

## Effects of testosterone enanthate in normal men: experience from a multicenter contraceptive efficacy study\*

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**Objective:** To evaluate the secondary impact of a prototype androgen contraceptive regimen on physical, metabolic and behavioral variables.

**Design:** Prospective, open, noncomparative contraceptive efficacy study.

**Setting:** International multicenter study comprising 10 centers in seven countries.

**Subjects:** Two hundred seventy-one healthy men, age  $31.8 \pm 5.4$  years (mean  $\pm$  SD), range 21 to 45 years.

**Interventions:** Weekly IM injections of 200 mg T enanthate.

**Main Outcome Measures:** Adverse effects and discontinuations; biochemical and hematologic changes and interpopulation differences.

**Results:** Chinese subjects were shorter and lighter and their baseline hemoglobin, plasma lipid, and liver enzyme levels were lower than in non-Chinese subjects. The most common side effects were painful injections, acne, fatigue, and weight gain. Gynecomastia and prostate problems were detected in 24 and 9 men, respectively, though no men stopped injections for such reasons. Testosterone enanthate increased body weight, hemoglobin, and urea but decreased testicular volume and creatinine. Plasma triglyceride, cholesterol, and low-density lipoprotein cholesterol were unchanged; high-density lipoprotein cholesterol decreased by 14% to 18% in non-Chinese but was unchanged in Chinese men. Liver transaminases were increased by 36% to 51% in Chinese but were unchanged in non-Chinese subjects. These T enanthate-induced effects were reversible within 6 months of stopping injections and were not related to the duration of T exposure.

**Conclusions:** Testosterone enanthate administration in a contraceptive trial produced significant but reversible effects on skin, muscle, liver, lipid metabolism, and hemopoietic functions that varied between population groups. These effects reflect the relatively high peak levels and fluctuations of plasma T produced by the weekly T enanthate regimen rather than an inherent feature of hormonal male contraception. The results highlight the need for long-acting preparations of T with more stable delivery kinetics.      Fertil Steril 1996;65:626–36

**Key Words:** Testosterone enanthate, safety, male contraception, hormonal contraception, family planning, testis, pharmacology, pharmacodynamics

New approaches to contraception for men have been explored actively in the last decade. The ap-

proach most likely to be further developed is the suppression of spermatogenesis by hormonal inhibition of pituitary gonadotropin secretion. An ac-

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ceptable contraceptive for men, in addition to being uniformly efficacious, should have minimal effects on general metabolism and nonreproductive physiological functions. The present multicenter study has shown that azoospermia induced by a prototype hormone regimen, weekly IM injections of 200 mg of T enanthate, provided effective and reversible contraception in healthy men aged 21 to 45 years (1).

The safety of androgens, used as long-term physiological replacement therapy in hypogonadal men over the last 40 years, has been well documented (2). However, there is a dearth of systematic information on the use of androgenic steroids in eugonadal men, especially after more prolonged (over 12 months) exposure (3). It is therefore important to document the clinical experience gained from using an androgen-based contraceptive for up to 18 months in a large group of healthy men aged 21 to 45 years. Although the present study was designed to investigate the contraceptive efficacy of hormonal suppression of spermatogenesis, safety information, including patterns of possible adverse reactions to this prototype regimen, may have an important bearing in evaluating the feasibility of androgen-only male contraceptives, as well as improving future formulations of combination male contraceptive regimens in which androgens are required as replacement therapy.

This analysis therefore aimed to evaluate the secondary impact of a prototype androgen contraceptive regimen, known to produce elevated plasma levels of T, on various physical, metabolic, and behavioral variables in the setting of a contraceptive efficacy trial (1). Specifically, the following issues were addressed: [1] the incidence of adverse effects and discontinuations; [2] their relationship to the level of T and duration of exposure; [3] the reversibility of any adverse effects; and [4] the interpopulation differences in response to exogenous T.

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## MATERIALS AND METHODS

### Study Design

The design of this study has been reported in detail previously (1). Briefly, healthy men were recruited in 10 centers (3 in China and 7 in other countries) and given weekly IM injections of 200 mg of T enanthate (0.8 mL Testoviron Depot; Schering AG, Berlin, Germany or 1.0 mL Delatestryl; ER Squibb, Princeton, NJ). The suppression phase commenced from the date of the first injection until either azoospermia (defined as three consecutive semen samples at 2-weekly intervals showing no detectable spermatozoa) had been achieved or 6 months had elapsed without azoospermia being attained. On achieving azoospermia, the couple entered a 12-month efficacy phase during which no other form of contraception was used except continued T injections. Testosterone injections were discontinued in men who failed to achieve azoospermia within 6 months. All subjects entered a recovery phase from the time of the last T injection irrespective of the time of, or reason for, discontinuation and were followed until spermatogenesis recovered.

### Subjects and Monitoring

Healthy fertile men between 21 and 45 years of age requesting contraception underwent medical examinations before entry and at 3 monthly intervals during the study, in addition to the regular semen analyses to assess the degree of spermatogenic suppression. The examinations included measurement of height, weight, blood pressure, testis volume by orchimeter, and rectal palpation of the prostate gland. At each examination, a venous blood sample was obtained for measurement of hemoglobin, urea, creatinine, liver enzymes (aspartate aminotransferase [SGOT], alanine aminotransferase [SGPT], gamma glutamyl transferase [ $\gamma$ -GT]), and lipids (total cholesterol, high-density lipoprotein [HDL] and low-density lipoprotein [LDL] cholesterol fractions and triglyceride) and reproductive hormones (T, LH, and FSH). Only volunteers with normal semen analyses and normal anthropometric, hematologic, and biochemical variables were admitted into the study. At least two baseline serum and semen samples were obtained from each volunteer.

At each medical review, each subject was asked about any complaints or symptoms noticed during the past 3 months. Acne was defined as "pimples, spots, or pustules" on the back, shoulder, chest, or face. Testosterone administration was to be discontinued in the event of adverse drug reaction, significant intercurrent medical illness, persistent rise in blood pressure, abnormal liver enzymes, increase in

hematocrit to >55%, abnormal HDL or LDL cholesterol, or if injections were delayed by >2 days from schedule.

### Laboratory Methods

Routine hematologic and biochemical assays were performed by the standard methods in each center. Low-density lipoprotein cholesterol was calculated from total and HDL cholesterol by Friedwald et al.'s formula (4). Testosterone was measured by established RIA at each center. The reference ranges supplied by each center were used for the interpretation of individual and within-center results. Where the range of the baseline observations was discrepant from the supplied reference range, the former was used as the reference for comparison with that particular variable.

### Data Analysis

Because not all measurements were taken at the exact scheduled 3-monthly intervals, particularly after stopping injections, observations within a window ( $\pm 30$  days) were allowed. In cases where no such measurements were available, linear interpolation was used between adjacent values to estimate a value at the midpoint. This reduced the impact of any missing observations. To adjust for between-center differences in routine laboratory methods and reference ranges, serial observations were expressed as percentage change from the subject's own baseline pretreatment values. The three Chinese and seven non-Chinese centers also were analyzed separately because of the observed baseline differences in anthropometric and a number of physiological variables and the previously reported difference in rates of spermatogenic suppression (1). Comparison between groups were made by two-sample *t*-test and analysis of variance for continuous variables and contingency table methods for categorical variables. Data that were not normally distributed were log-transformed. Values were expressed as arithmetical means  $\pm$  SD unless otherwise stated. Body size was estimated by body surface area (BSA,  $m^2$ ) and body mass index (BMI,  $kgm^{-2}$ ) as defined previously (1).

## RESULTS

Two hundred seventy-one subjects (age  $31.8 \pm 5.4$  years; mean  $\pm$  SD) started T injections. The subjects included 82 Chinese ( $35.2 \pm 4.5$  years) and 189 non-Chinese ( $30.3 \pm 5.1$  years) men (Table 1). One hundred fifty-seven men (58%) achieved azoospermia and therefore proceeded into the efficacy phase of the study. Sixty-eight men (25%) failed to suppress

to azoospermia by 6 months; T enanthate was discontinued and they entered the recovery phase. The remaining 46 men (17%) discontinued during the suppression phase for a variety of reasons, including pregnancy ( $n = 8$ ); injection difficulties ( $n = 8$ ); medical conditions ( $n = 11$ ); incidental medical conditions ( $n = 2$ ) including aphthous ulcer and acute prostatitis; no further need for contraception ( $n = 12$ ); and loss to follow-up ( $n = 5$ ). During the efficacy phase, a further 38 subjects discontinued because of pregnancy ( $n = 1$ ); protocol violation ( $n = 2$ ); injection difficulties ( $n = 7$ ); medical conditions ( $n = 10$ ); incidental medical conditions (4) including pneumonia, Gilbert's disease, and dysmenorrhoea and an unspecified neurological illness in the partner; personal-social circumstances ( $n = 13$ ), and loss to follow-up ( $n = 1$ ). Recovery information on physical, biochemical, and hematologic parameters was available from 82% of subjects.

### Baseline Observations

The baseline anthropometric, biochemical, hematologic, and hormonal characteristics in 271 subjects at entry to the study are summarized in Table 1. There were significant differences between the three Chinese (82 subjects) and the seven non-Chinese centers (189 subjects). Men in Chinese centers were significantly older (35.2 versus 30.3 years), smaller (height, weight, and BSA), and thinner (BMI) than those in other centers; they also had slightly smaller testicular volumes (22.0 versus 24.2 mL) and lower systolic blood pressure (117 versus 125 mm Hg). Total, LDL, and HDL cholesterol and triglycerides were significantly lower and the HDL:LDL cholesterol ratio was higher in Chinese men. Serum transaminases, urea, and hemoglobin were significantly lower but hematocrit and creatinine were higher in Chinese compared with non-Chinese men. There were no significant differences in mean baseline LH, FSH, and T concentrations between Chinese and non-Chinese subjects (Table 1).

### Testosterone Concentration

The regimen of 200 mg T enanthate every 7 days delivered an average daily dose of approximately 20 mg T. Total duration of T exposure in this study was 2,720.3 man-months (1,000.4 man-months in Chinese and 1,719.9 man-months in non-Chinese centers) in the suppression and efficacy phases. The mean trough T level at 90 days was  $44.7 \pm 17.1$  nmol/L or 132% (95% confidence interval [CI] 118% to 146%) above baseline with no significant differences between Chinese and non-Chinese subjects. However, the mean increase from baseline levels

**Table 1** Baseline Variables

|                                      | All centers        | Chinese centers   | Non-Chinese centers | <i>P</i> value† |
|--------------------------------------|--------------------|-------------------|---------------------|-----------------|
| <b>Physical variables*</b>           |                    |                   |                     |                 |
| Body weight (kg)                     | 72.4 ± 12.8 (271)  | 62.8 ± 9.7 (82)   | 76.6 ± 11.7 (189)   | <0.001          |
| Mean testicular volume (mL)          | 22.0 ± 5.0 (271)   | 20.2 ± 3.7 (82)   | 22.8 ± 5.3 (189)    | <0.001          |
| Blood pressure systolic (mm Hg)      | 122.8 ± 13.6 (271) | 117.2 ± 10.5 (82) | 125.2 ± 14.0 (189)  | <0.001          |
| Blood pressure diastolic (mm Hg)     | 76.7 ± 9.7 (271)   | 77.1 ± 8.1 (82)   | 76.5 ± 10.3 (189)   | 0.640           |
| Body mass index (kgm <sup>-2</sup> ) | 23.5 ± 3.3 (271)   | 22.0 ± 2.8 (82)   | 24.2 ± 3.2 (189)    | <0.001          |
| Body surface area (m <sup>2</sup> )  | 1.87 ± 0.2 (271)   | 1.7 ± 0.1 (82)    | 1.9 ± 0.2 (189)     | <0.001          |
| <b>Clinical chemistry*</b>           |                    |                   |                     |                 |
| Hemoglobin                           | 15.0 ± 1.0 (267)   | 14.4 ± 1.0 (80)   | 15.2 ± 0.8 (187)    | <0.001          |
| Hematocrit                           | 45.3 ± 3.0 (263)   | 46.3 ± 4.0 (80)   | 44.9 ± 2.3 (183)    | <0.001          |
| Blood urea                           | 5.2 ± 1.3 (263)    | 4.7 ± 0.9 (80)    | 5.5 ± 1.3 (183)     | <0.001          |
| Serum creatinine                     | 94.3 ± 14.4 (264)  | 97.7 ± 21.1 (79)  | 92.8 ± 10.1 (185)   | 0.011           |
| <b>Liver function‡</b>               |                    |                   |                     |                 |
| SGOT                                 | 20.8 — (267)       | 15.9 — (80)       | 23.3 — (187)        | <0.001          |
| SGPT                                 | 20.0 — (261)       | 12.0 — (80)       | 25.2 — (181)        | <0.001          |
| γ-GT                                 | 16.8 — (268)       | 14.1 — (80)       | 18.2 — (188)        | <0.001          |
| <b>Lipids‡</b>                       |                    |                   |                     |                 |
| Total cholesterol                    | 4.90 — (262)       | 4.21 — (74)       | 5.20 — (188)        | <0.001          |
| LDL cholesterol                      | 3.00 — (215)       | 2.56 — (74)       | 3.25 — (141)        | <0.001          |
| HDL cholesterol                      | 1.20 — (254)       | 1.15 — (74)       | 1.23 — (180)        | 0.030           |
| HDL:LDL ratio                        | 0.40 — (215)       | 0.45 — (74)       | 0.38 — (141)        | 0.002           |
| Triglycerides                        | 1.05 — (212)       | 0.88 — (71)       | 1.15 — (141)        | 0.002           |

\* Values are means ± SD with number of subjects in parentheses.

† Difference between centers (two sample *t*-test).

‡ Values are geometric means with number of subjects in parentheses.

after 180 days was higher in Chinese than in non-Chinese subjects (182% versus 132%, *P* = 0.003) and similarly after 270 days (151% versus 115%, *P* = 0.02).

### Complaints and Adverse Reactions

Fifteen subjects (eight during suppression and seven during efficacy) discontinued because of discomfort or pain at the site of injections (cumulative annual discontinuation rate of 7.5%). Other specific symptoms reported by the subjects are summarized in Table 2. A total of 80 subjects (29.5% of 271 recruits) complained of increased acne, predominantly of a truncal distribution affecting the shoulder and

back, and/or increased oiliness of the skin at least once during T enanthate treatment. Of these, 32 subjects (40%) registered this complaint for the first time within 3 months and a further 33 (81.3% cumulative) after 6 months of T enanthate exposure. The acne was severe enough to warrant discontinuation from the study in nine subjects (all non-Chinese), three of whom required treatment with tetracycline (2) or isotretinoin with ultraviolet light (1). In the majority of subjects, acne resolved within 6 months of termination of treatment. Weight gain was reported by 10 non-Chinese men who remained in the study. However, two Chinese subjects complained of weight gain (3 and 5 kg) during the first 3 months of T enanthate treatment and discontinued for this reason. Twenty-two men (17 Chinese and 5 non-Chinese) remarked on increased fatigue and tiredness. One of these discontinued after 6 months. An increase in aggression was reported by seven subjects (all non-Chinese); three of these discontinued, one having received only one injection of T enanthate. Four non-Chinese men noticed cyclical changes in mood, one of these discontinued because of depression and increased libido. Decline in sexual interest was reported in four, but an increase was noted by eight subjects. Two men who experienced increased sexual interest also reported increased aggression and discontinued from the study because of the latter symptom. Decrease in testis size, increase in breast tissue, and disturbed sleep were reported by two, two, and three non-Chinese subjects, respectively, none resulting in discontinuation from the

**Table 2** Symptoms Reported by Volunteers During Study

| Symptom                 | Subjects reporting symptom at least once |                     |             | No. of subjects discontinued for this reason |
|-------------------------|--|---------------------|-------------|--|
|                         | Chinese centers                          | Non-Chinese centers | All centers |  |
| Acne                    | 12                                       | 68                  | 80          | 9  |
| Fatigue                 | 17                                       | 5                   | 22          | 1  |
| Increased weight        | 2  | 10                  | 12          | 2  |
| Increased sex drive     | 0  | 8                   | 8           | 0  |
| Aggressiveness          | 0  | 7                   | 7           | 3  |
| Mood change             | 0  | 4                   | 4           | 1  |
| Decreased sex drive     | 0  | 4                   | 4           | 0  |
| Increased breast tissue | 0  | 3                   | 3           | 0  |
| Disturbed sleep         | 0  | 3                   | 3           | 0  |
| Increased muscularity   | 0  | 2                   | 2           | 0  |
| Decreased testis size   | 0  | 2                   | 2           | 0  |

study. All symptoms resolved during the recovery phase.

Gynecomastia was detected in 24 non-Chinese subjects; 17 of these were from a single center. Thirteen subjects had detectable gynecomastia at the pretreatment examination before T enanthate treatment; 11 of these continued to have gynecomastia during treatment and/or recovery. Nine subjects apparently developed gynecomastia during T enanthate treatment and 2 developed it during recovery. No men stopped injections because of gynecomastia nor were any men treated for the condition.

There were nine observations of prostatic problems. One Chinese subject, who also complained of excessive tiredness and sleepiness, was reported to have acute prostatitis. Eight non-Chinese subjects, six from one center, were found to have prostatic abnormalities, which were described as "increased volume" (1), "slightly enlarged" (5), and no details provided (2). Two of these prostatic problems were recorded for the first time in the recovery period. The other six were reported during T enanthate treatment but not during recovery. None of these men stopped injections for this reason.

Similar levels of T before or during T enanthate administration were found in subjects who discontinued (Table 2) compared with the rest of the group or between those who discontinued for medical and nonmedical (personal-social or injection difficulties) reasons. Plasma T was not significantly different in those subjects reported to have acne or prostatic abnormalities compared with those who did not.

### Changes in Physical Parameters

Serial percentage change from baseline in body weight, blood pressure, and testicular volume during T enanthate administration and recovery are shown in Figure 1A. Body weight increased by  $3.6\% \pm 3.8\%$  at 90 days and  $5.0\% \pm 4.6\%$  at 360 days. There was no significant difference between these two time points to suggest a progressive effect of T enanthate on body weight. After discontinuing treatment, mean body weight had declined significantly and was still slightly above baseline ( $+1.8\%$ ) by 180 days (Fig. 1A). There was no difference between Chinese and non-Chinese subjects in the percentage weight gain. Systolic blood pressure increased persistently by 2.0% to 3.3% during T enanthate treatment but the increase in diastolic pressure was only significant at 180 days (2.7%) (Fig. 1A). These observed mean blood pressure increments were moderate and probably not clinically significant. One subject was discontinued from the study because of a persistently elevated diastolic blood pressure  $>95$  mm Hg in the first 6 months of the study. Testicular volume

decreased progressively with T enanthate treatment to a nadir of  $-19.5\%$  of baseline in Chinese subjects by 360 days whereas non-Chinese subjects showed an abrupt decline at 90 days ( $-19.4\%$  of baseline) and less of a decline between 90 and 360 days ( $-26.2\%$  of baseline) (Fig. 2E). In both groups, testicular volume regained pretreatment dimensions by 180 days after discontinuing T enanthate (Figs. 1A and 2E).

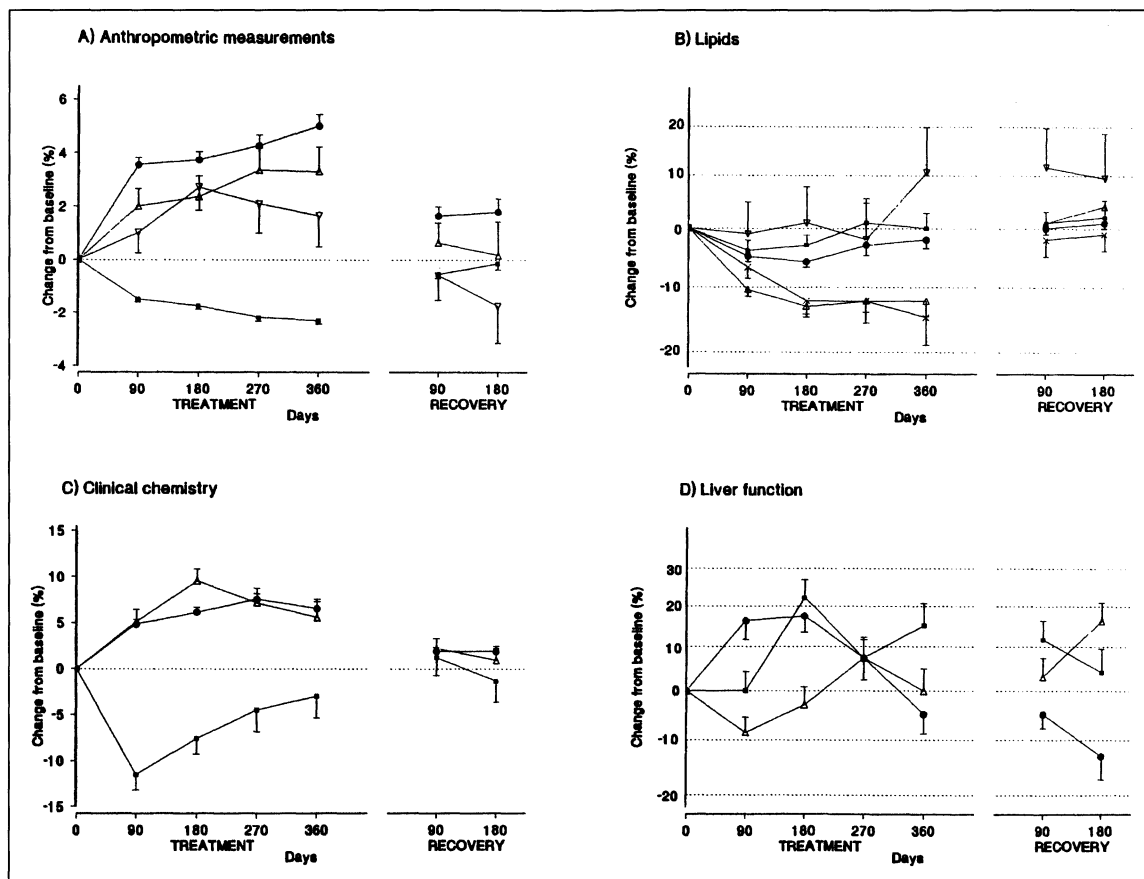
### Changes in Laboratory Measures

Hemoglobin and hematocrit increased by 7.6% and 6.4%, respectively, during T enanthate treatment and returned to baseline values by 90 days post-treatment (Fig. 1C, hematocrit not shown). Although the Chinese men showed only a modest ( $<2.7\%$ ) but progressive rise, hemoglobin in non-Chinese men displayed a greater and more abrupt increase by 7.0% to 9.5% from 90 days (Fig. 2F). Two non-Chinese men were discontinued because of elevations in hematocrit  $>55\%$ .

Blood urea decreased and creatinine increased reciprocally during T enanthate treatment (Fig. 1C). The changes were greatest during the first 180 days of treatment and reversed completely by 90 days post-treatment. There were no consistent differences between Chinese and non-Chinese subjects.

The aspartate and alanine aminotransferase enzymes showed marked population differences in response to exogenous T (Fig. 2C and D). Although these hepatic enzymes in non-Chinese subjects were unchanged throughout the study, increases of up to 36% for SGOT and 51% for SGPT were detected in Chinese subjects during T enanthate treatment. However, despite these rises, the absolute values of SGOT and SGPT remained within the physiological ranges. Insufficient hepatic enzyme data in the recovery phase were received from the three Chinese centers to confirm that these changes reversed, although there were no reports of clinical signs of liver damage. Mean  $\gamma$ -GT levels were not changed significantly in either population during T exposure.

Serum triglyceride did not change significantly during the study (Fig. 1B). Total cholesterol decreased by 5% and 6% at 90 and 180 days of treatment, respectively. This predominantly represented changes in non-Chinese men because no significant changes in total cholesterol were observed in the Chinese subjects. Similarly, HDL cholesterol decreased only in non-Chinese subjects by 14% to 18% during T enanthate treatment (Fig. 1B and 2A). Two non-Chinese subjects discontinued from the study as a result of lowered HDL cholesterol levels. Low-density lipoprotein cholesterol did not alter signifi-



**Figure 1** Time course of changes in (A) anthropometric (●, body weight; •, testis size [ $\times 10$ ]; △, systolic BP; ▽, diastolic BP) (B) lipid (●, total cholesterol; •, LDL cholesterol; △, HDL cholesterol; ▽, triglycerides; ×, HDL:LDL ratio), (C) biochemical-hematologic (●, hemoglobin; •, urea; △, creatinine), and (D) liver function parameters (●, SGOT; •, SGPT; △, γ-GT) in healthy men from 10 centers during and after treatment with T enanthate 200 mg IM weekly in a male contraceptive study. Results are expressed as mean  $\pm$  SE percentage changes from baseline. The lipid and liver function data are on a log scale. The break in the x-axis indicates that duration of treatment and, hence, entry into the recovery phase was before 360 days in those individuals who discontinued if they did not achieve azoospermia by 180 days or for other reasons (see Materials and Methods and Data Analysis).

cantly except at 90 days of treatment by  $-6\%$  in non-Chinese subjects (Fig. 1B). The HDL:LDL cholesterol ratio was unaltered in Chinese subjects but showed a sustained reduction of  $14\%$  to  $18\%$  during T enanthate treatment in non-Chinese men (Fig. 2B). These lipid changes were fully reversible by 90 days after discontinuation of T (Fig. 1B).

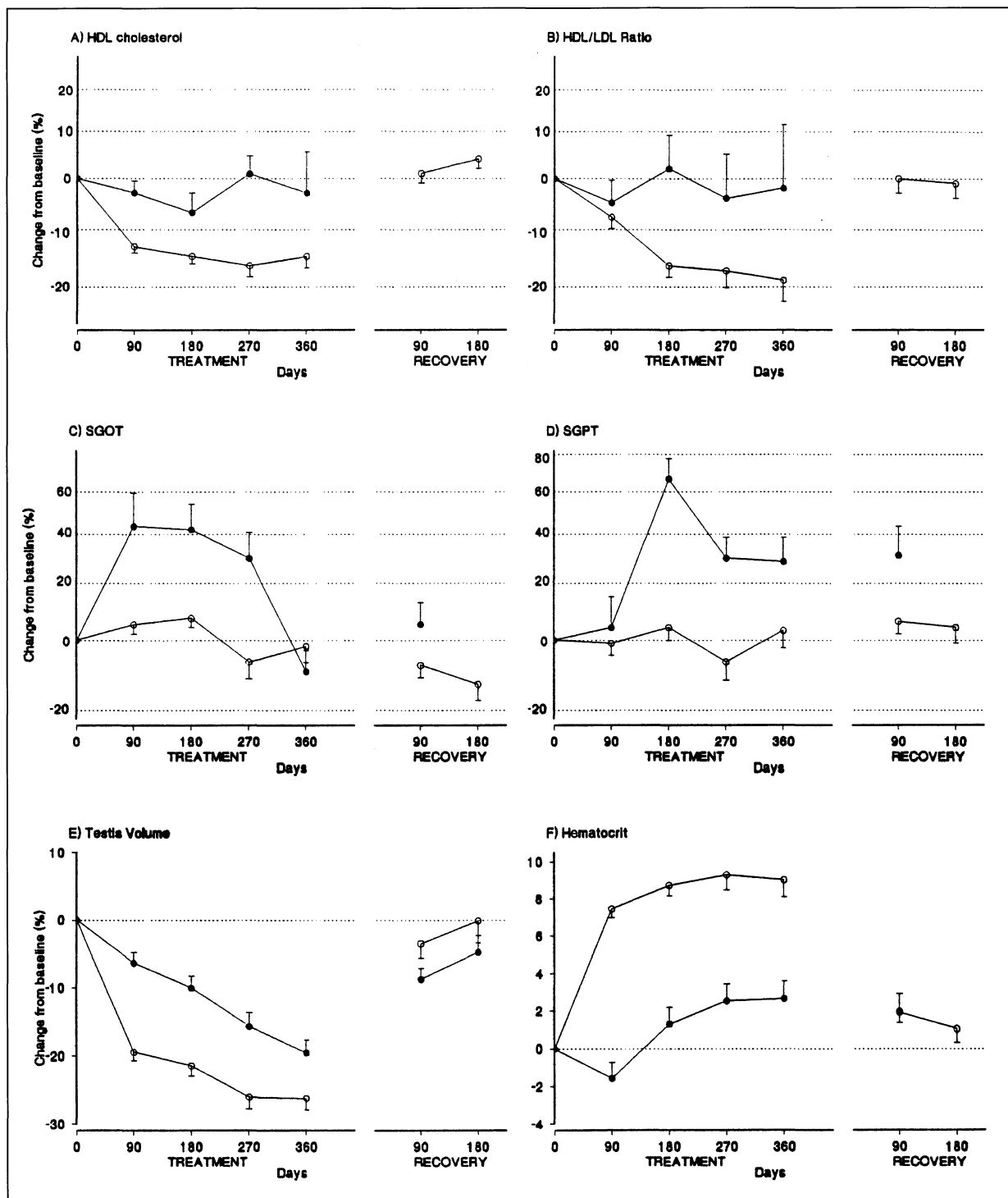
## DISCUSSION

Suppression of spermatogenesis to a level compatible with adequate contraception through gonadotropin inhibition can be achieved only if endogenous T production also is reduced. Thus, T administration, for either physiological replacement to maintain extratesticular androgen-dependent functions or, as in the present study, for suppression of gonadotropins, is an indispensable component of a hormonal male contraceptive method. Even though the unfavorable

pharmacokinetics of weekly T enanthate injections make it an unlikely candidate as a future contraceptive androgen for men, the current data, being the largest available on the effects of exogenous T in normal men, present a unique opportunity to assess the effects of an androgenic ester on metabolic and other physiological functions. They also provide a benchmark against which the secondary effects of other hormonal male contraceptive methods can be compared.

## Testosterone Enanthate Regimen and T Concentration

Weekly IM injections of 200 mg of T enanthate is a prototype regimen used in this study to examine the principle that hormonal suppression of spermatogenesis to azoospermia can provide effective and reversible contraception. The relatively short duration



**Figure 2** Time course of changes in (A) HDL cholesterol, (B) HDL:LDL cholesterol ratio, (C) aspartate aminotransferase SGOT, (D) alanine aminotransferase SGPT, (E) testis volume, and (F) hematocrit in healthy men from three Chinese centers and seven non-Chinese centers during and after treatment with T enanthate 200 mg IM weekly in a male contraceptive study. Results are expressed as mean  $\pm$  SE percentage changes from baseline. The number of observations in the recovery phase from Chinese centers were limited; some of these values therefore were omitted from the graphs. The lipid and liver function data are on a log scale. The break in the x-axis indicates that duration of treatment and, hence, entry into the recovery phase was before 360 days in those individuals who discontinued if they did not achieve azoospermia by 180 days or for other reasons (see Materials and Methods and Data Analysis). ●, Chinese; ○, non-Chinese.

of action of T enanthate and its pharmacokinetic characteristics generate striking fluctuations in plasma T that necessitate a 7-day injection interval to achieve adequate spermatogenesis suppression. Suppression of spermatogenesis therefore can be maintained only at the expense of accommodating repeated high peaks (and troughs) in T concentrations (5). After a single injection of 200 to 250 mg of T enanthate, plasma T concentrations peak 6 to 12 hours later, at concentrations 400% to 500% above baseline, followed by an exponential decline in the ensuing 10 to 14 days (6). Because of this fluctuation in T concentrations during the 7-day injection interval, the 132% increase in preinjection plasma T underestimates the overall androgen exposure in the subjects.

### **Adverse Effects**

The most common side effect reported was the pain of IM injections of T enanthate, which led to discontinuation in 15 subjects. Acne, affecting the upper back mostly, and associated with increased greasiness of the skin, was the second most common complaint. This is compatible with the observation that sebum excretion rates in the forehead and particularly the upper back both were increased significantly in normal men in response to weekly administration of 200 mg of T enanthate (Wu FCW, Anderson RA, abstract). The relatively high incidence (29.3%) of this complaint compared with eugonadal men given similar doses of T in a depot formulation that maintains stable circulating levels (7) may be a reflection of the higher and repeated peak elevations of ambient T concentrations after each T enanthate injection.

Weight gain was reported by 12 subjects although this was given as the main reason for withdrawal from the study in only 2 subjects. The average increase in body weight was between 4% and 5% or 3 and 4 kg, which was reversible in the majority of subjects. Dual-energy roentgenogram absorptiometry measurements of body composition in nonathletic men taking part in this study showed that the T enanthate-induced weight gain was associated with a decrease in fat mass of 15% and an increase in fat-free mass of 10% (8). That the gain in fat-free mass probably represented lean body mass was suggested by similar findings using electrical impedance measurements (Wu FCW, Anderson RA, abstract). These observations conform to the dose-response relationship between lean body mass and total androgen dose described by Forbes (9). At the current T enanthate dose, the magnitude of these changes in body composition was relatively modest and not associated with any major increase in muscle strength (8).

It is of interest that, out of the 24 instances of gynecomastia detected by the investigators, only 3 subjects reported this as a symptom and none discontinued. Furthermore, 71% of detected gynecomastia was documented in one center and 54% at the pretreatment examination.

Eight men noticed an increase in sexual interest, while four complained of diminished libido and seven were reported to have been more aggressive. In two instances of altered behavior, it was the partner who noticed both an increased sexual interest and behavioral changes. In addition, one of these men complained of frequent waking and sleep disturbance. Although these isolated examples of behavioral change are important, their real significance is difficult to assess in an open uncontrolled study where the possibility of placebo effects cannot be excluded. A recent placebo-controlled study in normal men given the same dose of T enanthate or placebo for 4 weeks did not show any increase in self-reported measures of "aggressive feelings" or the frequency of sexual activity (10).

Despite the chronic elevation of plasma T in these subjects, the overall incidence of the above adverse reactions and other side effects believed to be associated with T (such as raised hematocrit, blood pressure, behavior, and lipid disturbances) leading to discontinuation from the trial was low (21 men in 2,345 months of use): a cumulative annual discontinuation rate of 9.7 (95% CI 5.3 to 14.0) per 100 man-years. The present data also suggest that there is no significant influence of duration of T exposure on the incidence or severity of adverse effects up to a maximum of 18 months. However, a highly motivated group of volunteers, such as those in this study, may have a relatively high threshold for complaints and reported side effects compared with the general population.

### **Lipid Metabolism**

The present data showed that exogenous T induced a reversible and selective reduction in HDL cholesterol of 14% to 18% without any concurrent changes in LDL or triglyceride. This is in general agreement with findings of previous studies in eugonadal men (7, 11, 12), although the modest decline in total and LDL cholesterol was not confirmed in our large cohort. Both HDL<sub>2</sub> and HDL<sub>3</sub> subfractions and apoprotein A1 were depressed, although suppression of the former was greatest (12). In contrast, however, these findings differ from those of Friedl et al. (13) who found no significant changes, possibly because of the higher T dose (280 mg weekly), which produced higher levels of E<sub>2</sub>, thereby moderating some of the effects of T. The lowering of HDL chole-



terol was observed only in men of European but not those of Chinese origin. The reasons for this variation are unclear. Although plasma T was higher in Chinese compared with non-Chinese men during T enanthate treatment at 180 and 270 days, there was no difference in plasma T after 90 days when HDL cholesterol was significantly lower in non-Chinese subjects. The lower pretreatment levels of plasma triglyceride and lipoproteins in Chinese men may indicate that there are distinctive genetic, dietary, lifestyle, or environmental factors affecting lipid metabolism and/or liver function in this population group.

Testosterone lowers circulating HDL cholesterol by increasing hepatic triglyceride lipase activity in hypogonadal men (14). High-density lipoprotein is important in cholesterol removal from peripheral tissues to the liver via reverse cholesterol transport (15). Epidemiological data have shown an association between low levels of HDL and an increased risk for coronary artery disease (16). Low endogenous plasma T and low HDL cholesterol levels have been shown to be associated with increased cardiovascular disease risk in men (17). Whether the exogenous androgen-induced reduction in circulating HDL cholesterol in eugonadal men is associated with any impairment of tissue cholesterol removal is unknown. It also is uncertain whether lowered HDL alone, without simultaneous elevation in plasma levels of the atherogenic triglyceride-rich lipoproteins, has a direct pathogenic role in coronary artery disease or is merely an indirect marker for an underlying metabolic disturbance (18). It therefore is important to highlight the present findings that triglyceride, total cholesterol, and LDL cholesterol were unchanged during T enanthate administration. The complex interrelations of cholesterol, triglyceride, and many lipoproteins are such that it may be misleading to consider any single component of this system in isolation (16). Furthermore, T also may influence cardiovascular disease risk through other factors, such as decreased tissue plasminogen activator, lipoprotein(a), or vascular compliance (17). At present, the reduction in HDL cholesterol documented in this study therefore must be interpreted with caution and predictions concerning potential long-term hazards should not be based on a single surrogate marker for complex multifactorial diseases. More detailed studies on the overall effects of exogenous androgens on lipid metabolism and the endogenous thrombotic-antithrombotic factors undoubtedly are warranted.

### Prostate

Digital examination revealed prostatic enlargement in eight non-Chinese subjects. Of the six obser-

vations registered during T enanthate treatment, all became normal during recovery. No subject reported any urinary symptoms. No change in prostate-specific antigen was found in 30 men from one of the centers in this multicenter study but transrectal ultrasound demonstrated a 14% increase in prostate transverse area in four of five subjects who did not have any clinically detectable prostate enlargement (19). It is accepted that androgen plays a permissive role in prostatic development whereas androgen withdrawal or 5 $\alpha$ -reductase inhibition can decrease prostate size in patients with benign prostatic hyperplasia (20). The pathological and clinical significance of short-term prostate changes observed in this study is unclear at present. Whether prolonged androgen administration in young adults could predispose to prostatic disease in later life is obviously an important question. Monitoring of prostate function by all reliable means should be undertaken in future sex steroid-based male contraceptive studies and the safety of steroids proposed for general use as fertility regulating agents should be evaluated fully.

### Population Differences in Response to T

One of the most striking findings in this study are the differences in androgen-responsive variables such as acne, hemopoiesis, lipid metabolism, and levels of liver transaminases between Chinese and non-Chinese men. Some of these differences (hematocrit, lipids, and liver enzymes) were apparent before T administration. The pharmacokinetics of T enanthate are unlikely to be directly responsible because the responses to exogenous androgens apparently are not related to circulating T concentrations, differences in body size, or adiposity. These differences in androgen pharmacodynamics between Chinese and non-Chinese men appear not to be related to the observed differences in susceptibility to hormonal suppression of spermatogenesis (21). It is possible that variations in tissue-uptake of T, tissue-specific regulation of androgen action, environmental factors, or diet may be important. The apparent rise in transaminases in Chinese subjects had not been reported previously, and preliminary results from a second study using the same hormonal regimen do not confirm this pattern (WHO Task Force on Methods for the Regulation of Male Fertility, unpublished data). It is doubtful whether the observed rises in transaminase without any concurrent changes in  $\gamma$ -GT is indicative of hepatocellular damage. Regression toward the mean also could account for the apparent rise, in view of the unusually low baseline transaminase levels in the Chinese centers where transient elevations of these enzymes commonly are observed. Other factors, such as greater

degrees of tissue damage during IM injection in the Chinese men or technical laboratory problems also may have contributed to the observed patterns.

### Testosterone Enanthate and Nonreproductive Effects

The perturbations in metabolism and nonreproductive physiological functions documented in this study probably reflect the sustained elevation of plasma T and repeated high peak levels. It would seem prudent to minimize these disturbances by either lowering the dose of T and/or improving the pharmacokinetics of future regimens in order to avoid high peak concentrations of T. This, together with the impracticality and discomfort of weekly IM injections, makes T enanthate unsuitable for future use on a large scale. Long-acting androgen preparations such as T buciclate (22) or implantable crystalline pellets of T (7) may be able to effect a similar degree of spermatogenesis suppression at lower effective daily doses. Because of the dose-sparing property and more stable pharmacokinetics of these long-acting depot preparations, it is possible that androgen-related metabolic alterations and effects on the prostate and pilosebaceous units can be minimized without reducing efficacy. In addition to androgen-only contraceptive regimens, other approaches using GnRH antagonists (23) or progestogens (24) combined with physiological replacement doses of T also should be explored further.

The long-term pathophysiological consequences of the significant but reversible effects on the liver (transaminases and lipid metabolism), muscle, skin, and hemopoietic tissues during administration of T enanthate in a contraceptive trial are currently unknown. However, they probably reflect the widely fluctuating and high peak levels of plasma T produced by the present prototype T enanthate regimen rather than an inherent feature of the overall hormonal approach to male contraception. Now that the contraceptive efficacy of hormone suppression of spermatogenesis to azoospermia (1) and severe oligozoospermia (WHO Task Force on Methods for the Regulation of Male Fertility, unpublished data) is confirmed, the present results highlights the urgent need for long-acting preparations of T that can achieve stable plasma T levels over a prolonged period.

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