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A Long-term, Prospective Study of the Physiologic and Behavioral Effects of Hormone Replacement in Untreated Hypogonadal Men

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ABSTRACT: This study describes sexual activity, nocturnal penile erections, and mood states as a function of serum levels of androgens in previously untreated hypogonadal men before and during hormone replacement, selected infertile men (elevated serum follicle-stimulating hormone levels), and normal men. Nocturnal penile tumescence and rigidity were measured with a portable monitor, and sexual activity and mood were assessed by prospective, self-reported written forms. Nocturnal erections were absent or of very low amplitude and duration in the untreated hypogonadal men compared to the infertile and normal men. Nocturnal erections increased steadily during hormone replacement and were in the normal range within 6 to 12 months of treatment. In contrast, serum testosterone concentration rapidly reached the upper range of normal. During treatment, the hypogonadal men reported increases in several aspects of sexual activity, including sexual interest and the number of spontaneous erections. On mood inventories, the untreated hypogonadal men scored significantly higher in ratings of depression, anger, fatigue, and confusion than did infertile and normal men. During hormonal replacement therapy these scores decreased, although the hypogonadal men continued to score higher in "depression" than did infertile and normal men. In most instances, the men with infertility and the normal men were statistically indistinguishable in nocturnal penile tumescence and rigidity parameters, self-reported sexual activity, and mood state. These data support the hypothesis that androgen treatment increases nocturnal and spontaneous erections, and sexual interest, and has some capacity to improve mood.

Key words: Sexual behavior, androgens, mood, erection.

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Despite many reports on animal models, the role of androgens in human sexual function remains poorly understood (Davidson et al, 1982; Davidson and Myers, 1988). Insufficient production of testosterone results in various sexual deficits affecting both the erectile/ejaculatory components of sexuality (potency) as well as the motivational/appetitive components (libido; Davidson et al, 1979). Previous studies of hypogonadal men have indicated that nocturnal and spontaneous erections, which are exhibited without direct erotic stimulation, are reduced in the absence of androgens, whereas erections in response to erotic stimuli continue to be present (Bancroft and Wu, 1983; Kwan et al, 1983). However, clinical experience with untreated hypogonadal men (Davidson and Myers, 1988) suggests that profound androgen deficiency is accompanied by a marked reduction in all major aspects of sexual function, including libido and erectile potency.

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To assess the relationship between androgen status and sexual function, we compared two groups of men with varying degrees of androgen deficiency to age-matched men with normal androgen levels. The first group consisted of untreated, profoundly hypogonadal men who lacked endogenous androgen. The second group consisted of men with seminiferous tubule dysfunction manifested by infertility, a selective increase in the serum concentration of follicle-stimulating hormone (FSH), and a decrease in the testosterone production rate to half of normal (Booth et al, 1987). In all groups, we assessed nocturnal penile tumescence and rigidity (NPTR), serum hormone concentrations, and self-reported sexual activity/experience and mood state. Furthermore, we followed the hypogonadal men prospectively during hormone replacement to determine if sexual activity and mood varied with androgen repletion.

Materials and Methods

Subject Selection and Experimental Procedures

Six profoundly hypogonadal men between 25 and 40 years of age (mean ± SD = 32.3 ± 5.4 years) who had not previously received hormone replacement therapy participated in the study (Table 1). Two men had a diagnosis of congenital (prepubertal) isolated hypogonadotropic hypogonadism (IHH), and two others acquired IHH years after puberty. The fifth man (UP5) had profound testicular failure at age 14 following mumps orchitis. The sixth man (UP6), who had a diagnosis of idiopathic panhypopituitarism, had been treated with levothyroxine and growth hormone, but had never received androgens and remained prepubertal. (Subject UP6 did not require glucocorticoid maintenance.)

Eight men with seminiferous tubule dysfunction (ages 28 to 51 years; mean ± SD = 36.5 ± 7.5 years), manifested by severe oligospermia/azoospermia and infertility for at least 1 year and a selective increase in serum FSH concentration on initial laboratory screening, also participated (Table 1). Fourteen healthy, sexually active men aged 25 to 54 years (mean ± SD = 35.6 ± 7.7 years), age-matched to the hypogonadal men and infertile men, served as normal controls. Medical and sexual histories were obtained, physical examinations (including measurement of testicular volume) were performed, and routine laboratory studies (biochemical profile, complete blood count, urinalysis, and thyroid function tests) were undertaken for each man. The study protocol was approved by the National Institutes of Health Institutional Review Board, and informed consent was obtained from each man.

Hypogonadal men were studied on an inpatient basis. Nocturnal erections were monitored for two or three nights in the clinic and blood samples were taken at this time. Hormone replacement was begun just before discharge; the regimen was based on individual treatment goals. Three men (UP1, UP4, and UP5) received 200 mg testosterone enanthate intramuscularly (IM) every 2 weeks to cause virilization. The remaining three men (UP2, UP3, and UP6) were given 2,000 IU human chorionic gonadotropin (hCG: Pregnyl; Organon Pharmaceuticals, West Orange, NJ) and 75 IU FSH IM human menopausal gonadotropins (hMG: Pergonal; Serono Laboratories, Randolph, MA) three times per week in order to promote testicular growth, spermatogenesis, and virilization.

Three, 6, and 12 months after starting treatment, hypogonadal men were reexamined, blood samples were obtained, and nocturnal erections were monitored for two or three nights on an inpatient basis. We asked the men to complete a sexual activity log and mood state inventory daily for 2 weeks before their initial visit, and for 2 weeks after each follow-up appointment. However, because the hypogonadal men did not submit completed logs and inventories from every follow-up period, post-treatment data were pooled for comparison of effects before and after treatment. One hypogonadal man (UP5) complied poorly with testosterone enanthate injections and did not return after the 3-month visit; his data were excluded from analysis of post-treatment effects. Also, because subject UP6 entered the study much later than the other men, follow-up data were not available beyond his 3-month visit.

The infertile and normal control subjects were seen in the outpatient clinic, at which time blood samples were obtained, the use of the NPTR monitor demonstrated, and a 2-week supply of sexual activity logs and mood inventories dispensed. All of the normal men and six of eight infertile men completed the logs and mood inventories daily for a 2-week period.

NPTR Technique and Analysis

Nocturnal erections were assessed for up to three nights using the Rigiscan system (Dacomed Corporation, Minneapolis, MN), a portable monitoring device which measures both tumescence (circumference) and rigidity (hardness) at the tip and base of the penis (Bradley et al, 1985; Burris et al, 1989). Tumescence is expressed in centimeters (range: 5 to 15 cm), and rigidity in percent relative to a standard hard-rubber cylinder (range: 0% to 100% of standard). Men used the NPTR monitor for at least two nights (ses-

Table 1. *Clinical characteristics of hypogonadal men and infertile men*

Patient No.	Age (yrs)	Primary diagnosis	Secondary diagnoses	Daily medications
Untreated hypogonadal men				
UP1	31	isolated hypogonadotropic hypogonadism (acquired)	—	—
UP2	40	isolated hypogonadotropic hypogonadism (congenital)	anosmia	—
UP3	35	isolated hypogonadotropic hypogonadism (congenital)	anosmia, gynecomastia, bilateral cryptorchidism	—
UP4	28	isolated hypogonadotropic hypogonadism (acquired)	bipolar affective disorder	lithium carbonate
UP5	25	primary testicular failure (postorchitis at age 14 years)	marijuana, amphetamine abuse, 46XY karyotype	—
UP6	35	panhypopituitarism (congenital)	hypothyroidism, growth hormone deficiency	levothyroxine
Inferitile men				
PC1	28	maturation arrest*	azoospermia, 46XY karyotype	—
PC2	33	unknown	(L) varicocele, 2° hypospadias	—
PC3	33	germinal aplasia	azoospermia, 46XY karyotype	—
PC4	51	bilateral cryptorchidism	ankylosing spondylitis	—
PC5	41	orchitis, epididymitis	azoospermia	—
PC6	29	unknown	(L) varicocele	—
PC7	39	bilateral cryptorchidism	—	—
PC8	38	bilateral cryptorchidism	—	—

* Diagnosed by testicular biopsy.

sions) and were asked to abstain from alcohol and caffeinated beverages in the evening before each session. Nocturnal penile tumescence and rigidity parameters calculated for each session included sleep time (length of time the instrument was used), maximum tumescence (measured at the tip and base), delta-tumescence (maximum tumescence minus average minimum tumescence in cm), maximum rigidity, number of erectile episodes, and total tumescence time. An erectile episode was defined as a 0.75 cm increase in tumescence from baseline (average minimum tumescence), which was sustained for at least 10 minutes, and total tumescence time was defined as the total duration of erectile episodes. To incorporate both amplitude and duration in one measure we computed area-under-the-curve (AUC) values for tumescence and rigidity (at the tip and base). AUC was expressed as centimeter-hour for tumescence or percent standard-hour for rigidity. Only those tumescence or rigidity data points that fell within erectile episodes were used in the calculation of AUC. Because we previously observed no significant differences between consecutive NPTR sessions with the same subject (Burris et al, 1989), data for each man were combined from the two (or three) sessions to yield a mean for each NPTR parameter.

Assessment of Sexual Activity and Mood

The men were asked to complete a log of sexual activity in the evening before going to sleep. They recorded the number of episodes in each of eight categories: sexual events (feelings of desire, sexual thoughts, fantasies, etc.), spontaneous (waking) erections, sleep erections (morning erections), sexual intercourse with and without orgasm, masturbation with and without orgasm, and other sexual activity (oral–genital sex). Furthermore, they rated the episodes on a seven-point scale, 1 being "barely noticeable" and 7 being "the strongest you can imagine." Cumulative weekly totals of the number of episodes and the corresponding subjective ratings were used for data analysis.

The men also were asked to complete a Profile of Mood States (POMS: Educational and Industrial Testing Service, San Diego, CA). The form consists of a series of 65 questions answered on a scale ranging from 0 (not at all) to 4 (extremely). Mood state is scored in six categories: tension/anxiety, depression/dejection, anger/hostility, vigor/activity, fatigue/inertia, and confusion/bewilderment. Scores were converted to standardized T-scores for data analysis. Previous work indicates that POMS is well suited for measuring mood changes associated with pharmacologic intervention (Peterson and Headen, 1984).

Hormone Assays

Serum was separated from blood and stored at −20°C. At least three blood specimens were obtained at 20-minute intervals from the hypogonadal men, and at least two testosterone (Abraham, 1973) and estradiol (Jiang and Ryan, 1969) determinations were made. The intraassay and interassay coefficients of variation were 10% and 12% for T and 10% and 17% for E_2, respectively. Serum FSH and luteinizing hormone (LH) concentrations were measured in duplicate by double antibody radioimmunoassay using the second IRP standard (Odell et al, 1967). The detection limit of the assay was 2 mIU/ml (IU/L) for both LH and FSH. The intra-assay and interassay coefficients of variation were 8% and 10%, respectively, for both hormones. Testosterone-binding globulin-binding capacity (TeBG) was measured by a solid-phase method (Nisula and Dunn, 1979). Normal reference values of T, TeBG, E_2, LH, and FSH for healthy men are shown in Table 2.

Statistical Methods

Data are presented as the mean ± SE of the mean. An analysis of variance (ANOVA) was performed to test for group effects, comparing hypogonadal men, either before or after treatment, with infertile and normal men. Individual variability was used to test for significance of group differences overall. Tukey's studentized range test was performed for post-hoc comparisons between groups. A repeated-measures ANOVA was used to investigate within-subject effects of treatment among the hypogonadal men (Scheffe, 1959). A probability value of <0.05 was considered significant.

Results

NPTR Measurements

All NPTR measurements of the untreated hypogonadal men were significantly less than those of the infertile and normal men ($P \leq 0.03$) except sleep time (P = NS). Although sleep time was not independently confirmed, it is presented here for comparison. Four untreated hypogonadal men did not have nocturnal erections (Fig 1), and two had nocturnal erections of lower amplitude and duration. A progressive increase in the frequency and extent of nocturnal erections occurred during hormone replacement therapy in the hypogonadal men (Figs 2 and 3). Within 12 months of treatment,

Table 2. *Serum hormone concentrations in normal, infertile, and untreated hypogonadal men**

Group	Testosterone† (ng/dl)	TeBG (ug/dl)	Estradiol† (pg/ml)	Luteinizing hormone (IU/l)	Follicle-stimulating hormone (IU/l)
Normal (n = 14)	527 ± 44‡	0.90 ± 0.09	32.5 ± 5.0	10.4 ± 0.8	5.1 ±0.5
Infertile (n = 8)	383 ± 36‡	1.12 ± 0.16	26.4 ± 2.6	14.9 ± 1.8	26.7 ± 3.1
Hypogonadal	35 ± 4‡	2.03 ± 0.11‡	12.7 ± 1.9‡	—	—
hypogonadotropic (n = 5)				2.7 ± 0.2	1.7 ± 0.1
hypergonadotropic (n = 1)				53.7 ± 1.6	67.9 ± 2.6
Normal range	200–1000	0.37–0.70	<12–58	6–26	5–25

TeBG = testosterone binding globulin binding capacity.
* Values are presented as means ± SE.
† To convert testosterone to nmol/l, multiply by 0.035; to convert estradiol to pmol/l, multiply by 3.671.
‡ $P < 0.01$ when compared with other groups.

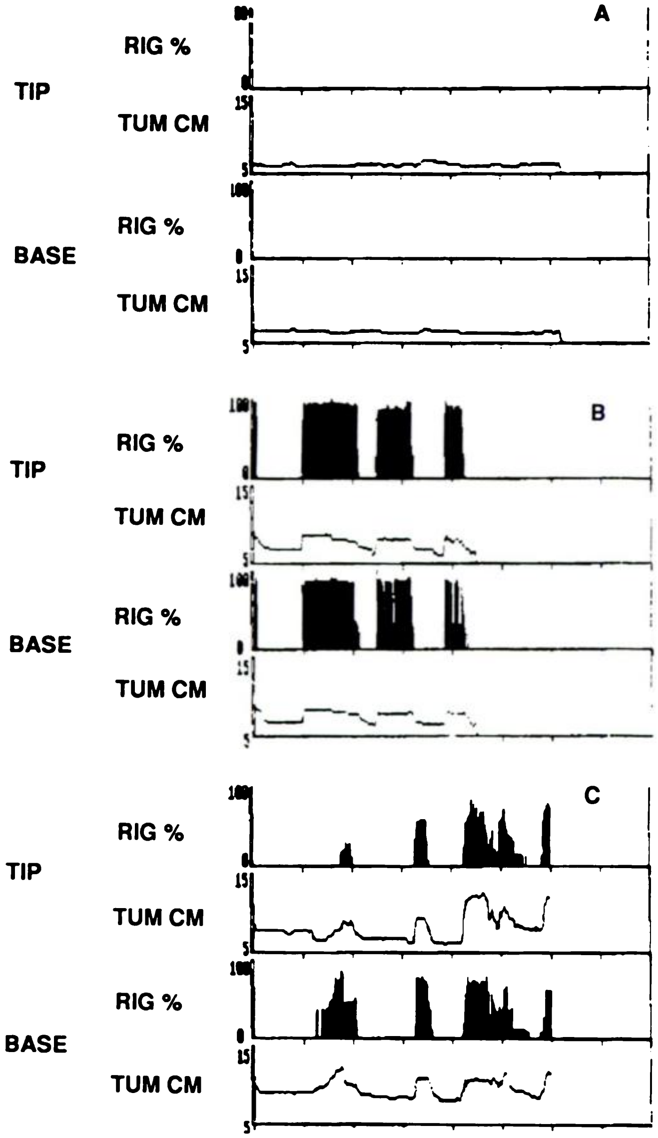

FIG. 1. Nocturnal penile tumescence and rigidity of a 35-year-old man with isolated hypogonadotropic hypogonadism before (A) and 12 months after (B) hormone replacement, and of a normal 35-year-old man (C). In each graph, penile rigidity (in percent standard) at the tip and base are shown in the first (top) and third segments, respectively, and penile tumescence (in cm) at the tip and base are shown in the second and fourth (bottom) segments, respectively. Time is plotted on the abscissa in 1-hour intervals.

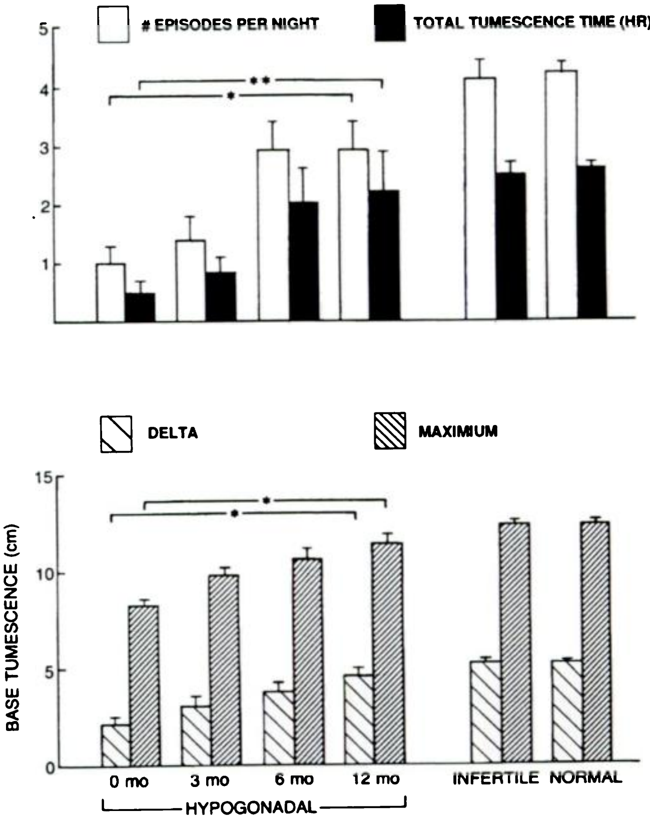

FIG. 2. Nocturnal penile tumescence and ridigity (NPTR) of infertile and normal men, and hypogonadal men before (0 months) and during (3, 6, and 12 months) hormone replacement. The top panel shows the mean (±SE) number of NPTR episodes per session (open bars) and total tumescence time per session (closed bars). The bottom panel shows mean (±SE) delta-tumescence (wide stripe) and maximum tumescence (narrow stripe), measured at the base. (*) indicates a significance level of $P \leq 0.01$ and (**) a significance of $P \leq 0.03$ for comparisons between groups (hypogonadal men at 0 and 12 months, versus other groups) and within the hypogonadal group during treatment.

the NPTR parameters of the hypogonadal men were significantly greater than the pretreatment values ($P \leq 0.03$) and similar in magnitude to those of the infertile and normal men (P = NS). Rigidity AUC values (Fig 3) exceeded those of infertile and normal men, corresponding to an increase in spontaneous erections on the self-reported sexual activity logs.

Nocturnal erections were recorded for all normal men and for seven of the eight infertile men. One infertile subject was unable to use the monitor. There were no significant differences in the NPTR parameters of the infertile and normal men.

Serum Hormone Concentrations

The mean serum testosterone concentration (Table 2) was lowest in the untreated hypogonadal men ($P < 0.01$) and was lower in the infertile men than in the normal men ($P < 0.01$). When first measured 3 months after the start of treatment, the mean serum testosterone concentration of the hypogonadal men (Fig 4) exceeded that of the infertile and normal men ($P = 0.01$) and remained unchanged for the duration of the study (P = NS, months 3 through 12). The mean serum TeBG binding capacity of 2.03 μg/dl of the hypogonadal men (Table 2) decreased to 0.94 ± 0.05 μg/dl during treatment ($P = 0.001$ compared to pretreatment val-

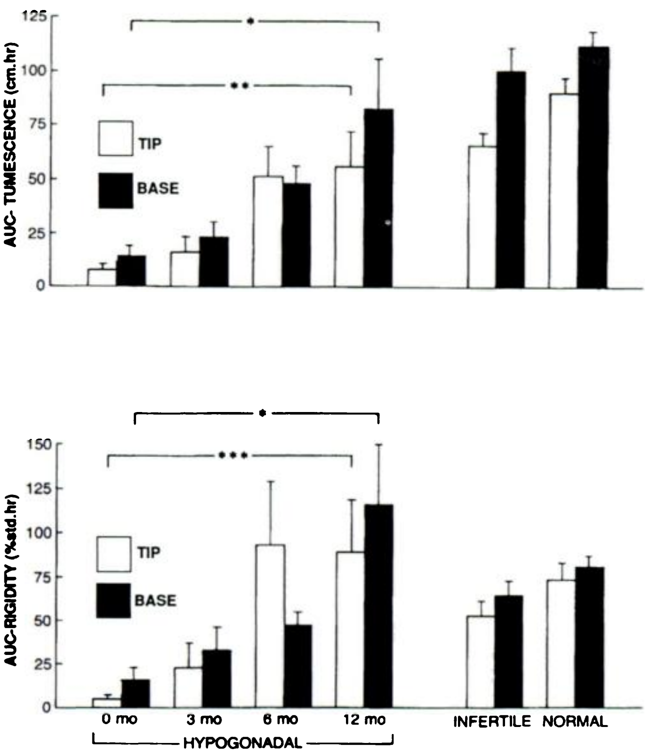

FIG. 3. Nocturnal penile tumescence and rigidity area-under-the-curve (AUC) measurements of infertile and normal men, and hypogonadal men before (0 months) and during (3, 6, and 12 months) hormone replacement. The top panel shows mean (±SE) AUC-tumescence and the bottom panel shows mean (±SE) AUC-rigidity. In both graphs, measurements presented are from the tip (open bars) and base (closed bars). (*), significance level of $P \leqslant 0.005$; (**), $P \leqslant 0.01$; and (***), $P \leqslant 0.03$. Comparisons were made between groups (hypogonadal men, at 0 and 12 months, versus infertile and normal men) and within the hypogonadal group during treatment.

ues; P = NS compared to other groups). The mean serum estradiol concentration increased from 12.7 to 57.6 ± 5.5 pg/ml during treatment (P = 0.0001 compared to pretreatment values, and P < 0.01 compared to other groups). No significant changes in TeBG or estradiol concentration were noted on subsequent sampling during treatment (P = NS). The serum TeBG and estradiol concentrations were similar for infertile and normal men (P = NS). Mean serum LH and FSH concentrations (Table 2) increased in three hypogonadal men who received human chorionic gonadotropin (hCG), and remained unchanged in two men who received testosterone enanthate (data not shown).

Sexual Activity and Mood State

When interviewed before hormone replacement therapy, the two men with acquired IHH (UP1 and UP4) described a profound loss of sexual desire (libido) and potency. The other untreated hypogonadal men, who had never undergone puberty, claimed to have normal erections during masturbation or sexual intercourse (Fig 5). As a group, the untreated hypogonadal men reported low sexual interest (number and rating of sexual events, P < 0.05 compared to other groups) and few spontaneous erections. The number of spontaneous erections reported by the untreated hypogonadal men was similar to that reported by the infertile men. Interestingly, the untreated hypogonadal men reported significantly more episodes of intercourse without orgasm (P < 0.05) and masturbation without orgasm (P = 0.02) than did the other groups. The hypogonadal men also reported fewer episodes of intercourse and masturbation with orgasm, although this was not statistically significant (P < 0.1).

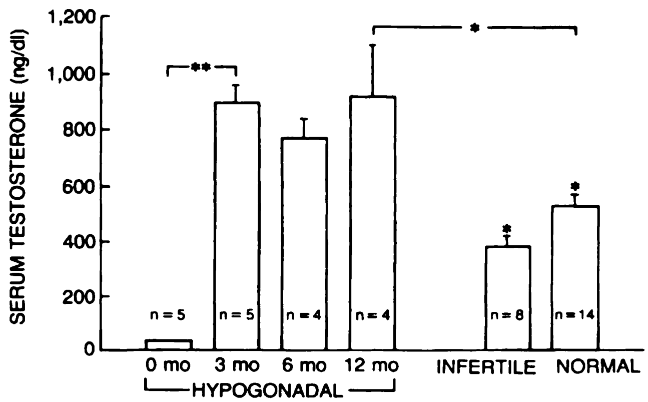

FIG. 4. Mean (±SE) serum testosterone concentration in infertile and normal men, and before (0 months) and during (3, 6, and 12 months) hormone replacement in hypogonadal men. (*), significance level of $P \leqslant 0.01$; (**), $P = 0.0001$. Comparisons were made between groups (hypogonadal men, at 0 and 12 months, versus infertile and normal men) and within the hypogonadal group during treatment.

Within the first 6 months of treatment, the hypogonadal men noted beard growth, an increase in body hair, body odor, acne, and the appearance of an ejaculate. During hormone replacement therapy, the two men with acquired IHH described a dramatic increase in sexual interest and potency within the first month of treatment, whereas the other hypogonadal men described a gradual increase in sexual interest and potency. As a group, the hypogonadal men reported that their sexual interest (both number and rating of sexual events) increased during treatment to a level comparable to the infertile and normal men (P = NS). The number and rating of spontaneous erections increased and surpassed values reported by the infertile and normal men (P < 0.01 and P = 0.02 for number and rating, respectively). The reported number of episodes of intercourse with orgasm and sleep erections also increased during treatment (P = 0.07), and the number of episodes of masturbation without orgasm declined to a level comparable to the other groups (P = NS).

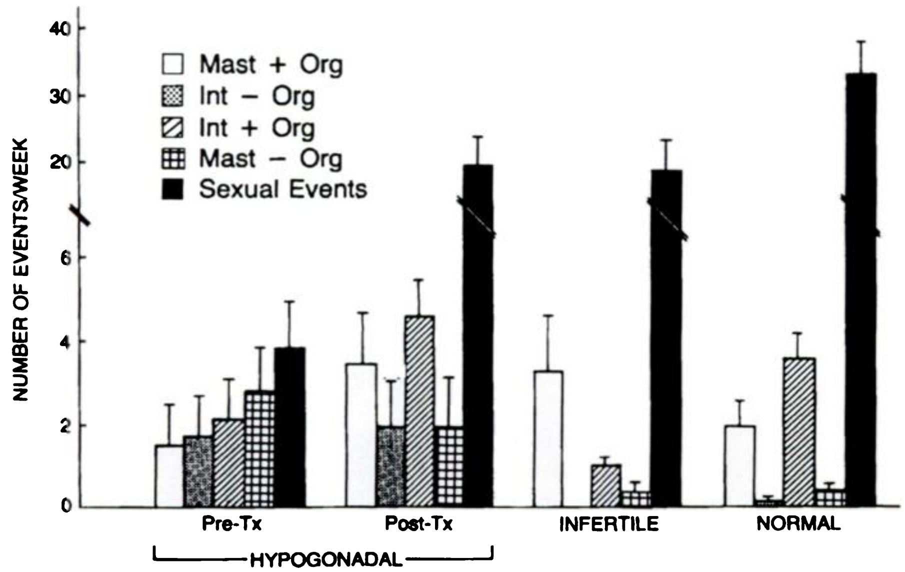

FIG. 5. Self-reported sexual activity of infertile and normal men, and hypogonadal men before (PRE-Tx) and after treatment (POST-Tx). The mean (±SE) weekly number of episodes are shown for five categories: sexual events (feelings of desire, sexual thoughts, fantasies, etc); intercourse with and without orgasm (int + org, int − org); and masturbation with and without orgasm (mast + org, mast − org). Note that sexual events are plotted on an expanded scale.

The untreated hypogonadal men had significantly higher POMS scores than the infertile and normal men ($P \leq 0.02$) in four categories: anger, depression, fatigue, and confusion (Fig 6). After treatment, the hypogonadal men reported increased vigor, (although less than normal men, $P = 0.04$) and more depression than the infertile and normal men ($P = 0.02$). In the remaining four categories, the treated hypogonadal men had scores similar to the infertile men (P = NS compared to other groups). No differences between the normal and infertile men were detected in any category.

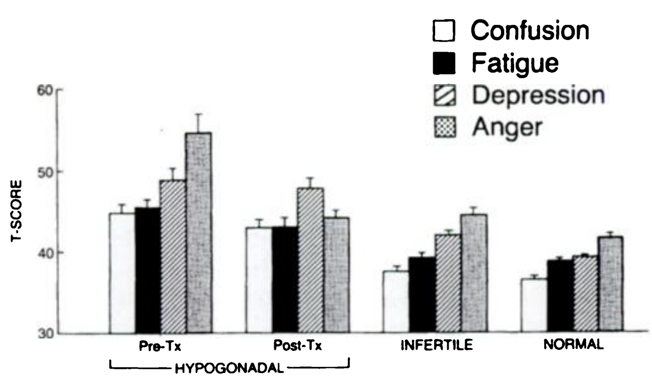

FIG. 6. Mood inventory scores of infertile and normal men, and hypogonadal men before (PRE-Tx) and after treatment (POST-Tx). Daily mean (±SE) T-scores are shown for four categories: confusion–bewilderment; fatigue–inertia; depression–dejection; and anger–hostility.

Discussion

This study demonstrates that androgens may modulate nocturnal erections, sexual interest, and mood state in untreated hypogonadal men. In contrast to most (Davidson et al, 1979; Bancroft and Wu, 1983; O'Carroll et al, 1985; Salmimies et al, 1982), but not all (Kwan et al, 1983) previous work, we limited our study to untreated, profoundly hypogonadal men with serum testosterone concentrations in the castrate range. These men are ideal subjects for studying the effects of exogenous hormone with minimal influence of endogenous hormone. We also studied a select subgroup of men with infertility associated with elevated FSH levels to determine whether the lesser, but significant, deficits in testosterone production associated with that group (Booth et al, 1987) have measurable effects on NPTR, sexual function, and mood.

Generalizations from this research are severely limited due to the small number of subjects, the heterogenous nature of the subject pool, and the fact that part of the hypogonadal subjects received exogenous androgens, whereas others produced endogenous androgen under gonadotropin stimulation. In another study (Burris et al, 1988), however, we noted that serum testosterone levels are similar in men receiving exogenous testosterone compared to those stimulated to produce endogenous androgens. The fact that the hypogonadal men were studied on an inpatient basis while the other groups were studied on an outpatient basis, and that we could not control or verify the behaviors of these subjects, also is problematic. Descriptive data from hypogonadal men before and during treatment are rare. In the present study, objective measures, including nocturnal penile tumescence, hormone levels, and behavior, were collected to allow comparisons with other groups of men and within-subject comparisons over time. It should also be noted that sleep quality was not measured in the present study, and although the subjects did not report sleep disturbances, the possibility that differential sleep patterns contributed to the NPTR results reported here remains to be investigated.

Because nocturnal erections are largely unaffected by daytime sexual activity (Rosen et al, 1986), NPTR serves as a measure of the integrity of the erectile mechanism. However, nocturnal erections may involve central mechanisms that are different from those controlling erections during sexual activity (Davidson and Myers, 1988). In the untreated hypogonadal men, NPTR was absent or markedly reduced in amplitude and duration, such that all parameters were below the fifth percentile for normal men (Burris et al, 1989). With hormone replacement therapy, all parameters fell within the normal range within 9 to 12 months. Since previous studies were short-term, it had not been realized that the effects of androgens on nocturnal erections were so gradual. It is possible that the prolonged time course was due to the long periods of androgen deprivation. The increase in NPTR was gradual, despite the fact that mean testosterone concentrations rose to within the normal range soon after hCG (Burris et al, 1988) or testosterone treatment (Snyder and Lawrence, 1980). In a concurrent analysis of the hypogonadal subjects studied here, we found progressive declines in the tactile sensitivity of the penis measured over the course of 12 months of androgen exposure (Burris et al, 1991). Together, these results suggest that maximal effects of androgens on penile function in hypogonadal men are expressed gradually, even in men who have a prior history of androgen exposure.

The relationship between nocturnal erections and androgens is supported by previous studies involving untreated hypogonadal men (Kwan et al, 1983) and previously treated hypogonadal men (O'Carroll et al, 1985). These short-term studies used somewhat different methods (ie, strain-gauge NPT), and subjects who were primarily men with acquired hypogonadism.

Previous studies have indicated that testosterone stimulates sexual behavior in general, and, particularly, it increases the number of spontaneous erections during consciousness and sleep and facilitates libido (Davidson and Myers, 1988). Indeed, the untreated hypogonadal men in our study reported low sexual interest, or a low number of sexual events on their sexual activity logs. The number of sexual experiences appears to be a sensitive means for assessing sexual interest since it reflects activity that is not partner-dependent. During treatment there was a pronounced increase in the number of sexual experiences; a similar response has been observed in hypogonadal men who receive testosterone after a period of hormone withdrawal (Davidson et al, 1979; Bancroft and Wu, 1983; Salmimies et al, 1982). The increase in the number of sexual experiences during hormone replacement resembles the increase in sexual behavior modulated by endogenous testosterone during normal puberty (Udry et al, 1985). The two untreated hypogonadal men in our study who had acquired IHH after puberty described a sharp reduction in sexual interest and a decrease in potency, both during masturbation or with a partner. In contrast, the men who had never undergone puberty, and thus have a different sexual frame of reference, claimed to have erections during sexual activity, reporting episodes of masturbation and sexual intercourse with orgasm, but without ejaculation. These unsustained assertions seem inconsistent with the NPTR results of absent or markedly reduced erections. However, two studies have shown that untreated hypogonadal men (Kwan et al, 1983) or previously treated hypogonadal men given placebo (Bancroft and Wu, 1983) are able to attain normal erections in response to highly erotic films. It also is possible that the self-reported frequencies of masturbation and intercourse reflect social expectations rather than actual events, as has been reported in adolescents (Udry et al, 1985). It should be noted that, since we were unable to examine the time course of changes in sexual activity (or mood), emphasis should be placed on overall trends rather than the absolute numbers.

The changes in sexual activity noted during hormone replacement may reflect, in part, changes in mood. The hypogonadal men scored higher on the POMS test in several categories before treatment, but during treatment they resembled the infertile and normal men, similar to a recent study of previously treated hypogonadal men (O'Carroll et al, 1985). However, even during treatment, the hypogonadal men remained depressed. The prolonged and delayed puberty in these men may be related to their depression: they were first referred for treatment when, on average, 32 years old, whereas normal puberty begins at 9.5 to 13.5 years (Griffin and Wilson, 1985). Other factors, including the emotional, and in the case of subject UP4, psychiatric history of the patients could explain the continued dysphoria during hormone-replacement therapy.

The differences between the infertile and normal men regarding NPTR, sexual activity, and mood were few and minor. Apparently, NPTR does not reflect the diminished testosterone production of the infertile men (Booth et al, 1987). Other work (Davidson et al, 1982) also suggests that altering androgen levels within the normal range has little effect on sexual function. The differences in self-reported sexual activity (ie, number of episodes of intercourse with orgasm) could reflect psychological effects of infertility or sociologic factors (partner availability).

The relationship between endocrine events, somatic virilization, sexual behavior, mood, and nocturnal erections in the untreated hypogonadal men serves as a model of normal pubertal development. Perhaps the lag in NPTR and somatic virilization in hypogonadal men during hormone treatment resembles changes that occur during normal pubertal development (Griffin and Wilson, 1985). The supranormal AUC rigidity values, increased number of spontaneous erections on self-reported sexual activity logs, and increased erectile response of the treated hypogonadal men during physical examination correspond to the experiences of normal boys during puberty (Udry et al, 1985). The data suggest that in the untreated hypogonadal adult man there is both impairment of the erectile mechanism and diminished sexual interest and desire, and that androgens increase both nocturnal erections and sexual interest. The site(s) of androgen action in modulating human sexual behavior remain to be determined.

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