A comparative analysis of the role of androgen in human male and female sexual behavior: Behavioral specificity, critical thresholds, and sensitivity

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Accumulated evidence suggests that testosterone enhances sexual motivation in both men and women. Hormone replacement studies in hypogonadal men and in ovariectomized women suggest that, above a certain threshold, increased quantities of testosterone are behaviorally irrelevant in both sexes. The observation that sexual motivation in females is enhanced by levels of testosterone much below those required for normal sexual interest in men raises the possibility of a difference in neural sensitivity to testosterone. An alternative explanation for such findings, based on the evidence that changes in levels of hormones may be more important for behavior than absolute levels, is proposed.

It has long been recognized that some product secreted by the testes plays a critical role in human male sexual behavior; castration had been carried out for hundreds of years for religious or punitive reasons. Much more recent, however, is the idea that androgens have purported libido-enhancing effects in women. This idea dates to the early 1940s, when testosterone (T) was first synthesized and subsequently used to treat a variety of gynecological disturbances (Foss, 1951; Greenblatt, 1942). By now, the available evidence suggests the following propositions: First, T differentially influences the sexual motivation and arousal components of human sexual behavior, and it does so in a similar manner in both men and women. Second, in both sexes, there is a critical threshold for circulating plasma T above which increased concentrations of the hormone are behaviorally irrelevant. In this paper, evidence for these propositions derived from studies of both non-human primates and humans will be reviewed. In a final section, the observation that females appear to be behaviorally responsive to their physiological T levels, which are one tenth of those of the normal male, and to which males are unresponsive, will be explored. This observation, if well founded, raises the paradoxical possibility that females are "more sensitive" to androgens than are males. Possible explanations of this phenomenon based on the cyclicity of female hormonal release will be discussed.

In the human male, the two steroids of primary importance in reproductive function are T and dihydrotestosterone (DHT). Over 95% of the total plasma concentration

of T is secreted by the Leydig cells of the testes, while the remainder is produced by the adrenals. The testes also secrete approximately 20% of the most potent androgen, DHT, and the weak androgens dehydroepiandrosterone (DHEA) and androstenedione. However, about 80% of DHT and estradiol (E_2) are derived by conversion, in peripheral tissues, of androgen and estrogen precursors secreted by both the testes and the adrenals. Dehydroepiandrosterone sulphate (DHEAS) is almost exclusively of adrenal origin (90%; Braunstein, 1986).

In women, both the adrenal and the ovary contain the biosynthetic pathways necessary for androgen synthesis and secretion. The ovary produces approximately 25% of plasma T, 60% of androstenedione, and 20% of DHEA, whereas the adrenal produces 25% of circulating T, 40% of androstenedione, 50% of DHEA, and 90% of DHEAS. The remainder of circulating androgens in the female are thought to arise through peripheral conversion, which likely accounts for the production rate of 50% of T and 25% of DHEA (Longcope, 1986).

Although there is evidence from animal studies that some actions of T and other aromatizable androgens come about through estrogen metabolites, the idea that androgens play a role in sexual behavior in women seems to imply androgenic activity at the level of androgen receptors, as distinct from estrogenic activity. There is little direct evidence for this, however; but the demonstration that high doses of estrogens do not affect behavior in the same way as high doses of androgens provides indirect evidence of specific androgenic action.

Assessing the Effects of Hormones on Specific Components of Sexual Behavior

In the study of male sexual behavior, it was recognized early that various components of sexual behavior, though ultimately integrated, were differentially controlled. When

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Beach (1956) introduced the concept of an arousal and motivational component of mating, he suggested that it could be separated neurally from the copulation component, which included the acts of intromission and ejaculation.

In 1976, Beach provided definitions of three sequential stages of the mammalian mating pattern. *Attractivity* referred to the female's stimulus value in evoking sexual responses by the male, *proceptivity* involved various reactions by the female toward the male that can be interpreted as invitation and/or solicitation, and *receptivity* was defined in terms of female responses necessary for the male's success in achieving intromission and ejaculation. Although researchers studying mating behavior in animals have been using these operational definitions since they were first proposed, it is only recently that investigators of human sexuality have ceased to refer to the various aspects of sexual behavior under the rubric "libido" and have assessed possible differential effects of steroid hormones on the component parts of this complex set of behaviors.

Perhaps the most compelling evidence that T enhances specific aspects of sexual behavior comes from studies of hormone replacement therapy given to hypogonadal individuals. In animals, this is accomplished experimentally by gonadectomizing the adult, then administering one or more of the sex steroids and observing the effects on components of mating behavior. In humans, most studies have been carried out on individuals with intact, nonfunctional gonads, but gonadectomized subjects have been investigated as well.

Nonhuman primates. In the male rhesus monkey, sexual activity diminished with time following castration and was effectively restored by T when it was given not too long after the castration (Phoenix, 1973). It has since been demonstrated that a significant increase in mounting, intromission, and ejaculation frequencies occurred following T treatment of long-term castrated male rhesus macaques (Phoenix & Chambers, 1982).

In female nonhuman primates, the effects of T on the various components of mating behavior have been studied more intensively. T administered to ovariectomized rhesus monkeys has been shown to increase proceptive behavior (i.e., increased attempts to solicit mounts from the male; see Keverne, 1976; Michael, Zumpe, Keverne, & Bonsall, 1972; Trimble & Herbert, 1968; Wallen & Goy, 1977). Proceptivity was further reduced in ovariectomized females after they were adrenalectomized and consequently devoid of all sources of endogenous androgen production (Everitt & Herbert, 1972; Everitt, Herbert, & Hamer, 1971). This occurred despite treatment with E_2 , and the behavior was restored to preoperative levels with subcutaneous implants of T (Everitt et al., 1971). Implantation of T into the anterior hypothalamus of adrenalectomized, unreceptive female rhesus monkeys also resulted in restoration of the behavior (Everitt & Herbert, 1975). Furthermore, when testosterone propionate (TP) was administered intramuscularly to ovariectomized

rhesus monkeys, leverpressing for access to a male partner increased in an operant situation (Michael et al., 1972). T treatment did not appear to increase the attractiveness of ovariectomized monkeys, however, for there was no corresponding increase in the sexual interaction of the pair (Michael et al., 1972).

Human males. There is some evidence that, in sexually functional eugonadal men, psychophysiological responses in a laboratory situation are associated with levels of circulating T. Two such studies have reported that plasma T correlated positively with penile tumescence and negatively with latency to 90% of full erection during exposure to erotic films (Lange, Brown, Wincze, & Zwick, 1980; Rubin & Henson, 1979). Furthermore, in men over 60 years old, higher levels of sexual activity were associated with higher levels of total T (Tsitouras, Martin, & Harman, 1982). A cross-sectional study of men between the ages of 40 to 93 years found a decrease in total and free plasma T with increasing age, which was paralleled by a decline in sexual function (Davidson et al., 1983). The consistency of the findings in these correlational studies suggests that variations in sexual activity, motivation, and potency in normal functional men may be due to the variations in endogenous T production.

Studies of androgen replacement therapy for the treatment of hypogonadal men have provided useful information on its behavioral effects. Table 1 contains a list of these studies and their major findings. Hormones were delivered either in a single, long-acting injectible form, or by tablets taken daily. In every study, increases in sexual interest and in sexual thoughts were reported during T replacement therapy, relative to baseline rates of these behaviors. Some investigators documented decreases with time in these proceptive behaviors and in the number of erections and ejaculations as the parenteral preparations were being depleted (Davidson, Camargo, & Smith, 1979; Salmimies, Kockett, Pirke, Vogt, & Schill, 1982) or after the oral tablets were stopped (Bancroft & Wu, 1983; Skakkeback, Bancroft, Davidson, & Warner, 1981). However, a recent study found that only sexual desire and interest decreased in association with decreasing plasma T levels across a treatment phase, whereas the frequency of sex acts and ejaculations remained stable (Gooren, 1987).

The finding of a differential impact of T on specific aspects of male sexual behavior gains support from two studies of men in whom the onset of impaired testicular functioning occurred sometime after puberty. First it was found that although the frequency, duration, and magnitude of spontaneous erectile responses were reduced in untreated hypogonadal men, as opposed to men with normally functioning gonads, the frequency of erections that occurred during the viewing of erotic films did not differ (Bancroft & Wu, 1983; Kwan, Greenleaf, Mann, Crapo, & Davidson, 1983). However, in the Bancroft and Wu (1983) study, when subjects were instructed to generate fantasies to induce erection, hypogonadal men responded poorly but improved significantly with T replacement.

Table 1
Androgen Replacement Studies with Hypogonadal Men

Study	T Dose(s) Given	Behavioral Effects	Circulating T Levels During Treatment
Davidson, Camargo, & Smith, 1979	100 and 400 mg testosterone enanthate	↑"overall" sexual activity	600–1,500 ng/dl 7 days postinjection
Skakkeback, Bancroft, Davidson, & Warner, 1981	160 mg testosterone undecanoate (oral)	↑sexual interest ↑sexual acts ↑ejaculations	6–17 nmol/l (173–490 ng/dl) 4 h after tablet injection
Salmimies, Kockott, Pirke, Vogt, & Schill, 1982	25, 50, 100, & 250 mg testosterone enanthate	↑sexual desire ↑erections ↑ejaculations with all doses but 25 mg	300–900 ng/dl 1 week after injection
Bancroft & Wu, 1983	160 mg testosterone undecanoate (oral)	↓in latency of erectile response to fantasy ↑sexual interest ↑subjective excitement	228–452 ng/dl
Kwan, Greenleaf, Mann, Crapo, & Davidson, 1983	200 + 400 mg testosterone enanthate	↑sexual interest ↑erections, orgasms ↑NPT	—
O'Carroll, Shapiro, & Bancroft, 1985	40, 80, 120, & 160 mg testosterone undecanoate (oral)	↑sexual thoughts ↑sexual arousal ↑sleep erections	15–25 nmol/l (432–721 ng/dl) 4 h after tablet ingestion
Gooren, 1987	(a) 250 mg testosterone enanthate	↑subjective quality of sexual acts	6.9–12 nmol/l (73–346 ng/dl) 12–14 days postinjection
	(b) 240 mg testosterone undecanoate (oral)	↑sexual thoughts	4.6–7.4 nmol/l (133–213 ng/dl)
		↑vigour ↑fatigue	2 h after tablet ingestion 2.8–5.2 nmol/l (81–150 ng/dl) 9 h after tablet ingestion

Kwan et al. (1983) found that only 3 of 6 untreated hypogonadal subjects failed to respond to fantasy. In a study by O'Carroll and Bancroft (1984), exogenous T increased sexual interest and desire in eugonadal men who complained of low desire, but it did not augment erectile responses in those with erectile dysfunction. Taken together, the evidence from the T replacement studies suggests that T plays an important role in the cognitive and motivational aspects of human male sexuality such as desire and interest. The finding that so-called spontaneous erections occurring during sleep and those generated by sexual thoughts and fantasy are both influenced by T is interesting and may have implications for an understanding of the mechanism underlying their generation.

Human females. A variety of models have been used to test the relationship between androgens and sexuality in women. Because plasma T levels peak around the time of ovulation and decrease in the late luteal phase, one investigational strategy has involved monitoring changes in several aspects of sexual behavior at different points during the menstrual cycle. Of course, plasma levels of E_2 also reach their highest point at the midcycle ovulatory phase. Therefore, the demonstration of an androgenic influence on sexual behavior during the menstrual cycle requires exclusion of concurrent estrogenic action to the extent that is possible in the intact woman. Several well-controlled correlational studies have failed to find evidence of an estrogenic enhancement of sexual behavior during the cycle but provide probable evidence for an androgenic effect. No relationship between E_2 levels and

sexual arousal, sexual fantasies, masturbation, sexual gratification, initiation of sexual activity, or frequency of coitus was found in young healthy women tested 3 times a week for 3 consecutive menstrual cycles (Abplanalp, Rose, Donnelly, & Livingston-Vaughan, 1979). Similarly, no relationships were found between levels of E_2 and sexual arousal, coital frequency, or sexual gratification in young married women tested twice weekly for 2 months (Persky et al., 1978). However, when this group of women was dichotomized on the basis of their plasma T profiles across their menstrual cycles, it was found that those with high-normal T profiles experienced more sexual gratification than those with the low-normal profiles (Persky et al., 1978). Correlations between mean plasma levels of T and mean behavior scores for each cycle found a negative association between plasma T and sexual avoidance and a positive association between T and sexual gratification (Persky et al., 1982). No relationship was found either between E_2 or T and orgasmic frequency.

Concurrent assessment of hormonal, behavioral, and psychophysiological changes across the menstrual cycle in regularly cycling women provided some support for these findings (Schreiner-Engel, Schiavi, Smith, & White, 1981). Whereas subjective reports of arousal did not differ between menstrual cycle phases, physiological arousal, as measured by vaginal photoplethysmography, was higher during the follicular and luteal phases than in the ovulatory phase. When three subgroups of women were formed on the basis of the relative average T concentration, the high T group exhibited higher subjective and

physiological capacities for sexual arousal compared to the medium and low T groups during the luteal phase of the cycle.

In an investigation of 55 women with normal ovulatory cycles, Bancroft, Sanders, Davidson, and Warner (1983) also failed to find an increase in any aspect of sexuality associated with the ovulatory phase of the cycle. In fact, a peak in sexual feelings, sexual activity with a partner, and orgasm frequency occurred in the midfollicular phase. No associations between E_2 and sexual behavior were apparent, but midcycle levels of T correlated positively with masturbation frequencies across the cycle.

Recently, it has been demonstrated that while average levels of plasma T throughout a menstrual cycle did not predict differences in frequency of coitus in married couples, midcycle peak values of both total T and free T did (Morris, Udry, Khan-Dawood, & Dawood, 1987). There was a positive correlation between the woman's midcycle free T level and the mean proportion of days on which she initiated sexual activity. Unfortunately, levels of E_2 were not measured in this study.

Information on the association between T and sexual behavior during other reproductive events generally tends to support findings from the menstrual cycle studies. In one study, women who were breastfeeding had both lower levels of T and lower ratings of sexual desire during the postpartum period. This association did not occur in the mothers feeding their infants by bottle (Alder, Cook, Davidson, West, & Bancroft, 1986). In another it was found that in normal untreated, postmenopausal women, sexual desire and interest were positively associated with levels of plasma T but not with E_1 or E_2 (Leiblum, Bachmann, Kemmann, Colburn, & Schwartzman, 1983).

The menstrual cycle studies allow only tentative conclusions to be drawn about influences of androgens on sexual behavior, because, as it has been already pointed out, the only evidence against an estrogenic effect that can possibly be demonstrated in cycling women is the absence of positive correlations between circulating levels of estrogens and sexual behaviors. However, the fact that there were no positive associations between E_2 and any aspect of sexual functioning in these studies, while there were positive relationships between T and the various measures of sexual interest and desire, is intriguing. On the other hand, these studies also fail to provide evidence of a peak in any aspect of sexual behavior at the time of the peak in plasma levels of T, which occurs at midcycle. Yet although this might appear to argue against the purported androgen-sexuality relationship, there is no reason to believe that an increase in the level of a hormone causes an immediate behavioral response. The latency between androgen administration and increases in sexual desire and fantasy in hypogonadal men ranges from several days to a week, and with the use of a long-acting injectible preparation, maximal behavior changes are manifested in about 2 weeks (Skakkeback et al., 1981). As it has already been suggested, it is very possible that the perimenstrual increase in sexual desire and coital fre-

quency is, in fact, due to the midcycle T peak (Bancroft, 1987). What does seem clear from these menstrual cycle studies is that in normally cycling women, the mean frequency of sexual desire, sexual interest, and autoerotic behaviors throughout the cycle are associated with the magnitude of the midcycle T peak and/or the average level of T throughout the cycle. In no study was there found to be an effect of T on orgasmic frequency, and in only one, an association between the midcycle peak of T and coital frequency (Morris et al., 1987). In summary, if one considers the limitations of the quality of the evidence they are able to provide, the menstrual studies show a positive relationship between midcycle levels of T and sexual motivation across the cycle in young women.

The paradigm that is perhaps most powerful for the study of the specificity of androgenic steroids on female sexuality involves administering hormone replacement therapy to women who have undergone total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). When both ovaries are removed from premenopausal women, circulating T levels decrease significantly within the first 24–48 h postoperatively (Vermeulen, 1976). It is common clinical practice to treat these patients with estrogen replacement therapy for the immediate control of vasomotor symptoms and for the long-term prevention of osteoporosis (Richelson, Wahner, Metton, & Riggs, 1984) and coronary heart disease (Wahl et al., 1983). The fact that women are deprived of ovarian androgen production following this surgical procedure has provided a rationale for administering both-sex steroids as replacement therapy. These studies have shown that the addition of androgen to an estrogen replacement regimen induces a greater sense of energy level and well-being and is associated with fewer somatic and psychological symptoms, compared with the administration of estrogen alone (see Sherwin, 1985; Sherwin & Gelfand, 1984, 1985). Furthermore, the intramuscular administration of T, either alone or in combination with E_2 , increased motivational aspects of sexual behavior (such as desire and fantasies) compared with the administration of E_2 alone or a placebo (Sherwin, Gelfand, & Brender, 1985). Levels of sexual motivation covaried with plasma T levels throughout a treatment month as the intramuscular drug was being metabolized (Sherwin, 1985). The androgenic enhancement of sexual motivation in women treated with the combined drug has been shown to persist with long-term, chronic administration of monthly injections that cause an initial surge in T levels and metabolize slowly over a period of several weeks (Sherwin & Gelfand, 1987). Taken together, the findings from these studies have allowed several conclusions. First, E_2 given alone to surgically menopausal women was associated with a decrease in sexual motivational behaviors, relative to both their own preoperative behaviors and those of T-treated women. Second, whereas exogenous T enhanced sexual motivation, it had no effect on the frequency of either coitus or orgasmic response. This specificity of androgenic action on what can be considered motivational or procep-

tive aspects of human female sexual behavior appears to be similar to its reported specificity in female rhesus monkeys (Michael et al., 1972) and hypogonadal men (Bancroft & Wu, 1983; Gooren, 1987).

Findings from two studies have suggested that E_2 alone can enhance sexual functioning in postmenopausal women. Dennerstein, Burrows, Wood, and Hyman (1980) reported that women who had undergone TAH and BSO 6 months to 27 years earlier experienced increased sexual enjoyment and desire when they were being treated with E_2 and E_2 + progestin compared with when they were being treated with progestin alone, or a placebo. Each woman received each treatment for 3 months. However, the considerable variability in time since surgery, the failure to counterbalance treatments, the increase in vaginal lubrication only in E_2 -treated women, and the 47% incidence of previous psychiatric disorders in this sample make interpretation of these results difficult. Improvement in sexual interest, satisfaction, and orgasmic frequency in postmenopausal women following treatment with subcutaneous implants of pellets containing either E_2 alone or E_2 and T was reported by Dow, Hart, & Forrest (1983). Interpretation of this study is confounded by the fact that 6 of the 40 subjects had experienced a natural menopause 2 years earlier and were also given a progestin for 7 days of each treatment month in addition to the E_2 or E_2 + T. Because hormone levels were not assayed, it is not known whether the naturally menopausal subjects were among the approximately 50% of women whose ovaries continue to produce androgens for several years beyond the menopause (Longcope, Hunter, & Franz, 1980). Furthermore, these subjects were preselected to ensure that loss of libido was a major complaint; however, no information is provided on the duration or the clinical features of the symptom. Currently, there is no evidence that exogenous T enhances sexual motivation in women whose T levels are within the normal range. In general, therefore, sexually dysfunctional women with normal ovarian function are not a suitable population for testing the androgen-sexuality relationship. With postmenopausal subjects, it would be important to determine whether the loss of sexual desire predated or followed the associated endocrine changes.

In summary, the evidence from T replacement studies in hypogonadal men and oophorectomized women, as well as the results from the menstrual cycle studies, permits the conclusion that T has a major impact on the cognitive, motivational, or proceptive aspects of sexual behavior in both men and women. Although much of the available evidence fails to support a critical role for E_2 in female sexual motivation, the issue remains somewhat controversial.

Critical Thresholds for Androgenic Effects on Behavior

Nonhuman primates. Although it has been shown that T enhances proceptivity in female rhesus monkeys, the dose of T needed to elicit this effect is critical. In all the

studies cited above, the replacement dose given to ovariectomized rhesus monkeys was 0.5–1 mg testosterone propionate (TP). This dose induced plasma T levels of 6–25 ng/ml, which were in the normal male rhesus monkey's range, and which, in most cases, far exceeded the normal female range (0.1–0.8 ng/ml). When 2.5–30.0- μ g doses of TP were administered to ovariectomized females, leading to circulating T levels within the physiological female range, proceptive behavior, as measured in an operant paradigm, was no greater than that elicited by E_2 and P (Michael, Richter, Cain, Zumpe, & Bonsall, 1978). Furthermore, significant positive correlations between circulating T levels and proceptive behavior during various phases of the menstrual cycle have not been found in intact animals (Wallen, Winston, Gaventa, Davis-Da-Silva, & Collins, 1984). At the present time, then, the available evidence suggests that whereas physiological levels of T are without effect on female rhesus monkeys' sexual behaviors, an increase in proceptivity can be induced under conditions of supraphysiological doses.

Human females. Although to date it has not been tested directly, findings from our own studies of hormone replacement therapy in surgically menopausal women support the conclusion from the studies on female rhesus monkeys that only supraphysiological doses of T are associated with increased sexual interest. In all our studies thus far, we have administered 1 ml of an estrogen-androgen (E-A) preparation every 4 weeks as the recommended dose for treatment of menopausal symptoms. One milliliter of this drug contains 150 mg T enanthate, 7.5 mg E_2 diethanthate, and 1 mg E_2 benzoate. We have consistently found that the 1-ml dose induces plasma T levels in surgically menopausal women between 120–250 ng/dl during the first 3 postinjection weeks, which far exceeds the normal female range (20–120 ng/dl). Recently, we have begun working with half the previously used dose, and we are finding circulating levels of T within the normal female range (Sherwin, 1988). Whether this physiological dose of T will have the same effect of enhancing sexual motivation in postmenopausal women as the pharmacological dose has awaits results of an ongoing investigation.

Although the dose of T that we have been using has not allowed us to determine the lower threshold for behavioral effectiveness, the limits of the upper threshold have been investigated. Considerable intersubject variability both in plasma T levels and in aspects of sexual behavior in oophorectomized women in response to a standard dose of the combined E-A preparation has been observed in our studies. These individual differences are manifest even when differences in weight and height are held constant (Sherwin & Gelfand, 1987). We hypothesize, therefore, that certain features of steroid dynamics might provide an explanation for the observed dose-response individual differences.

It is known that both E_2 and T bind to sex-hormone-binding globulin (SHBG) in plasma; only the free, unbound portion is thought to have potential for biological

activity (Anderson, 1974). Furthermore, the concentrations of the sex steroids themselves have a profound effect on SHBG production; estrogens increase the amount of this protein and androgens reduce it (Vermeulen, Verdonck, Van der Straeten, & Orie, 1969). In healthy people of average weight/height, it has been estimated that 60% of T is bound to SHBG and approximately 40% is bound to plasma albumin (Pardrige, 1981). SHBG-bound T cannot influence target tissues, but a considerable proportion of albumin-bound fractions can exert biological activity. In the subject population we have studied, the drastic alteration in the sex-steroid milieu following bilateral oophorectomy most probably affected SHBG production. It was not possible to know, then, how SHBG levels would be further affected by administering a combined E-A drug to these women. Measurement of SHBG as well as total T allows one to calculate the free testosterone index (FTI), which provides more complete information on T bioavailability ($FTI = \text{total T} / \text{SHBG} \times 100$).

In a recent study, the FTI was computed for 30 women who had undergone TAH and BSO at least 2 years earlier, and who had been chronically maintained on a monthly injection of the E-A preparation for 2 years prior to their recruitment. Blood samples were obtained 56 days after their last injection (baseline). The women then received an injection of the E-A drug and blood was again sampled on Days 2, 3, 8, 15, 21 and 28 postinjection. Several aspects of their sexual behavior were monitored daily for the 84-day duration of the study (Sherwin, 1988). T levels peaked on Day 4 postinjection and then remained fairly stable at levels that exceeded the normal female range for up to 28 days. Mean SHBG levels of these 30 women treated with both E_2 and T were within the normal female range (30–90 nmol/l), but the variability was considerable. When subjects were divided into 3 statistically distinct groups on the basis of their total T levels, two-way ANOVAs failed to reveal an interaction effect between the groups and any of the sexual behaviors. Then, three statistically distinct groups representing low FTI ($n=9$), medium FTI ($n=11$) and high FTI ($n=10$) were formed. Two-way ANOVAs on FTI group and sexual behavior scores showed that the sexual motivational behavior scores (desire, arousal, and fantasies) of the low FTI group were lower than those of both the medium and the high FTI groups at Weeks 1 and 2 postinjection, but that there were no differences between sexual behavior scores for the medium and the high FTI groups. This suggested that, above a certain threshold (FTI of 8 in this study), an increase in free plasma T is behaviorally irrelevant. This notion of a “ceiling effect” of plasma T with respect to female sexual behavior accords with the findings of Salmimies et al. (1982) and of Gooren (1987), who both documented an upper threshold of plasma T for sexual behavior in hypogonadal men who received T replacement therapy (see below).

Human males. Of the studies listed in Table 1, those in which more than one dose of T was administered in a repeated-measures design demonstrated a dose-response

relationship between sexual desire and fantasies and plasma T levels in hypogonadal men. It is also apparent that the doses administered induced plasma T levels that were well within the male physiological range (300–1,200 ng/dl). When one considers the breadth of this normal range and the difficulty of maintaining stability in circulating T levels in the face of powerful negative feedback effects, it becomes difficult to determine the lower threshold of plasma T necessary for the maintenance of the full range of sexual behaviors in hypogonadal men. Two recent studies have provided valuable information. Salmimies et al. (1982) treated 15 hypogonadal men with intramuscular injections of 25, 50, 100, and 250 mg T. Each dose was given for 4 weeks, and a range of sexual behaviors was monitored by means of daily diaries. The lower T threshold for sexual desire and arousal in men varied from 173–346 ng/dl. Similarly, Gooren (1987) found that a blood level of T between 144–317 ng/dl was needed to maintain sexual desire and interest in a group of 26 hypogonadal men. Furthermore, higher levels of plasma T were not associated with further increases in the frequency or intensity of these T-dependent behaviors. The idea that there is an upper threshold for behavioral effects of T was first proposed by Beach & Holz-Tucker in 1949. These investigators found that the administration of graded doses of T to castrated male rats led to increments in copulatory behavior up to a point, after which further increases were without additional effect. The recent studies on the effects of T in hypogonadal men make it appear that the same is true for human males.

Androgen Sensitivity

It is widely acknowledged that sexual behavior in humans is multidetermined. Although no attempt will be made to deal with these issues here, it should be pointed out that intrapsychic, social, and cultural factors can profoundly influence sexuality. The evidence presented in this paper serves primarily to underline the contribution of one biological factor as a powerful determinant of sexual behavior. The response of hypogonadal men to T replacement therapy is testimony to the critical role of T for sexual motivation in men. When we consider the human female, we have no directly comparable paradigm of hypoandrogenicity, except perhaps, the perimenopausal years when ovarian function is waning. Deficits in sexual motivation do occur, however, following bilateral oophorectomy in women, and they are reversed when exogenous T, albeit in supraphysiological doses, is administered. The menstrual cycle data show that women who have higher peak levels of T at midcycle also report higher frequencies of sexual interest, autoerotic behavior, and sometimes coitus, throughout the cycle. Clearly, more work needs to be done on the role of T in female sexuality, but the consistency in the available data pointing to its enhancing effects is compelling.

If physiological levels of T enhance sexual motivation in healthy, gonadally-intact men and women, then it is clear that vastly different hormonal requirements exist be-

tween the sexes. The normal range of T concentrations in male plasma is 300–1,200 ng/dl; that in the normal female is 20–120 ng/dl. Thus, endogenous levels of T in females are normally 6 to 10% of endogenous male levels. If female sexual motivation is enhanced by one tenth the amount of T present in the male, and considering also that males are behaviorally impaired under conditions of these same levels (Salmimies et al., 1982; Gooren, 1987), then the possibility exists that females are more sensitive to the behavioral effects of T. This might be considered paradoxical, in that prenatal exposure to T is found to sensitize animals to later effects of T (see, e.g., Pomerantz, Roy, & Goy, 1988). If this were also true for humans, it might be predicted that males would be more sensitive to the effects of T according to measures of sexual motivation. The question becomes how to account for the fact that a given quantity of T seemingly enhances sexual motivation in women but is insufficient to maintain it in men. One explanation might be found in the idea that significant changes in hormone levels are often accompanied by behavioral changes, but that differences in absolute levels seem frequently to make little difference. This suggests that the cyclic pattern of female sex-steroid secretion—that is, the pattern of secretion that causes peaks and troughs in circulating hormone levels over time—may be an important factor in the enhancement of female sexual behavior.

The situation in which the cyclicity of sex-steroid release in women is abolished provides interesting information with regard to this hypothesis. Women with premenstrual syndrome (PMS) experience physical and psychological symptoms in the late luteal phase of the cycle at the time of the nadir in concentrations of E_2 , T, and P. A luteinizing hormone-releasing hormone (LHRH) agonist can inhibit both gonadotropin release and gonadal steroid biosynthesis in a dose-related fashion when it is administered long-term. It is precisely this ability of LHRH agonists to inhibit ovulation that has provided the rationale for its use in the treatment of women with PMS. When an LHRH agonist was administered long-term in modest doses by nasal spray to 10 women experiencing PMS, ovulation was blocked in all women despite the fact that, overall, estrogen levels remained within the range of follicular phase values during treatment. There was a general leveling out of mood, with an overall improvement, and the pretreatment cyclicity in mood changes was no longer apparent (Bancroft, Boyle, Warner, & Fraser, 1987). These findings confirmed the results of Muse, Cetel, Futterman, and Yen (1984), who administered an LHRH agonist to women with PMS and found a marked attenuation of the pretreatment physical and psychological symptoms. The administration of low-dose danazol, which inhibits enzymes involved in ovarian steroidogenesis, also reduced PMS symptoms when given in the luteal phase of the cycle, while E_2 levels remained within the normal range (Sarno, Miller, & Lundblad, 1987). These findings suggest that when cyclicity is abolished and sex steroid levels

are maintained within the physiological range, physical symptoms and behavior also stabilize.

Other evidence of the dampening effect of ovulatory inhibition on behavior comes from a study comparing women who were taking oral contraceptives with women who were not. Adams, Gold, and Burt (1978) found an ovulatory peak in female-initiated autosexual and heterosexual activity among nonpill subjects but not in pill subjects. Although plasma hormone levels were not measured in this study, since then it has been shown that oral contraceptives block the midcycle peak in both E_2 and T (Bancroft et al., 1983). Taken together, these findings on the consequences of manipulating sex-steroid secretion during the menstrual cycle suggest that suppression of hormonal cyclicity suppresses behavioral variation.

Results of hormone replacement studies in postmenopausal women provide additional evidence that change in hormone levels and not their absolute values may be important for behavior. In Britain and Australia, subcutaneous implantation of pellets containing E_2 and T has been used as a treatment for menopausal symptoms for several decades. This route of sex-steroid administration results in a slow, constant release of the sex hormones over a period of at least 6 months. Studies in which hormone levels and behavior were measured concurrently are presented in Table 2. In all of them, concentrations of plasma T exceeded the normal female range (1–3 nmol/l) when they were measured 3 months postimplantation. By Month 6 postimplantation, levels of plasma T were significantly lower than Month 3 values, but they still remained at or above the upper limit of the normal female range. An enhancement in several aspects of sexual functioning relative to pretreatment intensities was found 3 months after implantation of the E_2 + T pellets. More important with respect to the present discussion is the finding that in the two studies that measured both sexual behavior and plasma T levels at 3 and at 6 months postimplantation (Burger et al., 1984; Burger, Hailes, & Nelson, 1987), levels of sexual functioning decreased to pretreatment values by 6 months. This occurred even though circulating plasma T levels were still above the upper limit of the normal female range by 6 months, although they had decreased significantly relative to Month 3 values. It is interesting to note that the frequency of night sweats, an E_2 -dependent symptom, increased to pretreatment levels by Month 6 at a time when E_2 concentrations were still in the midfollicular range (Burger et al., 1984). Similar findings come from investigations with the intramuscular preparation of E_2 + T. By Week 4 postinjection, women who received the combined drug reported significantly lower scores on sexual desire, fantasy, and arousal compared with scores at Weeks 1 and 2 postinjection, in spite of the fact that plasma levels of T still exceeded the upper limit of the female range at the time (Sherwin, 1985). These findings suggest that the change in sex-steroid concentrations may be an important factor in precipitating changes in both physical symp-

Table 2
Hormone Levels and Sexual Response to Combined Subcutaneous Implants of Estradiol (E₂) and Testosterone (T) in Postmenopausal Women

Study	N	Dose	3 Months Postimplantation			6 Months Postimplantation		
			Symptom Change from Pretreatment	E ₂ (pmol/l)	T (nmol/l)	Symptom Change from Pretreatment	E ₂ (pmol/l)	T (nmol/l)
Burger, Hailes Menelaus, Nelson, Hudson, & Balazs, 1984	17	E ₂ 40 mg T 100 mg	↑libido ↑enjoyment of sex ↑climax ↑initiation of sex	450	4.2	libido—n.s. enjoyment of sex—n.s. climax—n.s. initiation of sex—n.s.	493	3.9
Cardozo, Gibb, Tuck, Thom, Studd, & Cooper, 1984	120	E ₂ 50 mg T 100 g	↑libido	not provided	not provided	libido—n.s.	854	2.7
Burger, Hailes, & Nelson, 1987	20	E ₂ 40 mg T 50 mg	↑libido ↑enjoyment of sex	?	3.5	libido—ns enjoyment of sex—ns	?	?

toms and behavior, and that absolute levels of hormone may be relatively unimportant.

Two studies have reported on long-term effects of E₂ + T replacement in postmenopausal women who took doses that induced plasma levels of T within the male range for over 2 years. Brincat et al. (1984) reported that symptoms (including "loss of libido") recurred 6 months following implantation of a pellet containing E₂ 50 mg + T 100 mg in women who had had pellets implanted every 6 to 8 months for nearly 3 years. According to Thom, Collins, & Studd (1981), these pellets resulted in T levels that peaked at 5 nmol/l after 1 month and decreased to values that were still at or above the upper limit of the normal female range at 6 months postimplantation. Thus, in the face of chronically elevated T levels, decrements in behavior were apparent when concentrations of this hormone were still supraphysiological, but had decreased relative to their previous levels. The same observation has been reported when E₂ + T was administered intramuscularly long-term (once a month for at least 2 years) to surgically menopausal women (Sherwin & Gelfand, 1987). These findings argue against an explanation of the observed sex difference in response to T in terms of absolute differences in sensitivity of neural structures to T. If the sheer quantity of the hormone was the critical determinant, then it would not be possible to explain the consistent and significant decreases in sexual desire and arousal at the end of the treatment phases, when plasma T levels are supraphysiological, in the hormone replacement studies just cited. When high average T concentrations are induced in women long-term, they appear not to be able to maintain effectiveness when they decrease modestly.

No evidence is available to address the possible importance of cyclicity versus absolute levels of T on sexual behavior in men. Although it has been shown that patterns of sexual behavior do not change in accordance with seasonal shifts in T secretion in males (Reinberg & Lagoguey, 1978), this may only mean that, in humans, other factors (i.e., work activities, availability of a partner, etc.) are more important in determining when sexual activity may take place than are subtle changes in hor-

mone levels. These same social factors likely constrain the evidence regarding the effect on behavior of the circadian rhythm of T release in the male. Of possible relevance, however, is the finding that the administration of T to eugonadal men with low sexual interest did increase their sexual interest (O'Carroll & Bancroft, 1984). This occurred even though the mean pretreatment levels of plasma T in these sexually dysfunctional men was 660 ng/dl, which far exceeds the lower limit of the T levels shown to be necessary for the maintenance of sexual interest in hypogonadal men (Gooren, 1987). It is tempting to speculate that intramuscularly administered T enhanced sexual desire in these eugonadal men by creating peaks and troughs in their circulating T levels.

Although the evidence presented here argues for the role of cyclicity in the enhancement of female sexual behavior, it is not meant to imply that the absence of cyclicity in women would result in the abolishment of behavior. Rather, this argument holds that the instatement of a tonic pattern of T secretion such as occurs with oral contraceptive or LHRH agonist use, or, naturally, in perimenopausal women, would result in decrements in behavior relative to their frequencies under the condition of cyclic release. It is also acknowledged that because the ovary produces a multitude of sex steroids whose quantities are influenced by endocrine feedback mechanisms, a direct test of this hypothesis would present a formidable challenge.

Finally, it must be acknowledged that there is an alternate and more common explanation for some of the psychoendocrine data presented in this discussion. It is possible that the frequency of sexual desire decreases in many women in the late luteal phase of the menstrual cycle, during the postpartum period, and at postmenopause, because concentrations of T at those times are simply too low to maintain them. In view of the fact that the lower threshold of hormone values for the maintenance of female sexual behaviors has not yet been established, this remains a viable hypothesis. However, it is also possible that the presence of some minimal concentration of a hormone and its cyclic pattern of release together constitute the optimal conditions for the manifestation and enhancement of certain behaviors.

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