

## A Clinical Trial of 7 $\alpha$ -Methyl-19-Nortestosterone Implants for Possible Use as a Long-Acting Contraceptive for Men

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Several preparations of testosterone and its esters are being investigated alone or in combination with other gonadotropin-suppressing agents as possible antifertility agents for men. We studied the effectiveness of 7 $\alpha$ -methyl-19-nortestosterone (MENT) as an antispermatogenic agent in men. MENT has been shown to be more potent than testosterone and to be resistant to 5 $\alpha$ -reduction. For sustained delivery of MENT, we used a system consisting of ethylene vinyl acetate implants containing MENT acetate (Ac), administered subdermally. Thirty-five normal volunteers were recruited in 3 clinics and were randomly assigned to 1 of 3 doses: 1 (12 men), 2 (11 men), or 4 (12 men) MENT Ac implants. The initial average *in vitro* release rate of MENT Ac from each implant was approximately 400  $\mu$ g/day. Implants were inserted subdermally in the medial aspect of the upper arm under local anesthesia. The duration of treatment was initially designed to be 6 months. However, in 2 clinics the duration of treatment was extended to 9 months for the 2-implant group and to 12 months for the 4-implant group. Dose-related increases in serum MENT lev-

els and decreases in testosterone, LH, and FSH levels were observed. Effects on sperm counts were also dose related. None of the subjects in the 1-implant group exhibited oligozoospermia (sperm count, <3 million/ml). Four subjects in the 2-implant group became oligozoospermic, 2 of whom reached azoospermia. Eight subjects in the 4-implant group reached azoospermia, with 1 exhibiting oligozoospermia, whereas 2 were nonresponders. Side effects generally seen with androgen administration, such as increases in erythrocyte count, hematocrit, and hemoglobin and a decrease in SHBG, were also seen in this study and were reversible. Changes in lipid parameters were moderate and transient. Liver enzymes showed small changes. This study demonstrates that MENT Ac, when administered in a sustained release fashion via subdermal implants, can inhibit spermatogenesis over a prolonged period after a single administration and has the potential to be used as a male contraceptive. (*J Clin Endocrinol Metab* 88: 5232-5239, 2003)

THE DEVELOPMENT OF highly effective, practical, and acceptable nontraditional male contraceptives has proven to be a daunting challenge for more than 3 decades. Steroid hormones that inhibit gonadotropin secretion have been used in women for over 40 yr as contraceptives. Similar approaches are being investigated in men. Methods of fertility control in men that depend on the sustained suppression of gonadotropins will require the concomitant administration of an androgen as an essential part of the method. Results of a 1979 Population Council study (1) and two WHO studies conducted in the 1980s and early 1990s (2, 3) suggested that hormonal induction of azoospermia, but not oligozoospermia, could achieve contraceptive efficacy. Frequent injections of testosterone enanthate (TE) were used in the latter studies. To improve efficacy, new testosterone (T) formulations requiring less frequent administration are being tested alone or in combination with potent synthetic progestins or GnRH antagonists (4-14).

7 $\alpha$ -Methyl-19-nortestosterone (MENT) is a synthetic an-

drogen that is more potent than T for gonadotropin suppression and is resistant to 5 $\alpha$ -reduction, with potential advantages when used as a contraceptive (15-17). MENT acetate (Ac) has diffusion characteristics that are well suited for delivery via subdermal implants. MENT Ac is rapidly hydrolyzed *in vivo* to MENT, the biologically active molecule (18). Before undertaking this trial, the MENT implant system was studied in a 4-wk trial in normal men (17) and in a 6-wk trial in hypogonadal men (19). No adverse toxicological effects were observed in either trial, permitting initiation of the dose-finding trial described here.

This study examines the effect of one, two, or four MENT Ac implants on serum gonadotropins, sex hormones, and spermatogenesis in normal men.

### Subjects and Methods

#### Subjects

A total of 36 normal men, 20-45 yr of age, were to be enrolled, 12 at each of 3 clinics with 4 men/clinic/treatment level. Before examination and testing, volunteers gave written informed consent to randomization and to the schedule of tests, examinations, and related procedures. Volunteers judged as healthy by physical examination, medical history, clinical chemistry, and hematology; with 2 semen samples showing normal sperm counts; and having completed a short questionnaire concerning recent sexual history were eligible for participation. Volunteers

Abbreviations: Ac, Acetate; BP, blood pressure; CV, coefficient of variation; MENT, 7 $\alpha$ -methyl-19-nortestosterone; PSA, prostate-specific antigen; T, testosterone; TE, testosterone enanthate; TU, testosterone undecanoate.

with history of androgen use or hormonal therapy within the past 6 months, prostate disease, prostate cancer in first degree relatives, or abnormal findings on preentry laboratory screening or physical examination were excluded from the study.

### Methods

MENT Ac implants were manufactured at The Population Council (New York, NY). Each implant is an ethylene vinyl acetate copolymer tube containing a central core that is a mixture of MENT Ac and silicone elastomer base. The ends of each tube are sealed with ethylene vinyl acetate polymer. Each implant was 4.9 cm long with a diameter of 2.66 mm. MENT Ac content ranged from 136.2–140.2 mg/implant. The initial *in vitro* release rate from a single implant was approximately 400  $\mu\text{g}/\text{day}$ , decreasing over the course of a year to about 200  $\mu\text{g}/\text{d}$  (our unpublished results). Levels of LH, FSH, T, SHBG, and prostate-specific antigen (PSA) were determined before treatment. Successful candidates were assigned subject numbers in chronological sequence of qualification for the trial and availability for implant placement. Contained in prenumbered, sealed envelopes, the randomly assigned implant sets were placed subdermally. Volunteers received one, two, or four implants, as determined by randomization lists. Insertion was through a trocar, after induction of local anesthesia with 2% lidocaine, in the medial aspect of the upper nondominant arm. All implants were inserted through a single incision, one at a time, and fanned out in a manner to keep them separated. For implant removal, local anesthesia was administered, and a small incision was made at the placement site; each implant was maneuvered to the incision site, and its end was grasped and removed. The procedures were similar to those used for female implant contraception (20).

Subjects or their partners were required to use an established method of contraception for pregnancy prevention. Adverse events and medications taken during the trial were recorded. Vital signs, blood pressure (BP), body weight, and sexual histories were recorded, and semen samples were analyzed. Volunteers provided samples of ejaculated semen monthly beginning on day 60 of treatment. Semen analyses were performed according to instructions in the WHO laboratory manual (21). Orchidometer or ultrasound was used to measure testes volume. Ultrasound was used to measure prostate volume in only one clinic (22). Hematology, clinical chemistry, PSA, SHBG, MENT, T, LH, and FSH were monitored at regular intervals. All hormone assays were performed centrally at the Steroid Research Laboratory, University of Helsinki. RIA for MENT and T used methods described, respectively, by Kumar *et al.* (23) and Sufi *et al.* (24). Time-resolved fluoroimmunoassay, using kits (DELFLIA) from Wallace Oy (Turku, Finland) were used to measure FSH and LH. The limits of detection for MENT, T, LH, and FSH assays were 0.65 nmol/liter, 0.5 nmol/liter, 0.05 IU/liter, and 0.05 IU/liter, respectively. The intraassay coefficients of variation (CV) were 7.0%, 6.8%, 5.0%, and 3.4%, and the interassay CVs were 13.8%, 13.3%, 7.0%, and 4.9% for the same hormones. Local laboratories analyzed clinical chemistry, hematology, and PSA. Lipids were measured in fresh serum samples on the morning of blood collection. The subjects were advised to fast overnight. Data on sexual performance were obtained using a self-rating standard questionnaire (25).

*In vivo* MENT Ac release rate was estimated from recovered implants, following the extraction procedure described by Noe *et al.* (17). Monthly postremoval visits continued until sperm concentrations returned to 20 million/ml or higher. PSA, SHBG, MENT, T, LH, and FSH were monitored 1 month after removal. General physical and prostate examinations and testes volume measurements were scheduled 2 months after removal of implants.

### Enrollment and modification of treatment and examination schedule

The treatment phase of the study was initially designed to be 6 months. However, enrollment time differed markedly at the three participating clinics, with clinic A (Munster, Germany) completing much of the study, while clinics B (Santiago, Chile) and C (Santo Domingo, Dominican Republic) were still recruiting subjects. Attainment of azoospermia in three of four men in the four-implant group at clinic A and the capacity of the multiple implant regimens to maintain substantial serum MENT levels at 6 months were very encouraging and led to

modification of the protocol. With the aim of obtaining as much information as possible from this small study, the treatment period was increased in the two-implant regimen to 9 months and in the four-implant regimen to 12 months at clinics B and C. This protocol amendment took effect, however, after removal of all implants at clinic A. Enrollment was capped at a total of 35 individuals due to time constraints in recruitment. Hence, there were only 11 subjects in the two-implant group.

### Ethical and regulatory considerations

The trial conformed to good clinical practice guidelines and the Declaration of Helsinki and had Investigational New Drug status from the U.S. FDA. Institutional ethics committees of the participating institutions approved the protocol and amendments. All subjects gave informed consent to participate in the study, and consents were obtained again in clinics where the study was extended. The Population Council conducted monitoring of the clinical studies.

### Statistical analysis

The following statistical analyses were performed: descriptive statistics (Tables 1 and 2), two-way ANOVA including repeated measures ANOVA (Tables 3 and 4), ANOVA (Table 1 and Figs. 1 and 3), and Kruskal-Wallis ANOVA and median test (Fig. 2). McNemar tests were used to examine the significance of changes in frequencies of abnormal clinical chemistry values.

## Results

### Subject characteristics at baseline

The characteristics of the subjects are presented in Table 1. At baseline no significant differences by dose group in physical indexes, sperm, or hormonal concentrations were found by two-way ANOVA. Several statistically significant differences among the clinics were detected by two-way analysis (Table 1).

### Drug dosage levels

Sequentially scheduled serum assays of MENT and *ex vivo* extractions of MENT from used implants permitted independent estimates of the amount of drug received by the subjects. Serum MENT levels are presented in Fig. 1. Pre-treatment values registered above zero because of cross-reactions with T and other molecules. Increases in measured MENT levels above baseline values were significant for each dose throughout the treatment period ( $P < 0.001$ ), as were differences by dose ( $P < 0.001$ ) in the first 6 months. At 6 months of treatment the mean increment over baseline in assayed MENT levels for the four-implant regimen was 85% higher than that of the two-implant regimen ( $P < 0.001$ ); however, at 6 months MENT levels for the two lower doses

TABLE 1. Selected characteristics of subjects at admission

Parameter	Mean	SD	Between-clinic	
			P	P
Age (yr)	29.5	6.5	0.044	NS
Height (cm)	174.7	6.8	0.003	NS
Weight (kg)	73.3	9.3	0.023	NS
BMI ( $\text{kg}/\text{m}^2$ )	24.0	2.5	NS	NS
Systolic BP (mm Hg)	116.0	7.5	0.003	NS
Diastolic BP (mm Hg)	72.7	7.0	0.001	NS
Sperm count (million/ml)	100.4	75.6	NS	NS
Testes (2) volume (ml)	46.5	11.1	NS	NS
Morning erections (n/wk)	3.9	2.2	NS	NS

Probabilities were determined by two-way ANOVA.

did not differ statistically. At termination of treatment, the amount of drug remaining in the recovered implants was extracted, and the results were fitted to a nonlinear curve in the square root of time. The estimated average *in vivo* daily release rates of MENT Ac from each implant during 6, 9, and 12 months of use were 339, 277, and 240  $\mu\text{g}/\text{day}$ , respectively.

#### Semen parameters

**Sperm counts during the first 6 months of the study.** Baseline sperm concentrations averaged 100.4 million/ml and did not differ by dose (Table 1). Mean sperm concentrations for all doses are shown in Fig. 2. During 6 treatment months, none of the 12 men in the 1-implant group ever reached oligozoospermia, defined as sperm counts less than 3 million/ml;

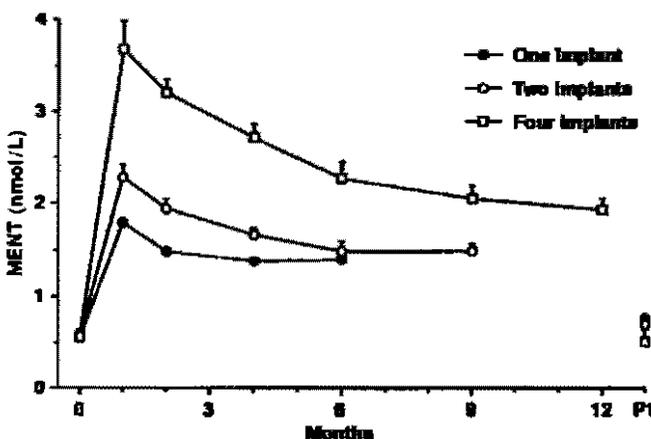


FIG. 1. Serum MENT levels in subjects receiving one, two, or four MENT Ac implants. The study was amended to extend the duration of treatment to 9 months for the two-implant groups and to 12 months for the four-implant groups in two clinics. P1 denotes the 1 month posttreatment time point. Values are the mean  $\pm$  SEM.

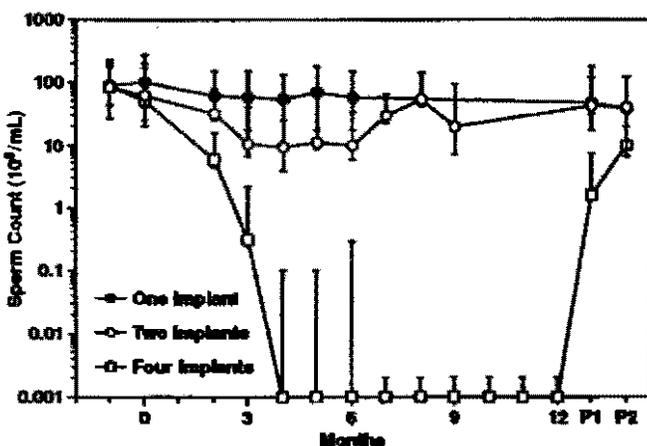


FIG. 2. Sperm concentrations (median and upper and lower quartiles) during treatment with one, two, or four MENT Ac implants. P1 and P2 represent 1 and 2 months posttreatment points. For months 3–6 the difference between doses was significant at  $P < 0.001$ , and at months 7–9 the difference between the two- and four-implant doses was significant at  $P < 0.01$ . Note that the concentrations shown as 0.001 were, in fact, azoospermic.

mean sperm concentrations during treatment were never less than 60 million/ml in the 1-implant group.

Four subjects in the two-implant group achieved oligozoospermia (36%), with two of them (18%) exhibiting azoospermia during the first 6 treatment months (Table 2).

One subject in the four-implant group was discontinued from the study soon after initiation due to hypertension; hence, semen parameters were available from only 11 subjects in this group. Nine subjects (82%) exhibited oligozoospermia in the first 6 treatment months. All oligozoospermic men had counts of 100,000/ml or less for at least 2 months of treatment. Six months after treatment initiation 8 of these 9 had sperm concentrations less than 100,000/ml; the ninth subject's count was less than 300,000/ml. Seven men (64%) at the highest dose achieved azoospermia at least once within the 6-month period. One other subject had multiple counts below 100,000/ml, including 1 count of 5,000/ml.

Findings of azoospermia or severe oligozoospermia in this group were not attributable to very recent sexual activity. During the first 6 treatment months only two subjects at this dose ever reported abstinence of less than 3 days, and both men were repeatedly azoospermic at subsequent measurements with 3 or more days of abstinence.

**Sperm counts during extended treatment.** Findings during the extended treatment period are presented in Table 2 and Fig. 2. No subjects in the single implant group continued treatment beyond the original 6-month schedule. Seven men with two implants received extended treatment through 9 months. One of the two subjects who had reached azoospermia continued to be azoospermic until month 7. None was oligozoospermic at month 9. In the four-implant group, six subjects continued through 12 months; five who were azoospermic maintained azoospermia until month 12. The other had a count less than 1 million/ml, which increased to 3.65 million/ml by the 12th month.

Over the entire study course, 2 (18%) of the 11 men with 2 implants became azoospermic, as had 8 (73%) of the 11 men with 4 implants. Median time to azoospermia was estimated to be less than 4 months in this group. Men with 4 implants were azoospermic an estimated 22% of treatment time in the first 6 months, but were azoospermic 79% of the time in the second 6 months.

**Recovery of sperm counts.** All subjects with one MENT Ac implant had sperm counts at or above 20 million/ml at 30 days posttreatment. Recovery time increased at the higher doses. Median time to recovery ( $\geq 20$  million/ml) was about 3 months in the four-implant group. One subject at this dose, who had attained marked oligozoospermia, but not

TABLE 2. Percentage of men achieving azoospermia and/or oligozoospermia during MENT Ac implant use

Implants (n)	n	% Azoospermic	% <3 million
First 6 months of use			
1	12	0	0
2	11	18	36
4	11	64	82
Months 7–12			
2	7	14	14
4	6	83	100

azoospermia, required 16 months to achieve a sperm count of 20 million/ml. No significant change in semen volume was noted during the study course.

#### Sexual performance

Little change during or after treatment was noted in four measures of sexual performance. The numbers of morning erections, unsustained erections, total erections, and ejaculations reported for the week preceding the clinic visit did not significantly differ from baseline means for any or all doses. The mean number of morning erections reported was 3.9 before treatment and 4.2 during the first 6 treatment months; reported total erections were 8.4/wk before treatment and 8.8 during treatment. Unsustained erections averaged 0.1/wk both before and during the initial 6 months of treatment for all subjects.

#### Physical changes during treatment and adverse events

**Testes and prostate.** Testicular volume was unaffected in the one-implant group during treatment. In the two- and four-implant groups, paired *t* tests indicated volume decreases at 6 months of treatment to 75% and 61%, respectively, of baseline means ( $P < 0.005$  in each group). In men using four MENT Ac implants for a full year, testicular size decreased to 56% of the baseline volume. Two months after implant removal, testicular volume in the two- and four-implant groups had returned, respectively, to 88% and 86% of the mean pretreatment volume.

Prostate volumes by ultrasonography were measured only in clinic A. The volumes (mean  $\pm$  SE) before treatment and at 180 days (end of treatment) were  $21.7 \pm 3.4$  vs.  $19.6 \pm 2.0$  for the one-implant group;  $17.3 \pm 1.2$  vs.  $16.1 \pm 1.9$  for the two-implant group, and  $21.4 \pm 1.0$  vs.  $18.4 \pm 1.9$  for the four-implant group. Although there was a decrease in prostate volume in all groups, the differences were not statistically significant (ANOVA). The prostate volumes showed some recovery at 240 days in all groups.

**BP.** BP measurements were taken for a maximum of 3 days in the month before treatment initiation. Randomization achieved statistically similar baseline systolic and diastolic BP for the three treatment groups, although baseline BP differed significantly by clinic (Table 1). During the first 6 treatment months, mean systolic BP increased by 4.8 ( $P < 0.05$ ), as determined by repeated measure ANOVA. A smaller apparent increase in diastolic BP was not statistically significant. Neither systolic nor diastolic BP differed by dose during treatment.

Two men exhibited elevations of systolic and diastolic BP beyond the normal range. Each had levels of 140/90 mm Hg on the day of implant placement, but lower levels during screening. Subject A, who received a single implant, had a systolic BP of 150 mm Hg on days 30, 60, 90, and 180, but had levels of 120 and 140 mm Hg at the other two scheduled visits. In addition, the systolic level at 30 days postremoval was 160 mm Hg, but returned to normal at 60 days. This subject's diastolic BP was 100 mm Hg on day 90, but was 70 or 80 mm Hg at all other times. Subject B received four implants. On day 30 his BP was recorded at 160/100 mm Hg.

One week later it was 160/90 mm Hg. A follow-up visit next showed a BP of 140/100 mm Hg. A cardiologist recommended implant removal after a diagnosis of stage I–II hypertension. One month after implant removal, with dieting and cessation of smoking, the subject's BP was 130/80 mm Hg.

Several other subjects who showed elevated BP sporadically had baseline readings below 135/85 mm Hg. Subject C had a single elevated systolic reading of 150 mm Hg on day 60. Subject D had systolic readings of 150, 160, and 150 mm Hg on days 90, 120, and 180, respectively. The 150-day visit was missed. Although his diastolic BP at baseline was 65, two readings of 90 mm Hg were recorded on days 60 and 120. Subject E showed a single high reading of 170/90 mm Hg on day 150. Subject F with a baseline diastolic reading of 75 mm Hg had readings of 95 mm Hg on days 30 and 90, and readings of 90 mm Hg on days 60 and 150. He had no abnormal systolic reading during treatment, but had a systolic reading of 140 mm Hg at the 30 day visit compared with a baseline of 115 mm Hg. At 30 and 60 days posttreatment, all subjects had normal diastolic BP. Two men had elevated systolic BP 30 days after removal, but both were normotensive 60 days postremoval.

**Other adverse events.** The most commonly reported adverse events were upper respiratory conditions, headache, and minor injuries. Several complaints related to the implants included pain and other reactions at the site, bruising at removal, long removal time, and multiple or long incisions for removal. Five men, at least one per clinic and one per dose, reported instances of impotence. There were also single reports of decreased libido, ejaculation failure, and premature ejaculation.

#### Discontinuation from the trial

Two men had implants removed before the scheduled date. One removal was the case of hypertension, discussed above. The second occurred early in the sixth month for personal reasons in a subject scheduled for removal at the end of 6 months; the subject returned for posttreatment evaluations.

#### Hormone levels

Serum MENT levels during treatment (Fig. 1) exhibited dose-related increases. Peak levels were seen at the initial 30-day postinsertion measurements. Mean MENT levels declined gradually thereafter until the end of treatment. Mean baseline levels of serum FSH, LH, and T did not differ among clinics or implant groups (Fig. 3). During treatment, significant dose-dependent decreases in FSH, LH, and T occurred with or without suppression of spermatogenesis. Men treated with four MENT Ac implants exhibited rapid and continued suppression of FSH, LH, and T and relatively rapid posttreatment recovery (Fig. 3). One of the two individuals in the high dose group who did not achieve oligozoospermia exhibited markedly less suppression of LH and FSH than the group as a whole, whereas the other subject's hormone levels were similar to those of the group as whole.

### Hematology, lipids, clinical blood chemistry, SHBG, and PSA

Hemoglobin and hematocrit showed small overall increases during treatment. Increased levels were largely confined to the highest treatment dose, which exhibited mean increases of 6–8% in hemoglobin and 6–10% in hematocrit levels (Table 3). Red blood cells increased significantly in the first 4 treatment months, rising 10% in men receiving four implants. By 1 month after removal, levels of these parameters fell back to or below pretreatment values. Other than a

transient decrease in high density lipoprotein, there were no remarkable changes in serum lipid levels during treatment.

Most clinical chemistry parameters showed no remarkable changes during MENT use (Table 4). Significant decreases in the SHBG levels were seen in the two-implant group, whose starting levels were considerably higher than those in the other groups. PSA did not change significantly in any treatment group, remaining at the initial low levels in all subjects throughout the study (Table 4).

### Discussion

As in the case of the 4-wk study (17), MENT Ac implants were well tolerated. In the present study 4 MENT Ac implants administered once were able to suppress spermatogenesis to a degree comparable to that reported in studies with multiple injections of TE or testosterone undecanoate (TU) or with T implants in normal men (2–5, 10–12). With 1, 2, and 4 MENT Ac implants, 0%, 18%, and 82% of the subjects, respectively, achieved azoospermia, concomitant with a clear dose-dependent suppression of serum LH and FSH levels. In 1 WHO multicenter study (2), weekly im TE injections (200 mg) induced azoospermia in 65% of 271 men by 6 months. In a subsequent WHO study (3) weekly im injections of 200 mg TE induced severe oligozoospermia (<3 million/ml) or azoospermia in 98% of men. In a study by Handelsman *et al.* (4), 6 long-acting, biodegradable, T implants (1800 mg) elicited azoospermia in 5 of 9 (56%) men, whereas weekly TE injections (200 mg) induced azoospermia in 25 of 38 (66%) men. Severe oligozoospermia of less than 1 million/ml occurred in 100% of the implant group and in 97% of the TE group. Both treatments suppressed LH and FSH to undetectable levels. TU, a new depot preparation of a T ester that has more favorable pharmacokinetics than TE, is currently being investigated in many studies. In a study in Chinese men, 92% of 12 subjects receiving 500 mg TU, im, in tea seed oil and 100% of 12 subjects receiving 1000 mg TU, im, every 4 wk became azoospermic over a 16-wk treatment period (5). Kamischke *et al.* (10) showed that 1000 mg TU given im in castor oil every 6 wk, with or without levonorgestrel daily (250  $\mu$ g, orally), over a 24-wk period induced azoospermia in nearly half of the subjects. Other studies by Kamischke *et al.* (11, 12) achieved greater sperm suppression with im TU (1000 mg, every 6 wk) plus either im norethisterone enanthate (every 6 wk) or daily oral norethisterone acetate (86–93% azoospermia). These results support findings in a large number of studies, suggesting greater suppression of spermatogenesis with a combination of progestins and androgens (9, 13, 14, 26, 27).

The median time to recovery to 20 million/ml (3 months in the current study) was similar to that observed in the WHO 1990 study.

After placement of the implants, serum MENT levels were highest at 1 month when the first measurements were made and then declined steadily. Serum gonadotropin levels were lowest at 1 month and remained well suppressed for up to 6 months. This was particularly evident in the high dose group despite the steady decline in serum MENT levels. This suggests that in the early months the subjects might have been exposed to supraphysiological levels of MENT. Relative

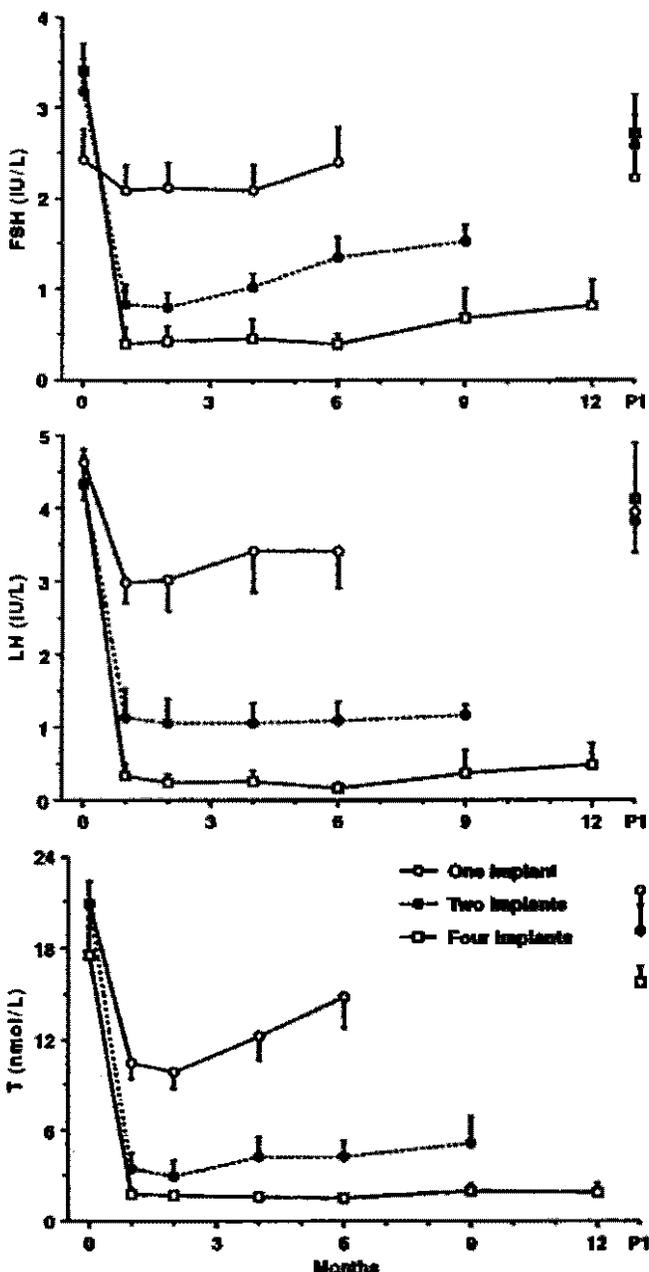


FIG. 3. Serum levels of FSH (top panel), LH (middle panel), and T (bottom panel) in three groups of subjects treated with one, two, or four MENT Ac implants. Values are the mean  $\pm$  SEM. P1 denotes the 1 month posttreatment time point.

TABLE 3. Mean values for hematology and lipids (all clinics)

Parameter (normal range)	No. of implants	Mean $\pm$ SD baseline	60 d	120 d	180 d	270 d	360 d	30 d post
RBC ( $3.9-6.0 \times 10^6/\mu\text{l}$ )	1	$5.30 \pm 0.39$	5.46	5.43	5.23	N/A	N/A	5.29
	2	$5.24 \pm 0.58$	5.21	5.43	5.20	5.07	N/A	4.96
	4	$5.15 \pm 0.31$	5.48 <sup>a</sup>	5.66 <sup>a</sup>	5.48 <sup>a</sup>	5.47	5.55	5.05
	All groups	$5.23 \pm 0.43$	5.39 <sup>b</sup>	5.51 <sup>a</sup>	5.30	5.25	5.55	5.10
	Hemoglobin (12–17.5 g/dl)	1	$15.89 \pm 0.89$	16.06	15.98	15.66	N/A	N/A
	2	$16.24 \pm 1.35$	16.20	16.50	15.92	15.89	N/A	15.24
	4	$15.12 \pm 0.84$	16.12	16.42 <sup>a</sup>	16.05	16.28	16.38	14.85 <sup>a</sup>
	All groups	$15.73 \pm 1.11$	16.12	16.29 <sup>a</sup>	15.87	16.07	16.38	15.34 <sup>a</sup>
Hematocrit (35–50%)	1	$46.68 \pm 2.54$	47.83	47.79	45.93	N/A	N/A	46.11
	2	$48.23 \pm 4.51$	48.42	49.97 <sup>a</sup>	47.24	46.77	N/A	45.37
	4	$45.11 \pm 1.78$	48.41 <sup>a</sup>	49.80 <sup>a</sup>	47.93	48.12	49.10	44.10
	All groups	$46.63 \pm 3.27$	48.21 <sup>a</sup>	49.15 <sup>a</sup>	47.00	47.39	49.10	45.25
	Total cholesterol (<200: <240 mg/dl)	1	$184.2 \pm 36.8$	183.0	186.3	177.9	N/A	N/A
2		$185.0 \pm 32.1$	183.2	203.5 <sup>a</sup>	196.3	203.0	N/A	189.5
4		$175.0 \pm 32.9$	180.4	182.8	188.7	195.8	186.3	182.6
All groups		$181.3 \pm 33.4$	182.2	190.7	187.4	199.7	186.3	187.5
HDL (35–80 mg/dl)		1	$45.5 \pm 9.8$	41.8	46.8	46.8	N/A	N/A
	2	$45.8 \pm 11.7$	43.5	45.0	46.5	38.0	N/A	43.6
	4	$45.67 \pm 9.90$	38.50 <sup>a</sup>	43.09	45.00	39.33	38.00	47.10
	All groups	$45.66 \pm 10.16$	41.23 <sup>a</sup>	45.03	46.15	38.62	38.00	45.03
	LDL (60–130 mg/dl)	1	$117.4 \pm 36.3$	116.4	115.8	109.4	N/A	N/A
2		$116.1 \pm 32.3$	117.7	128.6	123.0	131.6	N/A	118.2
4		$108.7 \pm 32.0$	114.2	116.5	120.2	132.0	131.2	109.7
All groups		$114.0 \pm 32.9$	116.1	120.2	117.3	131.8	131.2	115.5
Triglycerides (10–190 mg/dl)		1	$106.8 \pm 23.6$	124.0	115.3	107.5	N/A	N/A
	2	$115.0 \pm 50.7$	109.5	149.4	134.3	161.3	N/A	137.9
	4	$103.3 \pm 50.0$	138.5	108.5	122.7	122.8	127.5	130.2
	All groups	$108.2 \pm 42.0$	124.4	124.1	121.1	143.5	127.5	134.6 <sup>b</sup>

RBC, Red blood cells; HDL, high density lipoprotein; LDL, low density lipoprotein; N/A, not applicable. *P* values are calculated using repeated measures ANOVA (main effects; dose and time). <sup>a</sup> *P* < 0.01. <sup>b</sup> *P* < 0.05.

to T, MENT has been shown to be 10 times more potent in suppressing gonadotropin levels in rats and monkeys (15, 28). It has been suggested that in men estradiol and T may be more important than dihydrotestosterone in the feedback inhibition of gonadotropins (29). As MENT does not undergo 5 $\alpha$ -reduction, it may maintain a greater ability to suppress gonadotropin secretion. A study with T implants in combination with a 5 $\alpha$ -reductase inhibitor (finasteride) showed no significant enhancement of spermatogenic suppression produced by T implants alone (30). *In vitro* studies with human placental microsomes have shown that MENT is aromatizable to 7 $\alpha$ -methyl-estradiol, a compound with higher affinity for estrogen receptors than estradiol (31). The extent of *in vivo* metabolism of MENT to an estrogenic compound and its role in the suppression of gonadotropins are not known at present.

In the current study there were some treatment-related increases in hemoglobin, hematocrit, and erythrocytes, which remained within the normal range. The hemopoietic effect of testosterone is well established and has been observed in other studies (4, 5, 11, 12, 32). This effect most likely results from a direct effect of androgens on the bone marrow. An increase in hemopoiesis has been reported with transdermal dihydrotestosterone gel also (33). It has been reported that T replacement in older men leads to increases in hematocrit and hemoglobin greater than those seen in younger hypogonadal men (34). In older hypogonadal men receiving T supplementation, the increase in hematocrit and hemo-

globin was sufficiently high to be considered an adverse finding (35, 36). The long-term consequences of androgen treatment on hematological parameters in healthy men remain to be determined. At present, MENT is being investigated for use in young hypogonadal men for replacement therapy and in normal men for contraceptive purposes.

The clinical significance of elevated BP seen in some subjects in the current study remains unclear and will be further evaluated in ongoing studies. Elevations in BP have not been reported in studies with other androgens.

The higher than normal liver enzyme values noted sporadically were within the reference range and did not appear to be clinically relevant. No remarkable changes in lipid parameters were seen in the current study. A significant decrease in high density lipoprotein was noted only on day 60 in the high dose group. Some studies of androgens alone or in combination with progestins have reported some unfavorable changes in lipid parameters (3, 4, 11, 32). In contrast, a transdermal T replacement study in 65-yr-old men and a study in hypogonadal men did not indicate a deleterious effect on serum lipids (37, 38). A comprehensive review of the available literature suggests that the effects of androgens on atherogenic risk factors are unclear at present (39).

In the current study a significant decrease in mean testicular volume was observed in both the two- and four-implant groups. Significant reversible decreases in total testicular volume during treatment were also seen in other studies (5, 10–12). There was no significant change from baseline in

TABLE 4. Mean values for clinical chemistry (all clinics)

Parameter (normal range)	No. of implants	Mean $\pm$ SD baseline	60 d	120 d	180 d	270 d	360 d	30 d post
ALT (1–55 U/liter)	1	19.67 $\pm$ 10.1	21.60	21.08	17.58	N/A	N/A	18.75
	2	17.00 $\pm$ 7.44	18.18	19.82	26.27*	39.14	N/A	26.45*
	4	23.25 $\pm$ 16.6	23.33	22.55	22.55	41.00	44.67	33.92*
	All doses	20.06 $\pm$ 12.1	21.09	21.15	22.00	40.00	44.67	26.37*
AST (1–50 U/liter)	1	17.58 $\pm$ 6.33	20.83 <sup>b</sup>	18.92	16.75	N/A	N/A	16.17
	2	17.73 $\pm$ 7.04	19.82	20.45	23.18 <sup>b</sup>	29.71	N/A	20.82
	4	18.25 $\pm$ 6.33	20.50	21.55	20.45	33.17	28.67	22.96
	All doses	17.86 $\pm$ 6.37	20.40 <sup>b</sup>	20.26	20.03	31.31	28.67	19.68 <sup>b</sup>
LDH (110–250 U/liter)	1	163.9 $\pm$ 31.5	169.9	162.2	172.4	N/A	N/A	160.4
	2	171.5 $\pm$ 28.0	189.2	186.2	189.2	202.9	N/A	181.0
	4	157.2 $\pm$ 32.3	166.1	177.7	178.4	208.7	255	165.9
	All doses	164.0 $\pm$ 30.4	174.7	176.4	179.8 <sup>b</sup>	205.5	255	168.9
Creatinine (>1.3 mg/dl)	1	0.97 $\pm$ 0.16	0.96	0.97	0.97	N/A	N/A	0.96
	2	0.96 $\pm$ 0.16	1.03	1.05*	1.03	0.96	N/A	1.05*
	4	0.98 $\pm$ 0.16	1.06	1.12*	1.13*	1.03	1.06	1.05
	All	0.97 $\pm$ 0.16	1.02	1.06*	1.04*	0.99	1.06	1.02*
SHBG (10–55 nmol/liter)	1	32.51 $\pm$ 12.0	27.78	27.76	28.61	N/A	N/A	24.83
	2	41.39 $\pm$ 12.9	32.90*	32.95*	32.32*	26.39	N/A	31.45*
	4	31.96 $\pm$ 15.1	21.35	22.70	26.00	18.23	20.62	28.44
	All doses	35.11 $\pm$ 13.7	27.18*	27.80*	29.05*	22.62	20.62	28.52*
PSA (0.5–4.0 $\mu$ g/liter)	1	0.550 $\pm$ .37	0.580	0.569	0.598	N/A	N/A	0.667
	2	0.613 $\pm$ .25	0.628	0.616	0.611	0.393	N/A	0.555
	4	0.908 $\pm$ .60	1.025	0.940	0.843	0.872	0.795	0.583
	All doses	0.697 $\pm$ .45	0.753	0.708	0.684	0.632	0.795	0.604

ALT, Alkaline transferase; AST, aspartate transferase; LDH, lactate dehydrogenase; N/A, not applicable.

P values are calculated using repeated measures ANOVA (main effects; dose and time). \*  $P < 0.01$ . <sup>b</sup>  $P < 0.05$ .

semen volume, corresponding to the results of other studies using im TU with or without gestagens (10, 11). Prostate volumes measured by ultrasound at only one clinic were 10–17% lower on day 180 compared with the pretreatment values. The prostate-sparing effect of MENT has previously been shown in a study in castrated cynomolgus monkeys, where the effect of MENT was directly compared with that of T (28). In that study it was shown that a dose of MENT that was 10 times as potent as T in suppressing gonadotropins and maintaining body weight was only twice as potent in stimulating prostate volume. In other words, a dose of MENT that will completely replace T for its anabolic and antigonadotropic actions will be less stimulatory to the prostate. Hence, the use of MENT in men over the long term is expected to have health benefits. Serum PSA levels did not change in this study. Most studies of various preparations of T have not reported significant increases in PSA levels. However, in older men T supplementation led to sustained increases in PSA (38). In hypogonadal men T gel led to small increases in PSA in most subjects, with persistent elevated levels in a few subjects (39). The significance of the increase in PSA levels in older men and in young hypogonadal men on long-term androgen use for male contraception is not clear (40).

Maintenance of sexual behavior or functioning in this study, as determined from questionnaires, suggests that MENT Ac provided adequate androgen replacement while suppressing spermatogenesis and gonadotropins. Likewise, in studies by Kamischke et al. (10, 11) that included behavioral evaluation, sexual behavior during treatment was not altered. In a group of young hypogonadal men, the effect of MENT Ac implants on sexual behavior and mood was com-

pared with that of standard TE injection replacement therapy over a 6-wk period using a cross-over study design. Based on standard questionnaires of mood, sexual interest, and spontaneous erections, it was concluded that MENT had effects similar to those of T (19). In a study in hypogonadal men, transdermal administration of T by gel and patches improved sexual function and mood (38).

In conclusion, these results indicate that MENT Ac, when administered via subdermal implants, can provide sustained levels of MENT, leading to a profound suppression of gonadotropins and inhibition of spermatogenesis. The findings also show that such implants provide effective levels of the compound for up to 1 yr. Most observed changes were similar to findings in earlier studies with other androgens. These results warrant further investigation of the use of MENT Ac implants with or without other agents for male contraception.

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