-III-R (SCID)*. New York, NY: New York State Psychiatric Institute; 1989.
40. Jackson AS, Pollock ML. Generalized equations for predicting body density of man. *Br J Nutr*. 1978;40:497-504.
41. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
42. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry*. 1978;133:429-435.
43. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; 23:56-62.
44. Buss AH, Perry M. The Aggression Questionnaire. *J Pers Soc Psychol*. 1992;63: 452-459.
45. Derogatis LR. *Symptom Checklist-90-R: Administration, Scoring, and Procedures Manual*. Minneapolis, Minn: National Computer Systems Inc; 1994.
46. Catlin DH, Kammerer RC, Hatton CK, Sekera MH, Merdink JM. Analytical chemistry at the Games of the XXIIIrd Olympiad in Los Angeles, 1984. *Clin Chem*. 1987; 33:319-327.
47. Aguilera R, Becchi M, Casabianca H, et al. Improved method of detection of testosterone abuse by gas chromatography/combustion/isotope ratio mass spectrometry analysis of urinary steroids. *J Mass Spectrom*. 1996;31:169-176.
48. Cherek DR, Schnapp W, Moeller FG, Dougherty DM. Laboratory measures of aggressive responding in male parolees with violent and nonviolent histories. *Aggr Behav*. 1996;22:27-36.
49. Kouri EM, Lukas SE, Pope HG Jr, Oliva PS. Increased aggressive responding in male volunteers following the administration of gradually increasing doses of testosterone cypionate [published correction appears in *Drug Alcohol Depend*. 1998;50:255]. *Drug Alcohol Depend*. 1995;40:73-79.
50. Senn S. The AB/BA crossover: past, present and future? *Stat Methods Med Res*. 1994;3:303-324.
51. Freeman PR. The performance of the two-stage analysis of two-treatment, two-period crossover trials. *Stat Med*. 1989;8:1421-1432.
52. Schulte-Beerbuhl M, Nieschlag E. Comparison of testosterone, dihydrotestosterone, luteinizing hormone, and follicle-stimulating hormone in serum after ingestion of testosterone enanthate or testosterone cypionate. *Fertil Steril*. 1980; 33:201-203.
53. Nankin HR. Hormone kinetics after intramuscular testosterone cypionate. *Fertil Steril*. 1987;47:1004-1009.
54. SAS Institute Inc. *SAS/GIS Software* [computer program]: release 6.12. Cary, NC: SAS Institute Inc; 1997.
55. Kouri EM, Pope HG Jr, Katz DL, Oliva PS. Fat-free mass index in users and non-users of anabolic-androgenic steroids. *Clin J Sports Med*. 1995;5:223-228.
56. Kouri EM, Pope HG Jr, Oliva PS. Changes in lipoprotein-lipid levels in normal men following increasing doses of testosterone cypionate. *Clin J Sports Med*. 1996;6:152-157.
57. Allen TJ, Dougherty DM, Rhoades HM, Cherek DR. A study of male and female aggressive responding under conditions providing an escape response. *Psychol Rec*. 1996;46:651-664.