

## 7 $\alpha$ -Methyl-Nortestosterone (MENT): The Optimal Androgen For Male Contraception

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Many methods of contraception involve the use of drugs that affect the secretion of hormones essential for reproduction. Oestrogens and progestins have been used for contraception in women as inhibitors of gonadotrophin secretion and ovulation. Similarly, androgens must be used in methods of fertility control for men that block gonadotrophin secretion. Androgen supplementation currently involves large, frequent doses of testosterone esters that are associated with wide fluctuations of plasma testosterone levels. Hence, there is a need for an androgen preparation that provides appropriate, continuous replacement doses over long periods. To achieve this goal, 7 $\alpha$ -methyl-19-nortestosterone (MENT), a synthetic androgen that is considerably more potent than testosterone, is suitable. As a consequence, it is feasible to administer this androgen as a substitute for testosterone for 1 year by subdermal implants. Another important feature of MENT is that it does not undergo 5 $\alpha$ -reduction in prostate as does testosterone. As a consequence, a dose of MENT sufficient to maintain normal muscle mass and gonadotrophin secretion will not hyperstimulate the prostate because its action in this organ is not amplified as is that of testosterone. Thus, MENT can be administered to men with the assurance that it will be less prone to cause diseases of the prostate than testosterone. Conclusions: (I) MENT is the first androgen that has a health benefit compared to testosterone; (II) MENT will be promoted as one component of a two-implant system for male contraception, the other component being an implant that will release an LHRH analogue; (III) MENT has potential uses in patients with a variety of disorders, including hypogonadism, prostatic hyperplasia and muscle wasting.

**Key words** 7 $\alpha$ -methyl-nortestosterone; androgen; male contraceptive.

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### Introduction

Some methods of contraception involve the use of drugs that affect the secretion of hormones essential for reproduction. Combined oral contraceptives are used as inhibitors of pituitary gonadotrophins secretion, ovarian hormone secretion and ovulation. The oestrogens and progestins in these contraceptives effectively replace the steroid output of the ovaries that they so efficiently reduce. Methods of fertility control in men that block gonadotrophin secretion and sperm production will also decrease testosterone production. Therefore, androgens will be an essential part of such methods. The most

common androgen supplementation involves administration of large doses of testosterone esters that require frequent injections and that are, in turn, associated with wide fluctuations of plasma testosterone levels. Hence, an androgen preparation is needed that provides appropriate and constant drug delivery over long periods. To achieve this goal, a potent androgen is required that can provide effective treatment for a long period of time with the same mass of drug that is commonly used for testosterone. 7 $\alpha$ -methyl-19-nortestosterone (MENT) is a synthetic androgen that is considerably more potent than testosterone (Fig. 1). A major advantage of MENT is that it is feasible to administer adequate amounts of this androgen by way of subdermal implants. Another advantage of MENT is that it does not undergo 5 $\alpha$ -reduction to a 5 $\alpha$ -dihydrosteroid in the prostate as does testosterone. As an element of normal physiology, the action of testosterone is amplified 3–5-fold in the prostate by its conversion to 5 $\alpha$ -dihydrotestosterone (DHT). Since

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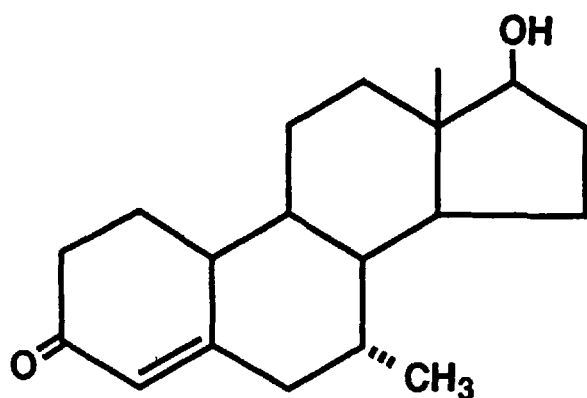


Figure 1. The structure of 7 $\alpha$ -methyl-19-nortestosterone.

MENT avoids this amplification, a dose of this androgen sufficient to maintain normal muscle mass and gonadotrophin secretion will not overstimulate the prostate. Thus, MENT can be administered to men with the assurance that it is less likely to lead to benign prostatic hypertrophy (BPH) than is testosterone. This may be the first androgen that has this particular health benefit.

Because of the high potency of MENT and its acetate (MENTac) adequate amounts of these androgens can be delivered from implants following subdermal placement. Implants are designed to deliver doses that mimic physiological doses of testosterone on muscle and sexual performance. Several studies have shown that the biological activities of MENT and MENTac are the same in a variety of tissues, probably because MENTac is rapidly converted to MENT *in vivo*. The diffusion rate of MENT from several controlled-release matrices is slow relative to that of MENTac. As a consequence, there is some latitude in the choice of a matrix for implant design. Accordingly, both MENT and MENTac are being examined in several possible implants.

The present review will examine the metabolism and the biological activities of MENT. These observations form the basis of the rationale to recommend MENT as a health-promoting androgen that can be administered by implant.

### Why Is There a Need for a New Androgen?

The goal was to select a new androgen that will be an integral part of any male contraceptive method that depends on the suppression of gonadotrophin secretion. Currently LHRH-vaccines as well as LHRH analogues are being investigated as pituitary blocking agents and MENT seems like a good candidate for use with both. In addition, the use of an androgen as a primary method of male contraception continues to be under intense scrutiny (1). The androgens most commonly used for these purposes are the various testosterone esters. They are absorbed slowly when injected s.c. or i.m. in an oil depot. Testosterone enanthate (TE) is the most widely used replacement androgen (2, 3). While the clinical

effectiveness and safety of TE is well established, it has the disadvantage of requiring i.m. or s.c. administration at 1–3-week intervals (1, 4). Testosterone cypionate must be injected at similar intervals (5). The pharmacokinetics following the administration of these preparations show that serum testosterone reaches superphysiological levels for 2 or 3 days and then, depending on the frequency of injection, can decline to levels below normal before the next injection (6). Clearly, the need for frequent intramuscular injections and the overdose/underdose variation is a drawback in the use of these esters. Anadur, a 19-nortestosterone ester must also be given i.m. at 1–3-week intervals at doses of 200 mg (7, 8).

Testosterone undecanoate, an orally active testosterone ester, is absorbed by the intestinal lymphatics; however, the drug must be taken three times daily to maintain adequate androgen support. In addition, the testosterone levels achieved are variable within a subject and among different subjects (9).

Pellet implants, made of compressed testosterone crystals, are cylindrical rods for subdermal implantation (10). They are popular in Australia and the United Kingdom for the treatment of hypogonadism. The implants are inserted subdermally by a minor surgical procedure and last for 4–5 months. Pharmacokinetic studies show that the serum testosterone levels reach a high concentration by 1 month and then decline steadily. Serum testosterone levels decline below the normal range before the implant completely dissolves.

To overcome the disadvantages of the highs and lows of the above parenteral preparations, NIH and WHO are investigating long-acting depot preparations. A testosterone ester (testosterone buciclate) has been shown to maintain serum testosterone levels in the normal range for up to 4 months in castrated cynomolgus monkeys after a single intramuscular injection of 40 mg of the ester (11). To achieve a similar goal in man would require the administration of approximately 1.0 g of the ester, a large dose by any measure. In another approach, testosterone is microencapsulated in a biodegradable matrix of lactide/glycolide copolymer that provide effective levels of testosterone for 2–3 months after a single intramuscular injection (12). The duration of action of this preparation is also limited by the mass that can be given.

In summary, all preparations that use testosterone require administration of a large mass of drug. In addition, esters with long side chains add additional bulk to the preparations. MENT, which is 10 times more potent than testosterone, will need to be administered in much smaller doses and thus reduced mass. The estimated daily dose of MENT is expected to be 300–500  $\mu$ g. Such quantities are easily administered subdermally via sustained release preparations that can be expected to last for 1 year or longer.

### *In Vitro* Metabolism of MENT

In the male reproductive tract and in skin, testosterone is enzymatically converted via 5 $\alpha$ -reductase and the 3-oxidoreductase(s) to androgens with increased activity. These metabolites of testosterone include DHT and the

5 $\alpha$ -diols. The increased activity of DHT is probably due to its increased affinity to the androgen receptor whereas the increased androgenic action of the 5 $\alpha$ -diols is due to oxidation to DHT (13). Testosterone can also be aromatized to oestradiol by the enzyme aromatase that is distributed widely in many tissues. The biological role of oestradiol in the male is complex and not fully understood in man. In view of the active products that can be formed from testosterone, it was pertinent to investigate the metabolism of MENT.

### 5 $\alpha$ -Reduction of MENT

The *in vitro* metabolism of MENT has been investigated in rat liver, ventral prostate, and epididymis (14). Radioactively labelled MENT was incubated with tissue homogenates. In liver homogenates three metabolites were identified: 7 $\alpha$ -methyl-estr-4-ene-3,7-dione; 7 $\alpha$ -methyl-5 $\beta$ -estrane-3,17 $\beta$ -diol; and 7 $\alpha$ -methyl-3-oxo-estr-4-ene-16,17 $\beta$ -diol. There was no evidence of 5 $\alpha$ -dihydro products. In prostate or epididymal homogenates there was no detectable metabolism of MENT. In parallel investigations, 48% of radiolabelled testosterone was converted to a 5 $\alpha$ -reduced product by the prostate and epididymis. We concluded from these observations that MENT does not undergo 5 $\alpha$ -reduction, probably because the 7 $\alpha$ -methyl group hindered the action of the 5 $\alpha$ -reductase. These observations lead to the postulate that compared to testosterone the relative biopotency of MENT on the prostate would be lower than that on muscle.

### Aromatization of MENT

Some investigators have postulated that 19-norsteroids cannot be aromatized because of the absence of the  $\beta$ -methyl group at position-19. To investigate this possibility,  $^3\text{H}$ -testosterone or  $^3\text{H}$ -MENT were incubated with human placental microsomes in the presence of a NADPH generating system, and the phenolic metabolites extracted. The extracted metabolites were evaluated by chromatography and by binding to oestrogen receptors. These studies indicated that MENT can be metabolized to an oestrogenic compound that is most likely 7 $\alpha$ -methylestradiol. Conversion of both analogues to oestrogens was blocked by an aromatase inhibitor (Table 1).

## Biopotency of MENT

In view of the apparent lack of 5 $\alpha$ -reduction of MENT, the *in vivo* biological potency of this steroid was compared to that of testosterone in castrated rats (15). The androgens were solubilized in a 45% aqueous solution of Molecusol<sup>TM</sup> (2-hydroxy-propyl- $\beta$ -cyclodextrin) and administered as a subdermal infusion via osmotic pumps for 14 days. This ensured that a constant dose of both androgens was given so that the relative potencies could be accurately estimated. At the end of the study, blood was collected for hormone assays and the ventral prostate, seminal vesicles, and bulbo-cavernosus and levator

**Table 1. Aromatization of [ $^3\text{H}$ ]-T and [ $^3\text{H}$ ]-MENT by placental microsomes.**

Addition to microsomes	Oestrogen (%)
1. [ $^3\text{H}$ ]-T + NADPH	100
2. [ $^3\text{H}$ ]-T + NADPH + R76713*	5
3. [ $^3\text{H}$ ]-MENT + NADPH	100
4. [ $^3\text{H}$ ]-MENT + NADPH + R76713	4

\*R76713 = aromatase inhibitor. The [ $^3\text{H}$ ]-steroids were incubated with placental microsomes and NADPH, and the phenolic metabolites extracted with 0.4 N NaOH. The radioactivity in the NaOH phase above background is an index of aromatization and designated 100%.

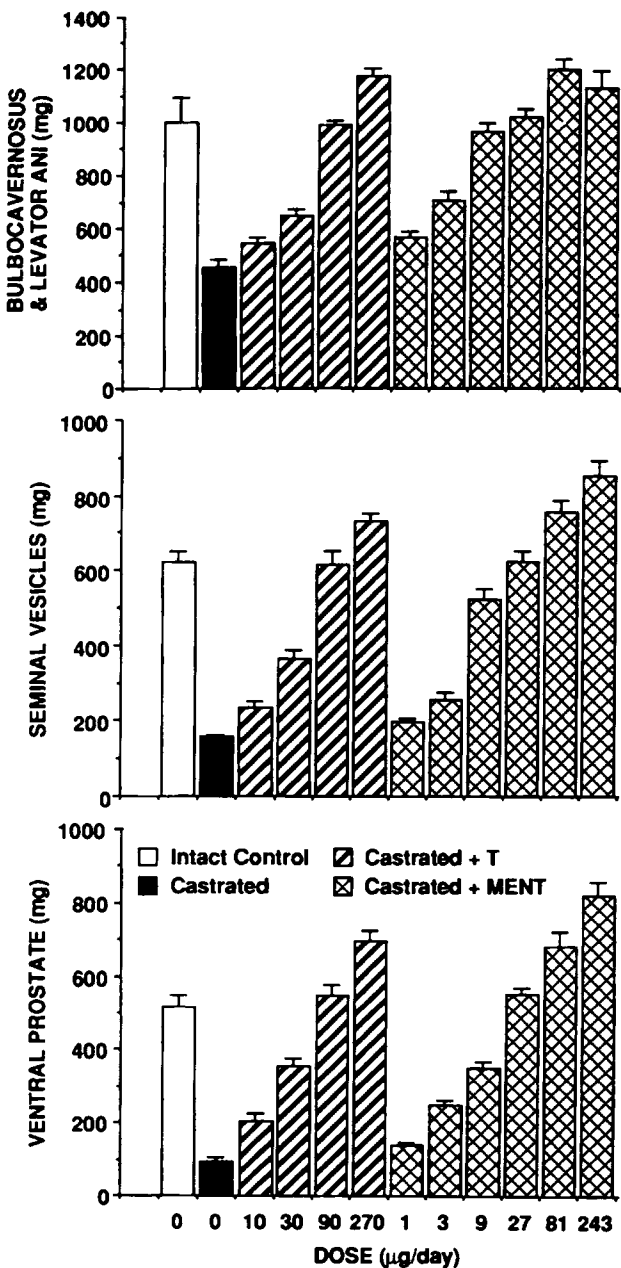
ani muscles (henceforth referred to as muscle) were weighed (Fig. 2). The biopotencies were compared using an ALLFIT computer program. Based on the weights of ventral prostate and seminal vesicles, MENT was nearly four times as potent as testosterone. By contrast, the potency as estimated from muscle response was 10 times that of testosterone. The effect of MENT on serum LH and FSH in castrate rats is shown in Fig. 3; the stimulatory effects of MENT on muscles are shown on the same scale. In the suppression of post-castration rise in gonadotrophin levels also MENT was 10 times more potent than testosterone.

In the castrated rat complete suppression of the post-castration rise in serum LH and FSH was achieved with a serum testosterone level of 1.21 ng/ml. On the other hand, an equal or better suppression of gonadotrophin levels was obtained with MENT levels of 0.04 ng/ml. Hence, based on the mass of MENT in blood, this steroid is approximately 30 times more potent than testosterone.

The differential potency of MENT on the sex accessory organs compared to its potency on the muscle and pituitary can be attributed to the finding that, unlike testosterone, MENT does not undergo 5 $\alpha$ -reduction to dihydrosteroids in the male reproductive tract. Because the affinity of DHT for the androgen receptors is 2-3 times greater than that of testosterone it leads to an amplification of testosterone action in the prostate and seminal vesicles. If this postulate is correct, then the action of testosterone but not MENT on prostate and seminal vesicles should be reduced by a 5 $\alpha$ -reductase inhibitor. Further, the inhibitor should not alter the action of either steroid on muscle.

## MENT is not 5 $\alpha$ -Reduced *in Vivo*

*In vivo* experiments were conducted using a 5 $\alpha$ -reductase inhibitor (L-644,829) (15). Castrated rats were treated with the androgens via osmotic pumps with or without L-644,829 for 1 week. As expected, both testosterone and MENT maintained the weights of ventral prostate and levator ani and suppressed the post-castration rise in serum LH (Table 2). L-644,829 inhibited the action of testosterone on the ventral prostate but not on the muscle. In the intact rat also, the action of endogenous testosterone on the reproductive tract tissue was



**Figure 2.** Dose-dependent effects of testosterone (T) and MENT on organ weights in castrated rats. One day following castration, 14-day androgen treatment was started at indicated doses via subdermally implanted osmotic pumps. Vertical lines represent SE (n = 6). (From ref. 15.)

inhibited by this agent. In contrast, L-644,829 did not interfere with the action of MENT on ventral prostate, muscle or pituitary. Furthermore, L-644,829 did not alter the effect of testosterone on serum LH levels. These results provide strong evidence that MENT does not undergo significant 5 $\alpha$ -reduction *in vivo*. These observations also provide an explanation for the comparatively low potency estimate of MENT on prostate relative to the muscle and pituitary. Finally, these results also suggest that 5 $\alpha$ -reduction of testosterone to DHT does not play a significant role in the short-term regulation of LH secretion.

**Effect of MENTac in Rhesus Monkeys**

Experiments to explore the use of MENT as the androgen supplement in a two-component male contraceptive were undertaken in rhesus monkeys (16). Four monkeys were treated with an LHRH agonist (histerilin, 100 µg/day) via subcutaneously implanted osmotic pumps. The pumps were replaced at monthly intervals. The monkeys were electroejaculated and the serum testosterone levels measured at 2-week intervals. Three months after the start of the LHRH agonist treatment, three of the four monkeys stopped providing an ejaculate upon electrical stimulation and the serum testosterone decreased to castrate levels. At 8 months after the start of histerilin treatment, monkeys were implanted subdermally with Silastic implants releasing approximately 50 µg of MENTac daily. The implants were replaced at 3-week intervals because of rapid loss of androgen from implants manufactured with this elastomer. When no change in ejaculatory response was observed, the dose of MENTac was increased to 100 µg/day (approximately 10 µg/kg). At this dose of MENTac, all monkeys responded to electroejaculation. Importantly, the ejaculates were devoid of spermatozoa. Under this regimen, azoospermia was essentially maintained in the three monkeys for about 8 months. All treatment was terminated at 18 months, and 2 months later serum testosterone levels as well as sperm counts returned to the normal range.

These studies in primates suggest that MENT has the potential to be developed into a clinically useful product when combined with an LHRH analogue. We hope that this androgen will be one component of a two-implant system for male contraception. The second implant will provide the LHRH analogue. These studies further suggest that the androgen replacement provided by MENT mimics many of the essential effects of testosterone. More studies will need to be performed to confirm these impressions.

**Basis for the Advantages of MENT**

Following the observation that testosterone was converted to DHT in the skin and male reproductive tract, and the realization of its importance in fetal development, it was proposed that testosterone is the physiologically active steroid in many target tissues such as kidney, muscle, pituitary and brain, since its conversion to DHT could not be demonstrated *in vivo* in these tissues. Thus, testosterone *per se* is the androgen that binds to the androgen receptors in these tissues, and the testosterone-receptor complex is the molecular entity that is localized in the nuclei of responsive cells (13). These observations alone provided reason to believe that testosterone is active in many tissues. This postulate, however, was strongly supported by the observations that 5 $\alpha$ -reductase inhibitors do not alter the action of testosterone on such tissues (17, 18). In the male reproductive tract (excepting the testis) and sexual skin, testosterone is metabolized to DHT by 5 $\alpha$ -reductase

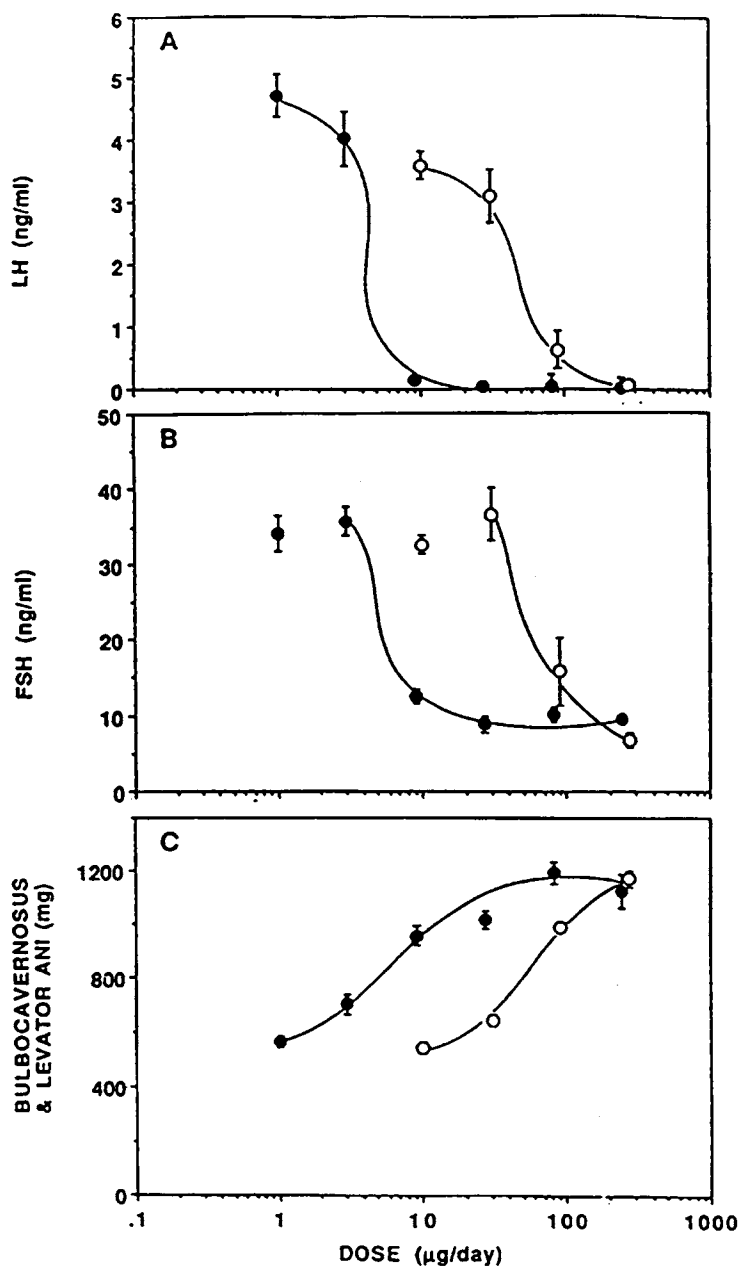


Figure 3. Log-dose response curves showing the effect of testosterone (○) and MENT (●) on serum levels of LH, FSH, and muscle weight from the study described in Figure 2. (From ref. 15.)

Table 2. Effect of the 5α-reductase inhibitor, L-644,829, on the antigonadotrophic activity of testosterone and MENT *in vivo*.

Treatment	Ventral prostate (mg ± SE)	Levator ani (mg ± SE)	Serum LH (ng/ml ± SE)
1. Intact control	372 ± 18	211 ± 6	0.33 ± 0.10
2. Castrated control (C)	43 ± 6	116 ± 6	5 ± 0.25
3. C+L-644*	41 ± 5	113 ± 7	4.75 ± 0.50
4. C+T-270†	374 ± 24	239 ± 8	0.25 ± 0.09
5. C+T-270+L-644	222 ± 10	260 ± 16	0.18 ± 0.10
6. C+MENT-27	265 ± 13	261 ± 10	0.06 ± 0.03
7. C+MENT-27+L-644	244 ± 16	247 ± 14	0.09 ± 0.07

\*L-644,829 (4 mg/day) was injected s.c. daily.

†Doses are μg/day. Rats were castrated and s.c. implanted with osmotic pumps releasing the steroids for 7 days.



(19). Since DHT is 3–5 times more active than testosterone (probably because of its greater affinity for androgen receptors) (20), the action of testosterone is amplified in such tissues. This enhancement of testosterone action is believed to be necessary for differentiation of the male reproductive tract in the fetus. This conclusion is based on studies of patients with genetically determined 5 $\alpha$ -reductase deficiency and on the effects of 5 $\alpha$ -reductase inhibitors on androgen-dependent differentiation (21).

In adult animals and humans, 5 $\alpha$ -reductase inhibitors reduce but do not abolish the action of testosterone on prostate and other reproductive organs since these inhibitors eliminate the amplification of but not the basal tissue response to testosterone. As a consequence, such agents have been recommended for use in men with BPH by a U.S. FDA advisory committee. Since 5 $\alpha$ -reductase is also present in sexual skin, these inhibitors may also retard beard growth and reduce androgen-dependent hair loss from the scalp. Other possible biological consequences of the blockade of this enzyme in adults are not evident from studies to date, but are being extensively evaluated as new inhibitors are further examined in men. Thus, there is considerable evidence to indicate that the action of testosterone is amplified in the prostate and other reproductive organs. However, at present there is no known physiological need for amplification of the action of testosterone in the adult. If this is the case then MENT should be able to provide suitable androgen replacement in hypogonadal men. The goal of treatment would be to select a dose that would maintain the metabolic and behavioural effects of testosterone without hyperstimulation of the prostate.

That there is no known physiological need for amplification of testosterone action in adults suggests that chronic use of 5 $\alpha$ -reductase inhibitors could prevent BPH and possibly prostate cancer. Although this postulate is attractive, the potent effects of 5 $\alpha$ -reductase inhibitors on fetal sexual differentiation and the possible transfer of these inhibitors from male to female in semen may preclude their widespread prolonged use in healthy men. Therefore, 5 $\alpha$ -reductase inhibitors can be recommended for use in men with established prostatic hyperplasia rather than as an agent that will prevent its occurrence. Based on these considerations, we propose that an alternative approach that could be used in healthy men is to suppress testosterone secretion with an LHRH analogue and then use MENT to maintain libido and the metabolic effects of testosterone. Replacement with MENT would be analogous to treatment with a 5 $\alpha$ -reductase inhibitor since MENT cannot be reduced by 5 $\alpha$ -reductase. If it can be demonstrated that an implant system that delivers LHRH analogue plus MENT can safely be used for contraception in men then similar implants could also be used to limit the development of BPH.

We conclude that the use of MENT instead of testosterone for androgen replacement in hypogonadal men and as a component of a male contraceptive could have health-promoting effects by reducing the occurrence of prostatic disease.

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