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# Effect of Finasteride on Human Testicular Steroidogenesis

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**ABSTRACT:** We studied the testicular function and some androgen-mediated events in 22 males (16–30 years of age) with male pattern baldness that was treated with finasteride (10 mg once daily) for 2 years. Patients were evaluated every 3 months. Prostatic volume was determined in six subjects by endorectal ultrasound scans. Serum gonadotropin, prostate-specific antigen (PSA), and sex hormone levels were determined basally and periodically during the treatment period. Fourteen subjects underwent gonadal stimulation with human chorionic gonadotropin (hCG), and the gonadotropin response to gonadotropin releasing hormone (GnRH) was determined in eight subjects, prior to and after 2 years of therapy. Finasteride treatment resulted in an improvement in the male pattern baldness and prostatic shrinkage that was associated with an increase in serum testosterone levels (17.2 ± 2.5 vs. 26.3 ± 1.7 nmol/L) and a decrease in dihydrotestosterone (DHT) levels (1.45 ± 0.41 vs. 0.38 ± 0.10 nmol/L), causing a marked increase in that testosterone /DHT ratio. A significant increase in the serum levels of androstenedione (3.67 ± 0.49 vs. 7.05 ± 0.70 nmol/L) and estradiol (132 ± 44 vs. 187 ± 26 pmol/L) was also noted, whereas androstanediol glucoronide (33.3 ± 6.4 vs. 10.7 ± 4.5 pmol) and PSA (1.6 ± 0.6 vs. 0.4 ± 0.1 ng/ml) were significantly decreased. No changes in basal or stimulated levels of gonadotropin were observed. There was a significant increase in the testosterone response to hCG during finasteride therapy (Δ: 16.7 vs. 35.5 nmol/L) that could be explained, at least in part, by the reduction of testosterone metabolism resulting from the blockage induced by finasteride. The decrease in the androstenedione to testosterone and estrone to estradiol ratios observed after hCG treatment, however, strongly suggests increased activity of the 17-ketosteroid reductase enzyme and an improvement of the testicular capacity for testosterone production.

Key words: Alopecia, baldness, 5α-reductase, 17-ketosteroid reductase, prostate.

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Finasteride is a 4-azasteroid testosterone analogue that inhibits 5α-reductase by competing with testosterone for the active site on the enzyme (Stoner, 1990). Recently, two isoenzymes of 5α-reductase have been identified in human tissue. The type 1 isoenzyme is found in skin tissue throughout the body (Moore and Wilson, 1976), and it is the dominant form of the enzyme on the adult scalp (Itami et al, 1991). The gene for this isoenzyme is located on the short arm of chromosome 5 (Jenkins et al, 1991). The gene for the type 2 isoenzyme is located on the short arm of chromosome 2, and its product is expressed predominantly in genital skin and prostate (Anderson et al, 1989). Men with male pseudohermaphroditism due to 5α-reductase deficiency lack only the type 2 isoenzyme (Anderson et al, 1991). Finasteride is a potent inhibitor of 5α-reductase type 2, with very little activity against the type 1 isoenzyme *in vitro* (Jenkins et al, 1992). However, this drug has been shown to be useful in the treatment of several dihydrotestosterone (DHT)-mediated conditions, regardless of the isoenzyme responsible for the reduction of testosterone to DHT. Finasteride has been shown to be an effective treatment for benign prostatic hyperplasia (Gormley et al, 1992), in which 5α-reductase type 2 is responsible for the reduction of testosterone to DHT. It has also been observed to be useful in the treatment of male pattern baldness (Diani et al, 1992; Dallob et al, 1994; Rhodes et al, 1994) and hirsutism (Moghetti et al, 1994), in which the reduction of testosterone to DHT is mediated by 5α-reductase type 1 isoenzyme. We recently evaluated a 16-year-old 46,XX male with primary testicular failure who experienced rapid hair loss during testosterone replacement therapy that was completely arrested by the concomitant use of finasteride. This observation and therefore the potential long-term use of finasteride led us to study the effects of this drug on testicular steroidogenesis as well as on androgen-mediated events. In spite of the profound effects of finasteride on androgen metabolism, the short- and long-term effects of finasteride on testicular steroidogenesis in young men have not previously been reported.

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## Materials and Methods

### Subjects

We studied testicular function in 22 healthy male subjects, ranging from 16 to 30 years of age, before and during finasteride treatment for male pattern baldness. The mean duration of baldness, assessed by history, was 1–7 years, and the predominant classifications of that baldness pattern, according to Hamilton (1951) were type IV (16 patients), type V (4 patients), and type VI (2 patients). All of the patents had achieved pubic hair stage V and had testicular values between 20 and 30 ml. The latter correspond to the volume between the mean and the 90th percentile for healthy males (Castro-Magana et al, 1988). X-rays of the left hand and wrist showed that their growth plates were already fused. The prostate gland was evaluated subjectively by digital rectal examination and considered to be normal in all patients. The mean (± standard deviation [SD]) body mass index (the weight in kilograms divided by the square of the height in meters) in the subjects was 20 ± 2 (normal: 20–24.5). The histories and physical examinations of the 22 subjects were otherwise unremarkable. Written consent was obtained from all study subjects, and the study protocols were reviewed and approved by the Institutional Review Committee.

### Study Design and Clinical Evaluation

All patients received 10 mg of finasteride daily for 24 months. Each subject had a physical examination every 3 months, at which time side effects and the degree of compliance with the treatment regimen were assessed. The degree of baldness was graded according to the Hamilton (1951) classification. Photographs of the scalp were taken every 6 months. Investigator assessment of clinical change and the patient self-assessment of hair growth were recorded. Testicular diameters (L, length; W, width) were measured with a caliper, and the volume was calculated from the formula $\pi/6 \times L \times W^2$. The prostate gland was evaluated subjectively by digital rectal examination in all of the subjects at the beginning and after 3, 6, 12, and 24 months on therapy. Prostate volume was determined in six subjects by endorectal ultrasound scans at baseline and after 3, 6, and 12 months of treatment. Transrectal sonography was performed with a $5MH_2$ transducer, and the maximal length (L) and thickness (T) of the prostate were determined from consecutive sagittal images. From these measurements the prostate volume was determined using the formula: volume = $0.52 \times L \times W \times T$ (ellipsoid method).

### Endocrine Evaluation

Basal serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, DHT, androstenedione, estrone (E1), estradiol (E2), androstanediol glucuronide (Adiol-G), and prostate-specific antigen (PSA) levels were measured in all 22 subjects at the beginning and after 3, 12, and 24 months of therapy. To determine the effects of finasteride on testicular steroidogenesis, 14 subjects underwent gonadal stimulation with human chorionic gonadotropin (hCG). Serum levels of testosterone, DHT, androstenedione, E1, and E2 were measured before and after the intramuscular (i.m.) administration of 2,000 IU hCG for three consecutive days, prior to and after 3 and 24 months of finasteride treatment. Serum FSH and LH concentrations were also measured in eight subjects before the intravenous (i.v.) administration of 100 μg of gonadotropin-releasing hormone (GnRH), and every 20 minutes thereafter, for a total of 120 minutes, prior to finasteride treatment and after 24 months on therapy.

### Hormone Assays

The serum hormones testosterone, DHT, androstenedione, Adiol-G, E2, E1, FSH, and LH were measured by Endocrine Sciences Laboratory (Calabasas Hills, California). Serum testosterone and DHT were measured by radioimmunoassay (RIA) after extraction with hexane ethylacetate (9:1) and chromatographic separation, using high-pressure liquid chromatography (HPLC) with hexane ethanol for DHT and alumina columns for testosterone. The sensitivity of each assay was 0.17 nmol/L for testosterone and 0.07 nmol/L for DHT. The interassay variation was 9.6% for testosterone and 11.7 % for DHT. Androstenedione was measured by RIA after hexane extraction from serum. The assay sensitivity was 0.14 nmol/L, and interassay variation was 8.4%. Serum Adiol-G was measured after extraction and hydrolysis as previously described (Rittmaster et al, 1988). E2 was measured by RIA after extraction with hexane ethylacetate and chromatographic separation on Sephadex LH-20 columns. The assay sensitivity was 0.2 nmol/L, and interassay variation was 9.9%. E1 was measured by RIA as previously described (Mikhail et al, 1970). Serum FSH and LH were measured by immunochemiluminometric assay (ICMA), utilizing paired monoclonal antibodies. In this two-site system, the gonadotropin (LH or FSH) is bound between an excess of solid-phase-linked monoclonal antibody (anti-human alpha subunit) and a second monoclonal antibody with a chemiluminescent tag (anti-human beta-subunit). The chemiluminescent signal generated by the bound, labeled antibody is measured in a luminometer and is proportional to the gonadotropin concentration over a wide range. The ICMA is highly sensitive and will measure as little as 0.05 mIU FSH/ml and 0.01 mIU LH/ml expressed in terms of World Health Organization Second International Standard Human Pituitary FSH 83/575, Human Pituitary LH 80/522. The interassay variation for LH ranged from 9% to 15% and for FSH from 6.7% to 11%. Serum levels of PSA were also measured by ICMA (Vihko et al, 1990).

### Statistical Analysis

Results were analyzed by paired *t*-test. A $P$ value of $<0.05$ was considered statistically significant. Data were expressed as the mean ± standard error of the mean (SEM).

## Results

### Tolerability and Safety

None of the 22 males treated with finasteride reported decreased libido, impotence, or other side effects. After 20 months of treatment, one subject reported prolonged ejaculation time. It was normalized after discontinuing the finasteride for 1 week and did not reappear after reinitia-

Table 1. *Serum hormone concentrations before and during administration of 10 mg/day finasteride*

| Hormone | Baseline | 3 Months | 12 Months | 24 Months |
|---|---|---|---|---|
| LH (IU/L) | 4.5 ± 0.6 | 5.4 ± 1.0 | 4.8 ± 0.7 | 6.0 ± 1.0 |
| FSH (IU/L) | 6.2 ± 1.3 | 5.5 ± 0.8 | 6.5 ± 1.2 | 5.8 ± 0.2 |
| Testosterone (nmol/L) | 17.2 ± 2.5 | 28.4 ± 2.4† | 26.3 ± 1.7 | 27.4 ± 1.0 |
| DHT (nmol/L) | 1.45 ± 0.41 | 0.35 ± 0.17* | 0.38 ± 0.10 | 0.35 ± 0.10 |
| Androstenedione (nmol/L) | 3.67 ± 0.49 | 7.15 ± 0.63‡ | 7.16 ± 0.73 | 7.05 ± 0.70 |
| Adiol-G (pmol/L) | 33.3 ± 6.4 | 12.8 ± 4.3* | 11.1 ± 2.1 | 10.7 ± 4.5 |
| E1 (pmol/L) | 177 ± 41 | 211 ± 67‡ | 226 ± 70 | 200 ± 41 |
| E2 (pmol/L) | 132 ± 44 | 191 ± 37‡ | 176 ± 29 | 187 ± 26 |
| PSA (ng/ml) | 1.6 ± 0.6 | 0.4 ± 01* | 0.4 ± 0.1 | 0.38 ± 0.08 |
| T/DHT | 11.8 ± 2.3 | 82 ± 3.5* | 69 ± 4.1 | 83 ± 4.6 |
| $\Delta_4$/T | 0.21 ± 0.08 | 0.20 ± 0.07 | 0.21 ± 0.09 | 0.21 ± 0.08 |
| E1/E2 | 1.34 ± 0.11 | 1.10 ± 0.14 | 1.28 ± 0.09 | 1.05 ± 0.09 |

T, testosterone. Values are given as mean ± SD.
* $P < 0.001$.
† $P < 0.005$.
‡ $P < 0.05$.

tion of the treatment. All safety parameters, including complete blood count (CBC), liver and kidney function tests, glucose, and lipids did not change significantly during the 2-year period.

### Clinical Effects

Complete arrest of hair loss during the 2 years of treatment was noted by all 22 patients. Sixteen patients reported mild to moderate hair growth as early as after 12 months, but a significant change, however, was documented only in six patients after 24 months of therapy. Four patients, previously classified with type IV baldness (Hamilton, 1951) experienced enough hair growth along the anterior border of the hairline in the fronto-parietal region to be reclassificated as type II, and two patients with baldness type V became type IV.

A progressive decrease in the size of the prostate by digital rectal examination was noted in all of the subjects during the first 6 months of therapy. This clinical observation was confirmed by endorectal ultrasound in six subjects (aged 17–30 years). The mean baseline prostate volume was 21.6 ± 4.4 ml; it decreased progressively, to be significantly smaller after 6 months (13.2 ± 3.6 ml; $P < 0.001$). After 12 months of therapy the prostate volume was 12.2 ± 4.0 ml; therefore, 6 months were required to achieve maximal prostate shrinkage. No changes in testicular volume were noticed.

### Hormonal Effects

As shown in Table 1, testosterone concentrations were significantly increased after 3 months of finasteride treatment ($P < 0.005$), whereas DHT was decreased approximately 75% ($P < 0.001$), causing a marked increase in the testosterone/DHT ratio. This indicated that 5α-reductase activity was significantly reduced as early as 3 months after the initiation of the treatment. Finasteride treatment also significantly decreased the levels of Adiol-G (from 33.3 ± 6.4 to 12.8 ± 4.3 nmol/L; $P < 0.001$) and serum PSA concentrations (from 1.6 ± 0.6 to 0.4 ± 0.1 ng/dl; $P < 0.001$). A significant increase in serum androstenedione was observed during the first 3 months of finasteride treatment (from 3.67 ± 0.49 to 7.15 ± 0.63 nmol/L; $P < 0.005$). Estrogen concentrations were also increased ($P < 0.05$) by finasteride treatment, but no significant change in gonadotropin levels was noted. The effects of finasteride on hormonal levels were seen after the first 3 months of treatment, and they were maintained without significant change throughout the 2 years.

### Response to the Administration of Human Chorionic Gonadotropin

Table 2 shows serum steroid level response to the administration of HCG before and after 24 months of finasteride treatment. The increase in serum steroid levels induced by hCG after 3 and 24 months of finasteride administration was not significantly different (results not shown). The increase in testosterone levels achieved with hCG during finasteride administration was significantly ($P < 0.005$) higher than before, resulting in a striking elevation of the testosterone/DHT ratio (from 10.4 ± 3.1 to 82.6 ± 6.8). However, the simultaneous increases in the levels of androstenedione and E1 induced by hCG stimulation were significantly ($P < 0.05$) lower than before finasteride. Most importantly, before finasteride therapy the administration of hCG induced a twofold increase in the androstenedione/testosterone ratio. In contrast, there was a decrease in the androstenedione/testosterone ratio during finasteride therapy. The stimulated (post-hCG) E1/E2 ratios were significantly ($P < 0.005$) lower after finasteride therapy than before. A slight increase in the stimulated (post-hCG) testosterone/E2 ratio was only noticed during finasteride therapy.

Table 2. *Response of serum steroids to hCG before and after 24 months on finasteride*

| Hormone | Before | | After | |
|---|---|---|---|---|
| | Baseline | Peak | Baseline | Peak |
| Testosterone (nmol/L) | 16.6 ± 1.8 | 33.3 ± 1.0 | 27.5 ± 1.7 | 63.0 ± 1.8† |
| DHT (nmol/L) | 1.69 ± 0.41 | 3.17 ± 0.55 | 0.39 ± 0.10 | 0.76 ± 0.28* |
| Androstenedione (nmol/L) | 3.84 ± 0.42 | 14.25 ± 0.98 | 7.03 ± 0.42 | 11.10 ± 0.63‡ |
| E1 (pmol/L) | 152 ± 30 | 329 ± 59 | 189 ± 44 | 281 ± 33‡ |
| E2 (pmol/L) | 139 ± 37 | 286 ± 29 | 187 ± 37 | 411 ± 37† |
| T/DHT | 9.8 ± 2.3 | 10.4 ± 3.1 | 59.0 ± 7.2 | 82.6 ∓ 6.8* |
| Δ/T | 0.23 ± 0.06 | 0.42 ± 0.08 | 0.25 ± 0.07 | 0.17 ± 0.05* |
| T/E2 | 119.4 ± 23 | 116.4 ± 21 | 147.0 ± 28 | 153.0 ± 29 |
| E1/E2 | 1.09 ± 0.11 | 1.15 ± 0.13 | 1.01 ± 0.14 | 0.68 ± 0.08† |

T, testosterone. Values are given as mean ± SD.
* $P < 0.001$.
† $P < 0.005$.
‡ $P < 0.05$.

### *Gonadotropin Response to GnRH*

As shown in Figure 1, there were no detectable differences between the gonadotropin response to GnRH before and after 24 months of finasteride therapy. The mean peak LH levels were 42 ± 25 IU/L before finasteride and 41 ± 24 IU/L after 24 months of therapy; both peaks were achieved 40 minutes after the administration of GnRH. FSH peaks were achieved 80 minutes after the administration of GnRH, and no statistically significant differences were found between peak FSH/basal FSH or peak LH/basal LH ratios before and after finasteride.

## *Discussion*

The progressive loss of scalp hair in male pattern baldness appears to be a genetic condition inherited in a dominant fashion, but its clinical expression is under androgen control. Hypogonadal men do not become bald even if there is a strong family history of male pattern baldness. Nonetheless, hair loss can be induced by testosterone replacement in these individuals (Hamilton, 1942). Male pseudohermaphrodites with 5α-reductase deficiency do not exhibit male pattern baldness, suggesting that DHT is the active androgen in the development of hair loss (Imperato-McGinley et al, 1974). Finasteride, a potent inhibitor of 5α-reductase type 2, significantly decreased DHT levels in the scalp skin of patients with male pattern baldness, suggesting the possible utility of oral finasteride administration in the treatment of this condition (Dallob et al, 1994). Because early treatment and prolonged exposure to decreased levels of DHT may be necessary for clinical efficacy, it is of paramount importance to know the long-term effects of finasteride on the testicular steroidogenesis of young men. According to the mechanism of action of finasteride, a significant decrease of DHT serum levels, associated with an increase in testosterone concentrations, was already observed after 3 months of treatment. The increase in testosterone observed in this study is in agreement with the findings of other researchers, who have documented a similar effect in males treated with different dosages of finasteride (Gormley et al, 1990). Previous studies have demonstrated that testosterone exerts a negative feedback on pulsatile LH secretion, either directly and/or after aromatization to estradiol (Marynick et al, 1979). Despite the marked increase in testosterone and the decrease in DHT, no changes in gonadotropin secretion were observed. Both basal and GnRH-stimulated secretions of LH and FSH during finasteride treatment were, in fact, similar to the values observed before drug administration. Our findings are in agreement with the observation of Rittmaster et al (1992) and Fruzzetti et al (1994), who failed to show any discernible effect of finasteride, and the induced low levels of DHT, on LH and FSH secretion. Therefore, changes in gonadotropin secretion cannot explain the observed increase of testosterone serum levels in our patients. The increase in serum testosterone can best be explained by a reduction in testosterone metabolism resulting from the blockage of a major metabolic pathway for testosterone, rather than by an effect on its secretion. However, the testosterone response to hCG stimulation after finasteride treatment was also significantly increased, indicating the testicular source of testosterone and making an adrenal overproduction of testosterone unlikely. Furthermore, several studies (Fruzzetti et al, 1994; Rittmaster et al, 1994) have shown that finasteride has no influence on adrenal steroidogenesis. The increase observed in the serum levels of androstenedione during finasteride therapy could be explained by inhibition of the 5α-reduction of androstenedione to androstanedione, supporting the concept that the inhibition of 5α-reduction may explain, at least in part, the observed accumulation of testosterone. Finasteride also induced a significant suppression in the

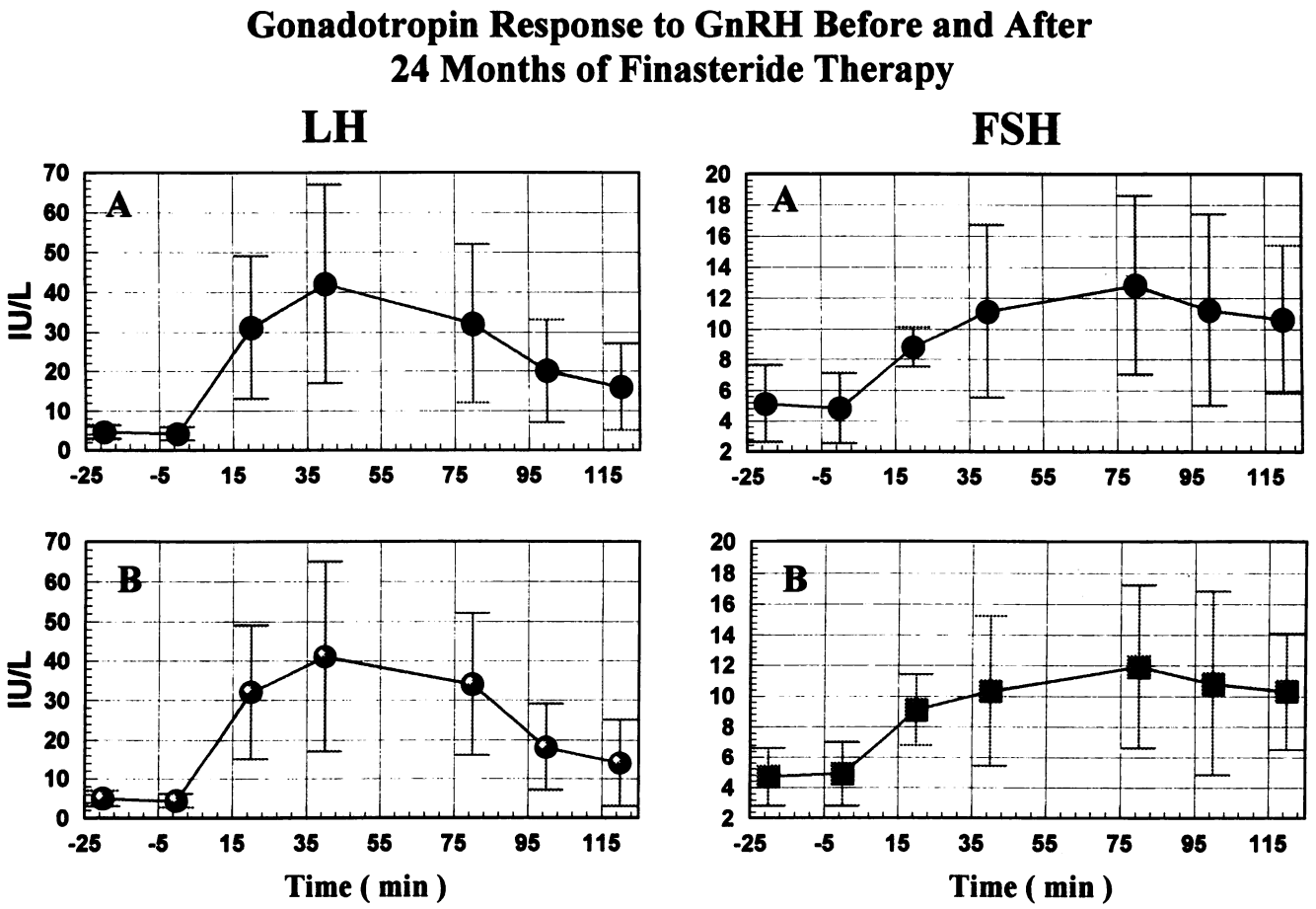


FIG. 1. Mean (± SD) serum gonadotropin concentrations in response to 100 μg GnRH, given i.v. to eight males with male pattern baldness before (A) and after (B) 24 months of finasteride therapy.

serum levels of Adiol-G, which has been proposed as a marker of peripheral androgen metabolism (Moghissi et al, 1984; Lookingbill et al, 1988).

The final step in the synthesis of sex hormones in the gonads is the conversion of androstenedione to testosterone and of E1 to E2 reactions that are catalyzed by 17-ketosteroid reductase (Castro-Magana et al, 1993). The significant decrease in the androstenedione/testosterone and E1/E2 ratios induced by the administration of hCG while on finasteride therapy suggests increased activity of this enzyme and therefore an improvement in the testicular capacity for testosterone production. The cause of the proposed increase in the activity of the 17-ketosteroid reductase is still unclear, but the increase in the testicular capacity for testosterone production associated with the simultaneous decrease in DHT levels during finasteride therapy might reflect a causal relationship. It is possible that DHT may play an inhibitory role in the activity of this enzyme, and therefore the reduction of DHT induced by finasteride would result in an increased activity of the testicular 17-ketosteroid reductase. However, a direct effect of finasteride on the activity of this enzyme or its increased activity as a consequence of an increase in its substrates cannot be ruled out. DHT has been shown to directly inhibit $P_{450}$ aromatase activity in ovarian tissue (McNatty et al, 1979). $P_{450}$ aromatase, as well as 5α-reductase, activities have been found to be present in the Leydig cells of human testis (Payne et al, 1982; Inkster et al, 1995). An inverse pattern exists between $P_{450}$ aromatase and 5α-reductase activities (Lephart et al, 1992). Thus, DHT may play an inhibitory role in testicular estrogen production. The moderate increase in E1 and E2 found in our patients on finasteride therapy could be explained by an increased activity of the $P_{450}$ aromatase, induced by the reduction of DHT.

In summary, the long-term treatment with finasteride in young males appeared to be safe and resulted in both an improvement of the male pattern baldness and prostatic shrinkage. Early and prolonged exposure to decreased levels of DHT may be necessary for the preven-

tion and clinical improvement of male pattern baldness. As expected, a significant and persistent decrease in serum DHT was achieved. The most striking finding, however, was the suggested increase in the activity of the testicular 17-ketosteroid reductase enzyme and the improvement in the testicular capacity for testosterone production induced by finasteride.

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