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A Clinical Trial of Injectable Testosterone Undecanoate as a Potential Male Contraceptive in Normal Chinese Men*

GUI-YUAN ZHANG, YI-QUN GU, XING-HAI WANG, YU-GUI CUI, AND WILLIAM J. BREMNER

Department of Endocrinology, National Research Institute for Family Planning (G.-y.Z), Beijing 100081, China; Population Center for Research in Reproduction, Department of Medicine, University of Washington, (Y.-q.G., W.J.B), Seattle, Washington 98195; Jiangsu Family Planning Research Institute, (X.-h.W.) Jiangsu 210029, China; and the Department of Endocrinology, Nanjing Medical University (Y.-g.C.), Jiangsu 210029, China

ABSTRACT

This is a pilot dose-finding study of spermatogenic suppression using testosterone undecanoate (TU) injections alone in normal Chinese men. Thirty-two healthy men were recruited. Volunteers underwent pretreatment evaluation, then a treatment period in which group I (n = 13) received 500 mg TU, group II (n = 12) received 1000 mg TU, and group III (n = 7) received placebo, respectively, at monthly intervals during the treatment period (or until azoospermia was achieved). Thereafter, they underwent a recovery period until all parameters returned to pretreatment levels. Eleven of 12 volunteers in the 500-mg TU group, and all volunteers in the 1000-mg TU group became azoospermic. Faster suppression of spermatogenesis was achieved in the 1000-mg TU group. Serum testosterone increased significantly in the higher dose group at weeks 8 and 12, but remained within the normal range. Mean serum LH and FSH were profoundly suppressed by both doses to undetectable levels at week 16. TU injections did not cause a significant change in high density lipoprotein cholesterol levels. No serious side-effects were found. We conclude that both dosages of TU can effectively, safely, and reversibly suppress spermatogenesis in normal Chinese men. (*J Clin Endocrinol Metab* **84:** 3642–3647, 1999)

TESTOSTERONE undecanoate (TU; 17-hydroxy-4-androsten-3-one 17-undecanoate) is an unsaturated, aliphatic, fatty acid ester of testosterone (T) that is partially absorbed via the gut lymphatic system after oral administration. Oral TU has been used for androgen substitution therapy and other purposes in clinical treatment for more than 2 decades (1–6). Oral TU has also been tested as a possible contraceptive alone or in combination with cyproterone acetate (CPA) for male fertility control (7, 8). The frequency of administration, fluctuation of serum T levels, and insufficient suppression of gonadotropins and spermatogenesis render an oral TU regimen impractical for male hormonal contraception. These previous studies indicated that an oral TU regimen alone or in combination with CPA was not sufficiently effective in spermatogenic suppression.

A number of clinical approaches to male hormonal contraception with T esters given alone or in combination with additional gonadotropin-suppressive agents have been investigated (9–12). In these studies weekly im injections of T enanthate (TE) were required for consistent suppression of gonadotropins and androgen replacement. Moreover, to attain physiological mean T levels, it is necessary to accept fluctuations in circulating T levels between injections, sometimes causing unwanted side-effects. These disadvantages hindered the acceptability of these regimens and highlighted the need for long acting preparations of T with more stable delivery kinetics. Crystalline T pellet implants that produce sustained elevation of serum T for 6 months and suppress gonadotropin levels were evaluated in clinical trials. When six 200-mg T pellet implants were administered to normal Caucasian men, the sperm concentration could be suppressed to a degree similar to that achieved by weekly TE injection (13). Drawbacks of the implant include the requirement for a surgical incision and the occasional spontaneous extrusion of an implant (which occurred in about 5% of subjects).

A new injectable formulation of TU in tea seed oil provides more stable long term release of T into the circulation (14, 15). Preclinical studies in long term orchidectomized monkeys showed that injectable TU has more favorable pharmacokinetics and pharmacodynamics (16) than TE, which is one of the most commonly used androgen preparations for treatment of androgen deficiency and for regimens of experimental male hormonal contraception (10, 17). A pharmacokinetic study in hypogonadal men demonstrated that mean serum T levels increased significantly from less than 10 to 47.8 and 54.2 nmol/L at the first week after a single dose of 500- and 1000-mg TU injections, respectively (18). Thereafter, serum T levels decreased progressively and reached the

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Address all correspondence and requests for reprints to: William J. Bremner, M.D., Ph.D., Department of Medicine, University of Washington, Box 356420, Seattle, Washington 98195. E-mail: wbremner@u.washington.edu.

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lower normal limit for adult men by days 50–60 without immediately apparent side-effects. In a prospective study on the efficacy of TU, at a dose of 500-1000 mg in combination with other drugs for treatment of 40 patients with aplastic anemia, no serious side-effects were found (19). These promising results prompted us to perform a clinical study of spermatogenic suppression with this injectable TU preparation. To define the effects of this injectable TU preparation this study aimed to determine the following. 1) Can the T ester alone uniformly suppress spermatogenesis? 2) Do the two doses of TU differ in effectiveness on spermatogenic suppression? 3) Are there detectable adverse effects?

Subjects and Methods

Subjects

Thirty-two normal Chinese men, aged 25–45 yr, were enrolled in this study. All of the men had normal medical histories, physical examinations, and screening laboratory tests. All of the men had basal sperm counts greater than 20×10^6/mL as well as serum gonadotropin and T levels within the normal range. The study and consent form were approved by the review board of the National Research Institute for Family Planning and the Jiangsu Family Planning Research Institute. Each man signed informed consent before beginning the study.

Androgen preparation

Injectable TU and placebo were provided by Zhejiang Xian Ju Pharmaceutical Corp. (Zhejiang, China). This TU preparation was available in ampules containing 250 mg of the ester in 2 mL tea seed oil. The same batches of TU and placebo were used throughout the study.

Clinical protocol

This was a double blind study consisting of a 4-week baseline period, a 16-week treatment period, and a 20-week posttreatment phase.

During the baseline period, all subjects were asked to provide 2–3 semen and fasting blood samples at 2-week intervals. The subjects were randomly divided into 3 groups: 1) 13 men received 500 mg TU injections, 2) 12 men were assigned to receive 1000 mg TU injections, and 3) 7 men received a placebo injection (tea seed oil only). One of the men in group 1 discontinued participation because of problems unrelated to TU administration.

During the treatment and posttreatment periods, subjects attended the clinic for physical examination and provided semen and blood samples at 4-week intervals. Subjects were asked to provide semen samples by masturbation after 3 days of sexual abstinence. Fasting blood samples were drawn before TU injections for analysis of hormone, plasma lipid, and chemistry parameters. Serum T levels therefore reflected the nadir (week 4) value. Each subject was given either TU or placebo im injections every 4 weeks until achieving two successive azoospermic ejaculates or until the end of the treatment period. The number of injections varied from man to man due to differences among subjects in the time required for spermatogenic suppression. Each subject received three or four injections; most received three injections. Serum samples were allowed to clot for 24 h and were centrifuged thereafter. All semen samples were stored at −70 C until analysis.

Measurements

Semen analysis was performed according to the WHO laboratory manual (20). Azoospermia was defined as the absence of sperm from seminal fluid, even after centrifugation. Severe oligozoospermia was defined as sperm counts 3×10^6/mL. Testis volume was estimated by Prader's orchidometer. Serum T, LH, and FSH were measured by commercial kits supplied by Diagnostic Products (Los Angeles, CA). All samples from one subject were analyzed in a single assay. The assay sensitivities were 0.35 nmol/L, 0.1 IU/L, and 0.7 IU/L for T, LH, and FSH, respectively. The intraassay coefficients of variation for serum T, LH, and FSH were 5.1%, 3.7%, and 4.4%, respectively. The mean interassay coefficient of variation was less than 10% for all three hormones. Total cholesterol, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol were measured by PTA-magnesium precipitation; the normal ranges are 3.12–6.69, 0.42–1.37, and 1.50–4.88 mmol/L, respectively.

Statistical analysis

Cumulative lifetable analysis was used to show the dynamics of spermatogenetic suppression. This software package was provided by WHO. ANOVA with repeated measurements followed by *post-hoc* test or Bonferonni test were used to determine statistical significance within each treatment group across time and between the study groups, respectively. Results are expressed as the mean ± SEM. $P < 0.05$ was considered significant.

Results

Sperm counts

The mean sperm concentrations of each group at baseline were similar (Fig. 1). The sperm concentration in the two treatment groups was progressively suppressed by TU injections, reaching a nadir by week 12. Significant suppression of spermatogenesis by TU injections at both doses was found by week 4 compared with their baseline levels and the placebo group. There was a tendency for spermatogenic suppression to occur more quickly in the higher dosage group. Eleven of 12 subjects in the 500-mg TU group and all subjects in the 1000-mg TU group achieved azoospermia. The man in the 500-mg TU group who never achieved azoospermia became severely oligozoospermic by week 12 (1×10^6/mL). After cessation of TU administration, the sperm concentration in the both treatment groups returned to the normal range during the recovery period. The sperm concentrations in the placebo group remained unchanged throughout the study.

Reproductive hormones

Mean serum T levels at baseline did not differ among the groups (Fig. 2). There was a clear dose-response relationship between the injected doses and serum T levels. Mean

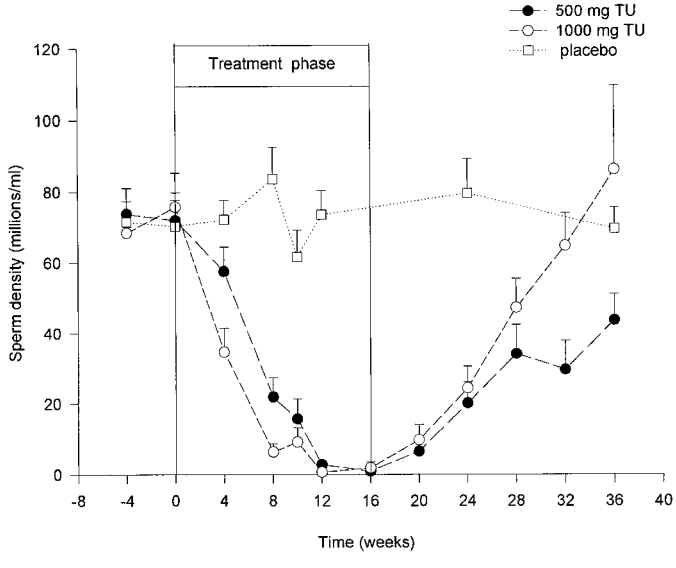

FIG. 1. Mean spermatozoal concentrations (mean ± SEM) in each group during baseline, treatment, and recovery periods.

serum T levels increased significantly in the higher dose group at weeks 8 and 12 compared with those in the 500-mg and placebo groups, but remained within the normal range. Mean T dropped to baseline levels at week 16 because eight men in the higher dose group and six men in the lower dose group received only three injections (the last one at week 8, as they all had achieved azoospermia before the last planned injection at week 12). Mean serum LH and FSH levels were profoundly suppressed by both doses of TU to undetectable levels (0.1 and 0.7 IU/L for LH and FSH) at week 16 (Figs. 3 and 4). Significant suppression of LH and FSH by both doses of TU was first found at week 4 compared with their own baseline levels and levels in the placebo group. The changes in serum reproductive hormones returned to baseline levels by week 4 of the recovery period. Mean serum reproductive hormones in the placebo group were stable within the normal range throughout the study.

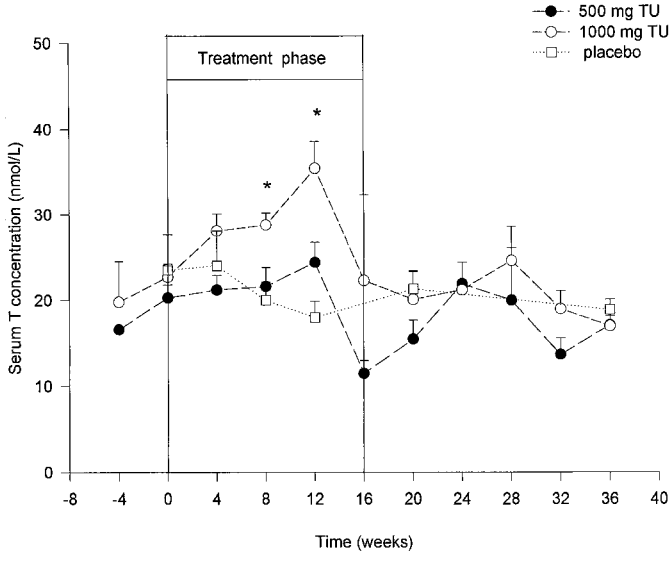

FIG. 2. Mean serum T levels at nadir (mean ± SEM) in each treatment dose group and in the placebo group during baseline, treatment, and recovery periods. *Asterisks* indicate a significant difference in the higher dose group compared with the lower dose and placebo groups ($P < 0.05$).

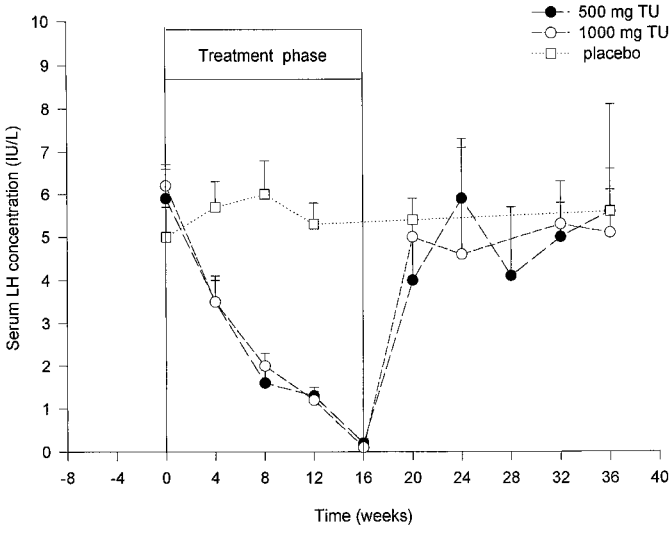

FIG. 3. Mean serum LH levels (mean ± SEM) in each group during baseline, treatment, and recovery periods.

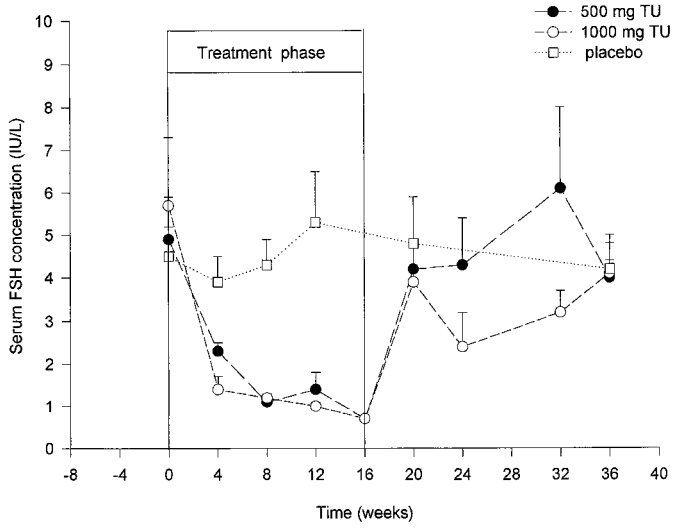

FIG. 4. Mean serum FSH levels (mean ± SEM) in each group during baseline, treatment, and recovery periods.

Lipid, hematology, and clinical blood chemistry

The baseline levels of total, HDL, and LDL cholesterol were similar among the groups (Table 1). Total cholesterol did not show any significant differences between the treatment and baseline periods. HDL and LDL cholesterol did not show any significant differences within each treatment group across time or between the treatment groups in any period of the study.

During the treatment period, TU caused a small, but significant, increase in hemoglobin levels in both groups compared with their own baseline levels, but this increase remained within the normal range. Hemoglobin levels in the 1000-mg TU group were significantly higher compared with those in the 500-mg TU and placebo groups. These changes in hemoglobin levels returned toward the baseline during the recovery period. No significant differences in lipid and hemoglobin levels were found in the placebo group.

Blood chemistry assessments of liver and kidney functions were within the normal reference ranges throughout the study and did not vary significantly with phase of the study.

Clinical features

Body weight increased in both dosage groups during the treatment period compared with their own baseline levels and values in the placebo group (Table 1). No significant difference in body weight was found between the two treatment groups. Body weight returned to pretreatment levels during the recovery period. Total testis volume (left and right) decreased significantly in all subjects in the two TU groups during the treatment period compared with their own baseline levels and values in the placebo group. No significant difference in testis volume was noted between the two treatment groups. Testis volume returned

TABLE 1. Parameters in each group in baseline, treatment (week 12), and posttreatment periods (week 36)

	500 mg TU (n = 12)			1000 mg TU (n = 12)			Placebo (n = 7)		
	Baseline	Treatment	Recovery	Baseline	Treatment	Recovery	Baseline	Treatment	Recovery
BW (kg)	64.6 ± 0.2	67.3 ± 3.8[a,b]	62.1 ± 3.0	62.5 ± 2.8	65.9 ± 2.9[a,b]	62.3 ± 2.8	62.9 ± 2.7	63.9 ± 2.6	60.5 ± 2.0
Total testis vol (mL)	37.3 ± 1.5	33.9 ± 1.3[a,b]	40.0 ± 0.8	39.3 ± 1.2	33.7 ± 1.0[a,b]	38.4 ± 1.0	39.7 ± 2.4	39.4 ± 2.1	41.3 ± 1.7
Total cholesterol (mmol/L)	4.2 ± 0.3	4.6 ± 0.3	5.2 ± 0.2[a]	4.3 ± 0.3	4.3 ± 0.2	4.7 ± 0.3[a]	4.7 ± 0.3	4.5 ± 0.4	4.9 ± 0.2
HDL cholesterol (mmol/L)	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	1.2 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1
Hemoglobin (g/L)	138 ± 3	150 ± 3[a]	145 ± 3	142 ± 3	160 ± 2[a,b,c]	149 ± 2[b]	140 ± 5	141 ± 5	140 ± 4

[a] $P < 0.05$ *vs.* baseline.
[b] $P < 0.05$ *vs.* placebo group.
[c] $P < 0.05$ *vs.* 500 mg TU group.

to the baseline during the recovery period. No changes in body weight and testis volume were found in the placebo group.

A common report from subjects was discomfort in the injection sites lasting about 3–6 days, which then disappeared. Some subjects reported that TU injections stimulated their appetite. There was an occasional self-reported change in sexual desire, more commonly increased rather than decreased. No changes in aggressive behavior and mood states were reported.

Discussion

This is the first dose-finding study of spermatogenic suppression induced by TU injections. TU was very effective when administered in this way. All subjects in the 1000-mg TU group became azoospermic. Eleven of 12 subjects in the 500-mg TU group also became azoospermic, and the one who failed to achieve azoospermia became severely oligozoospermic ($<1 \times 10^6$/mL). This result demonstrates that the T ester alone is an effective and reversible method for male contraception in China. Obviously, uniform and consistent suppression of spermatogenesis and fertility needs to be evaluated further by a large scale contraceptive efficacy trial.

The mean length of time required for achieving azoospermia by the two doses of TU was 12–16 weeks, which is close to that of weekly TE injections in Chinese men (21). However, TE in combination with CPA showed a more rapid onset of spermatogenic suppression in Caucasian men with a mean time course of 7–8 weeks (22). CPA is a synthetic steroid with potent progestational and antiandrogenic actions. CPA may interfere with androgen biosynthesis and action at the gonadal level (23, 24) and suppresses gonadotropins by acting synergistically with T. Another clinical study showed that TE in combination with an oral application of levonorgestrel also led to a rapid onset of spermatogenic suppression (25). Taken together, these results suggest the potential usefulness of a new regimen using injectable TU with oral CPA or levonorgestrel for shortening the time to spermatogenic suppression. The mean time course to allow return of sperm production after cessation of treatment by TU was about 16 weeks, which is close to that required by other methods of male hormonal contraception (12).

Serum T at the nadir value in both treatment groups was maintained at or above pretreatment levels during the treatment period. Because serum T at the peak value was not monitored in this study, serum T levels underestimated the integrated T levels to which subjects were exposed. Presumably, the integrated T levels reached a supraphysiological level, as there were increases in body weight and hemoglobin levels in the TU groups. Weight gain at both doses in this study was not as obvious as in the contraceptive efficacy trial of TE-induced azoospermia and severe oligozoospermia (21). The greater increase in body weight after TE injections could be caused by the higher serum T at peak value that may have exerted a more profound anabolic effect than the moderately elevated serum T levels after TU injections.

No change in serum levels of HDL, LDL, and total cholesterol was noted in any group between the treatment and baseline periods. Similarly, no significant changes in total, HDL, and LDL cholesterol were observed in Chinese men in the WHO multicenter study of TE administration. TE can cause mild suppression of HDL cholesterol in Caucasian men (26, 27). A lowering of HDL concentration, particularly in an individual with low baseline levels, might increase the risk of coronary artery disease (26). Unlike TE decreasing HDL cholesterol, T pellet implants and T buciclate injections to normal Caucasian men did not decrease HDL cholesterol levels (28, 29). This may be explained by supraphysiological T at peak values after TE injections that had greater impact on metabolic effects than the more physiological and less fluctuating T levels maintained by the T implants or T buciclate injections. A significant increase in hemoglobin, but still within the normal range, was observed in both treatment groups. A similar stimulation of erythropoiesis was reported when TE (30) and TB (29) were given to normal men for contraception. Our results suggest the TU preparation reported here can be developed as a male contraceptive in China with fewer biochemical effects on lipid and other metabolic parameters than are found with the currently available forms of T.

In the WHO clinical trial on contraceptive efficacy with weekly TE injections involving different ethnic groups, azoospermia could be achieved in only 45–70% of Caucasian subjects (10) compared with 88.9–100% of Chinese men. The

explanation for this nonuniform induction of azoospermia remains unknown. There were no differences in a variety of endocrine parameters between men achieving azoospermia as opposed to oligozoospermia in response to weekly injections of TE (31, 32) or in the pharmacokinetics of the exogenous T (33). It has been hypothesized that low levels of residual androgens in the testes may allow the persistence of spermatogenesis. A recent clinical study using a combined regimen of the antiandrogenic progestin CPA and TE in Caucasian men showed very effective suppression of spermatogenesis. All 10 men in 2 dose groups became azoospermic, whereas only 3 of 5 men treated with TE alone achieved azoospermia. This finding suggests that not only can CPA act at the hypothalamic-pituitary level synergistically with T in suppressing gonadotropins evidenced by undetectable levels of LH and FSH by week 4 in all 10 subjects, but CPA, as an antiandrogen, could act at the gonadal level by competitively inhibiting the stimulatory effect of androgen from an endogenous or exogenous source (22). It has been recently reported that there was higher 5-reductase activity in men who failed to achieve azoospermia completely compared to that in men who achieved azoospermia when treated by TE weekly injections (34). It has been proposed that Chinese men might have less 5-reductase activity than Caucasian men, but there is a lack of direct evidence to support this hypothesis. A recent study demonstrated no significant differences in 5-reductase activity between Chinese men, whether living in China or the United States, and Caucasian counterparts living in the United States. Environmental/dietary, but not genetic, factors may influence androgen production and explain the differences between Caucasian and Chinese men (35).

In summary, this is the first dose-finding study of injectable TU for male contraception. Our results demonstrate that both dosages of TU administrated to normal Chinese men can sufficiently and reversibly suppress spermatogenesis without serious side-effects. These results suggest that these two dosages of TU could be used for evaluation of contraceptive efficacy in further studies.

Acknowledgments

We are grateful to the Zhejiang Xian Ju Pharmaceutical Corp. (Zhejiang, China) for providing the injectable TU preparation. We thank Ms. Elaine Rost and Jenny Bullock for their excellent technical assistance and all staff members in the endocrinology laboratory for hormone assays. We also gratefully acknowledge the help of Liza Noonan, B.S., for performing the statistical analysis and Dr. Xiaojiang Liu for editorial assistance.

References

1. **Nieschlag E, Mauss J, Coert A, Kicovic P.** 1975 Plasma androgen levels in men after oral administration of testosterone or testosterone undecanoate. Acta Endocrinol (Copenh). 79:366–374.
2. **Skakkebaek NE, Bancroft J, Davidson DW, Warner P.** 1981 Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. Clin Endocrinol (Oxf). 14:49–61.
3. **Schurmeyer TH, Wickings EJ, Freischem CW, Nieschlag E.** 1983 Saliva and serum testosterone following oral testosterone undecanoate administration in normal and hypogonadal men. Acta Endocrinol (Copenh). 102:456–462.
4. **Holmag S, Maarin P, Lindstedt G, Hedelin H.** 1993 Effect of long-term oral testosterone undecanoate treatment on prostate volume and serum prostate-specific antigen concentration in Eugonadal middle-aged men. Prostate. 23:99–106.
5. **Carani C, Zini D, Baldini A, Casa LD, Ghizzani A, Marrama P.** 1990 Effects of androgen treatment in impotent men with normal and low levels of free testosterone. Arch Sex Behav. 19:223–234.
6. **Gooren LJG.** 1994 A ten-year safety study of the oral androgen testosterone undecanoate. J Androl. 15:212–215.
7. **Nieschlag E, Hoogen H, Bolk M, Schuster H, Wickings EJ.** 1978 Clinical trial with testosterone undecanoate for male fertility control. Contraception. 18:607–614.
8. **Meriggiola MC, Bremner WJ, Costantino A, Pavani A, Capelli M, Flamigni C.** 1997 An oral regimen of cyproterone acetate and testosterone undecanoate for spermatogenic suppression in men. Fertil Steril. 68:844–850.
9. **Wu FCW, Aitken RJ.** 1989 Suppression of sperm function by depot medroxyprogesterone acetate and testosterone enanthate in steroid male contraception. Fertil Steril. 51:691–698.
10. **WHO Task Force for the Regulation of Male Fertility.** 1990 Contraceptive efficacy of testosterone-induced azoospermia in normal men. Lancet. 336:955–999.
11. **Bagatell CJ, Matsumoto AM, Christensen RB, River JE, Bremner WJ.** 1993 Comparison of a gonadotropin releasing hormone antagonist plus testosterone (T) *vs.* T alone as potential male contraceptive regimens. J Clin Endocrinol Metab. 77:427–432.
12. **Cummings DE, Bremner WJ.** 1994 Prospects for new hormonal male contraceptives. Endocrinol Metab Clin North Am. 23:893–922.
13. **Handelsman DJ, Conway AJ, Boylan LM.** 1992 Suppression of human spermatogenesis by testosterone implants in man. J Clin Endocrinol Metab. 75:1326–1332.
14. **Li MH, Guo SB, Fang RY, Zhang YP.** 1994 Pharmacological and clinical effects of testosterone undecanoate. New Drugs Clin Remedies. 13:279–281.
15. **Chen ZD, Liu JD Kong ZL, et al.** 1991 Clinical studies on therapeutical efficacy of TU in the treatment of patients with sexual dysfunction and male infertility. J Zhejiang Med Univ. 20:127–129.
16. **Partsch CJ, Weinbauer GF, Fang RY, Nieschlag E.** 1995 Injectable testosterone undecanoate has more favorable pharmacokinetics and pharmacodynamics than testosterone enanthate. Eur J Endocrinol. 132:514–519.
17. **WHO Task Force for the Regulation of Male Fertility.** 1996 Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. Fertil Steril. 65:821–829.
18. **Zhang GY, Gu YQ, Wang XH, Cui YG, Bremner WJ.** 1998 A pharmacokinetic study of injectable testosterone undecanoate in hypogonadal men. J Androl. 19:761–768.
19. **Zhao SW, Sun CJ, Zheng BG.** 1993 Observation of the therapeutical efficacy of TU in the treatment of aplastic anemia. Chinese J Intern Med. 32:688.
20. **WHO.** 1992 WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction, 3rd Ed. Cambridge: Cambridge University Press.
21. **Zhang GY, Zhang GH, Zhu XH, et al.** 1992 Dynamic changes in hormonal profile and sperm functions in testosterone enanthate induced azoo-oligozoospermic men. Chinese J Reprod Med. 1:7–11.
22. **Meriggiola MC, Bremner WJ, Paulsen CA, et al.** 1996 A combined regimen of cyproterone acetate and testosterone enanthate as a potentially highly effective male contraceptive. J Clin Endocrinol Metab. 81:3018–3023.
23. **Satyawaroop PG, Gurpide E.** 1978 A direct effect of medroxyprogesterone acetate on 17-hydroxysteroid-dehydrogenase in adult rat testis. Endocrinology. 102:1761–1765.
24. **Worgul T, Baker HWG, Murray FT, Jefferson LS, Bardin CW.** 1979 Direct effect medroxyprogesterone acetate on the testis. Possible mechanisms examined by testicular perfusion. Int J Androl. 2:408–418.
25. **Bebb RA, Anawalt BD, Christensen RB, Paulsen CA, Bremner WJ, Matsumoto AM.** 1996 Combined administration of levonorgestrel and testosterone induces more rapid and effective suppression of spermatogenesis than testosterone alone: a promising male contraceptive approach. J Clin Endocrinol Metab. 81:757–762.
26. **Bagatell CJ, Heiman JR, Matsumoto AM, Rivier JE, Bremner WJ.** 1994 Metabolic and behavioral effects of high-dose, exogenous testosterone in healthy men. J Clin Endocrinol Metab. 9:561–567.
27. **Meriggiola MC, Marcovina S, Paulsen CA, Bremner WJ.** 1995 Testosterone enanthate at a dose of 200 mg/week decrease HDL cholesterol levels in healthy men. Int J Androl. 18:237–242.
28. **Handelsman DJ, Conway AJ, Howe CJ, Turner L, Mackey MA.** 1996 Establishing the minimum effective dose and additive effects of depot progestin in suppression of human spermatogenesis by a testosterone depot. J Clin Endocrinol Metab. 81:4113–4121.
29. **Behre HM, Baus S, Kliesch S, Keck C, Simoni M, Nieschlag E.** 1995 Potential of testosterone buciclate for male contraception: endocrine differences between responders and nonresponders. J Clin Endocrinol Metab. 80:2394–2403.
30. **Wu FCW, Farley TMM, Peregoudov A, Waites GMH, WHO Task Force for the Regulation of Male Fertility.** 1996 Effects of testosterone enanthate in

normal men: experience from a multicenter contraceptive efficacy study. Fertil Steril. 65:626–636.
31. **Wallace EM, Gow SM, Wu FCW.** 1993 Comparison between testosterone enanthate induced azoospermia and oligospermia in a male contraceptive study. I. Plasma luteinizing hormone, follicle stimulating hormone, testosterone, estradiol and inhibin concentrations. J Clin Endocrinol Metab.77:290–293.
32. **Handelsman DJ, Farley TMM, Peregoudov A, Waites GMH, WHO Task Force for the Regulation of Male Fertility.** 1995 Factors on nonuniform induction of azoospermia by testosterone enanthate in normal men. Fertil Steril. 63:125–133.
33. **Anderson RA, Wu FCW.** 1996 Comparison between testosterone enanthate-induced azoospermia and oligozoospermia in a male contraceptive study. II. Pharmacokinetics and pharmacodynamics of once weekly administration of testosterone enanthate. J Clin Endocrinol Metab. 81:896–901.
34. **Anderson RA, Wallace AM, Wu FCW.** 1996 Comparison between testosterone enanthate-induced azoospermia and oligozoospermia in a male contraceptive study. III. Higher 5α-reductase activity in oligozoospermic men administered supraphysiological doses of testosterone. J Clin Endocrinol Metab. 81:902–908.
35. **Santner SJ, Albertson B, Zhang GY, et al.** 1998 Comparative rates of androgen production and metabolism in Caucasian and Chinese subjects. J Clin Endocrinol Metab. 83:2104–2109.

Erratum

In the article "MS isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women" by Paul Nostel (*The Journal of Clinical Endocrinology & Metabolism* **84:**895–898), the author would like to make the following correction to the text.

The values for arterial compliance, in arbitrary units, should be multiplied by 0.01.