

SEX STEROIDS AND AFFECT IN THE SURGICAL MENOPAUSE: A DOUBLE-BLIND, CROSS-OVER STUDY

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SUMMARY

The effect of estrogen and/or androgen on mood in surgically menopausal women was investigated with a prospective, double-blind, cross-over design. Oophorectomized women who received either estrogen (E), androgen (A), or a combined estrogen–androgen preparation (E–A) parenterally attained lower depression scores during both treatment phases compared to a placebo group (PL), coincident with their higher plasma estrogen and testosterone levels. When steroids were withdrawn, depression scores of all oophorectomized women were significantly higher than those of a hysterectomized control group with intact ovaries (CON). The A group also had higher hostility scores than the E, PL, and CON groups. These data provide evidence of a covariation between circulating levels of estrogen and testosterone and certain affects in healthy women.

INTRODUCTION

ALTHOUGH it is a commonly held notion that estrogen has a positive effect on mood states in women, the evidence is scanty and inconsistent. Results of studies on the premenstrual syndrome do not allow discrimination between the contribution of estrogen and progesterone to the alleged increase in negative affect during the late luteal phase of the menstrual cycle, because the production of both hormones decreases at that time (Bäckström *et al.*, 1983). Elucidation of the possible hormonal etiology of depression that sometimes occurs postpartum is likewise confounded by the simultaneous decrease in both estrogen and progesterone subsequent to delivery (Nott *et al.*, 1976).

The common practice of administering hormone replacement therapy to menopausal women provides a unique opportunity to assess the effects of estrogen on mood. Unfortunately, however, the majority of these studies are methodologically flawed. Many were single-blind (George *et al.*, 1973; Furuhielm & Fedor-Freyburgh, 1976); they used psychometric instruments with unknown reliability and validity (Utian, 1972; Rauramo *et al.*, 1979); and they included heterogeneous populations of both naturally and surgically menopausal women without taking into account differences in endogenous steroid levels (Vanhulle & Demol, 1976; Meikle *et al.*, 1977). Results of investigations of estrogen and mood in which subjects were women undergoing gynecological surgery for both malignant disease and benign conditions are difficult to interpret owing to the differential psychological impact of their illnesses (Chakravarti *et al.*, 1977). Other investigators studied subjects with a history of affective illness who previously had been treated with psychotherapy and/or psychotropic medications, thereby confounding hormonal changes with premorbid personality (Strickler *et al.*, 1977; Dennerstein *et al.*, 1979). The available evidence, therefore, does not permit firm conclusions about the effect of estrogen on affect in women.

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It has been demonstrated that plasma testosterone levels (T) decrease significantly in premenopausally oophorectomized women compared to their own preoperative levels (Studd *et al.*, 1978). Furthermore, plasma T levels were significantly lower in bilaterally oophorectomized women than in similar aged women who were less than four years postmenopausal (Vermeulen, 1976). Botella Llusia *et al.* (1980) demonstrated that testosterone levels in ovarian vein blood were higher in postmenopausal than in reproductive-aged women. The clear implication, therefore, is that the postmenopausal ovary continues to secrete significant amounts of T for at least a few years, often in even greater quantities than during reproductive life. Premenopausally oophorectomized women are thus deprived of an important source of androgen production. Despite these known endocrine changes and the documented disturbances in affect following a surgical menopause (Furuhjelm & Fedor-Freyburgh, 1976; Dennerstein *et al.*, 1979; Rauramo *et al.*, 1979), the effect of androgen on mood states in the human female is virtually unknown.

In an attempt to resolve some of the theoretical and clinical issues with regard to the effects of estrogen and androgen on affect, a prospective, double-blind, cross-over study was undertaken. As part of a larger investigation, changes in several aspects of mood were measured as a function of postoperative administration of estrogen and/or androgen replacement therapy in generally healthy, surgically menopausal women. Plasma hormone levels were sampled concurrently in order to provide a physiological framework for interpretation of the behavioral data.

METHOD

Subjects

The participants in this study were premenopausal women who required a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) for reasons other than malignant disease (uterine fibroids; endometriosis). They were required to be in a stable heterosexual relationship for at least two years and to have had no past history of psychological disturbances for which treatment had been obtained. A further requirement was that they be in a state of good general health with no known contraindications to hormone replacement therapy. Informed, signed consent was obtained from 43 women who met these criteria by means of a form approved by both a hospital and a university Ethics Committee. Ten women who needed to undergo TAH but whose ovaries were to be retained were recruited to serve as an additional control group. Between September 1980 and February 1983, each patient who was booked for TAH and BSO from the practice of the Chief of the Department of Obstetrics and Gynecology of a large university teaching hospital was referred to the study. Subjects were told that they would be participating in 'an investigation of estrogen and androgen on physical and psychological functioning'. They were further informed that there was a one in four chance that they would receive a preparation 'with no active hormone' and that their medication might be changed during the course of the study. However, subjects had no way of knowing when that would occur, or indeed, if it would ever occur.

PROCEDURE

The study was a five (Groups) by four (Time Periods) repeated measures design. Preoperatively, patients were randomly assigned to either an estrogen-androgen group (E-A), to an estrogen group (E), to an androgen group (A), or to a placebo group (PL). The hysterectomy control group (CON) described previously constituted the fifth group. Thus there were two control groups in the design—one to control for the effects of an altered endocrine status consequent to BSO (PL group), and the second, to control for changes that may have been due to the surgical procedure itself (CON group).

Following one month of baseline monitoring, patients underwent surgery. Intramuscular injection of a hormonal preparation or placebo was administered monthly for the first three months (Treatment 1). At the beginning of the fourth postoperative month, all patients received an injection of placebo, following which they were then randomly crossed over to one of the four treatments they had not experienced during Treatment 1, for an additional three months (Treatment 2). The entire experimental procedure, therefore, encompassed eight months per patient.

Drug dosages

In order to ensure that patients in the hormone treatment groups would receive equal amounts of estrogen and androgen per dose, the molecular weights of the salts to which each of the estrogen and androgen preparations were bound were calculated. This sum was then subtracted from the weight of the total compound. Using 1 ml of the estrogen-androgen combined drug as the standard, equivalent doses of the sex steroids contained in the other preparations were computed. Table I contains the composition and dosages of the hormonal preparations used in this study. While it is recognized that different esters have different durations of action, there did not appear to be any way to equate these except to calculate free estradiol. It is acknowledged that this does not mean they were functionally equivalent with regard to potency. The fact that we measured plasma estrogen levels mitigates this to some extent. Furthermore, it has been shown that other sex steroid depot preparations induce maximal plasma hormone levels one to four days following injection, and that the half-life is 14 days (Dusterberg & Wendt, 1983). Postoperatively, drugs were administered intramuscularly at 28-day intervals.

Plasma hormone levels

Venous blood samples for measurement of plasma levels of total estrogens (estradiol and estrone) and testosterone were obtained between 0900 and 1100 hr at four different times during the study. The first sample was taken approximately one month preoperatively, the second and fourth were taken 72 hr following the third injection in both treatment phases, and the third was taken on the last day of the placebo month that occurred in between. The blood was immediately centrifuged and the plasma stored at -20°C . Total plasma estrogens were measured by radioimmunoassay using Endocrine Sciences antiserum No. E-17-94. The extraction of protein before the addition of antiserum ensured that free hormone was being assayed. The assay was sensitive to 12.5 pg/ml. Plasma testosterone levels were measured using the Covalent-Coat Radioimmunoassay Kit. The testosterone 125-I assay detects the total unconjugated form of this steroid. All samples from each patient were measured twice in the same assay at the conclusion of the study. The hysterectomy control group (CON) underwent the identical experimental procedure, save for the administration of monthly injections.

Materials

The Multiple Adjective Affect Checklist (MAACL) is a self-administered inventory that measures three affects—anxiety, depression and hostility (Zuckerman & Lubin, 1965). The 'Today Form', used in this study, is a sensitive, valid and reliable measure of current levels of the affect dimensions and was specifically designed for use in repeated measures studies. This measure has been used frequently in hormone-behavior studies in order to provide measures of affect as they relate to concurrent hormonal states. Each subject was tested four times during the study, immediately before venous blood collection.

TABLE I. COMPUTATION OF DRUG DOSE EQUIVALENCE

<i>Estrogen-androgen combined drug (Climacteron)</i>	
Each ml contains:	
Testosterone enanthate benzilic acid hydrozone	150.0 mg
Equivalent to testosterone	69.0 mg
Estradiol dienanthate	7.5 mg
Equivalent to estradiol	4.1 mg
Estradiol benzoate	1.0 mg
Therefore, 1 ml of Climacteron contains 4.8 mg of free estradiol	
<i>Estrogen drug (Delestrogen)</i>	
Each ml contains:	
Estradiol valerate	10.0 mg
Equivalent to estradiol	7.6 mg
Therefore, 1 ml of Climacteron and 0.63 ml of Delestrogen contain equivalent amounts of estradiol	
<i>Androgen drug (Delatestryl)</i>	
Each ml contains:	
Testosterone enanthate	200.0 mg
Equivalent to testosterone	144.0 mg
Therefore, 1 ml of Climacteron and 0.48 ml of Delatestryl contain equivalent amounts of testosterone	
<i>Placebo</i>	
Sesame oil	0.5 ml

RESULTS

Subject characteristics

There were 12 patients in the E – A group, 11 in the E group, 10 in the A group, 10 in the PL group, and 10 in the hysterectomy CON group. Pathology reports confirmed that two patients had endometriosis; one was in the E group and the other in the PL group. The rest of the sample (51 women) had surgery for benign uterine fibroids. An additional five subjects who met the selection criteria and who were initially interviewed did not continue in the study. Two of these women decided to defer surgery; one refused to comply with the experimental procedure after only one week; and a fourth was eliminated after the first postoperative month, because she withdrew her acceptance of the random assignment procedure. The fifth patient was found to have an unsuspected carcinoma of the ovary at the time of surgery and was eliminated from the study. All other subjects remained in the study through its entirety, and each provided a complete set of observations.

Subject characteristics measured at baseline (Table II) showed that patients in the hysterectomy CON group were significantly younger than those in the four treatment groups (36.3 ± 2.2 years vs 45.8 ± 3.3 years). This was an expected finding in view of the fact that age is the major criterion that guides the decision to remove or retain normal-appearing ovaries at the time of TAH undertaken for benign conditions. Subjects in all five groups were similar in occupational status (Pineo & Porter, 1967) and years of scholarship. There was, however, a wide range in these variables within groups, which increased the generalizability of the findings. Moreover, all subjects had normal personality profiles as measured by the Eysenck Personality Inventory (Eysenck & Eysenck, 1958) and satisfactory marital relationships as determined by the Marital Adjustment Scale (Locke & Wallace, 1959).

Total plasma estrogen [estrone and estradiol ($E_1 + E_2$)] and testosterone (T) levels

The hormonal and behavioral data were analyzed using the BMDP analysis of variance (ANOVA) for groups $\times$ time blocks. In addition, analysis of covariance was also carried out in order to eliminate possible effects of initial group differences in baseline scores. In both analyses, significant group $\times$ time interactions for $E_1 + E_2$ and T levels were found ($p < 0.001$). Post-hoc pairwise comparisons between means were performed using the Tukey test. Statistical significance reported in this article is based on results of the latter analyses.

TABLE II. SUBJECT CHARACTERISTICS

	Treatment groups ($N = 43$) Grand mean $\pm$ S.E.M.	Hysterectomy control group ($N = 10$) Mean $\pm$ S.E.M.	Significance
Age	45.9 ± 3.3	36.3 ± 2.2	$p < 0.01$
Years of scholarship	11.3 ± 5.8	11.2 ± 5.2	n.s.
Occupational status	45.2 ± 14.6	50.5 ± 15.6	n.s.
Eysenck Personality Inventory			
—neuroticism	11.6 ± 1.9	10.4 ± 1.4	n.s.
—extraversion	10.7 ± 1.4	10.8 ± 1.0	n.s.
Marital adjustment scale	121.3 ± 3.6	129.2 ± 2.9	n.s.

Table III contains the mean plasma levels of $E_1 + E_2$ and T at the four test times. The inter-assay coefficient of variation of $E_1 + E_2$ was 9%. At baseline the younger hysterectomy CON group had significantly higher $E_1 + E_2$ levels than the four treatment groups ($p < 0.01$), whose levels did not differ from each other. This was the only measure on which there was any significant difference between the five groups at baseline, testifying to the success of the randomization procedure. At 72 hr following injection in both treatment phases, all groups had higher $E_1 + E_2$ levels than the PL group ($p < 0.01$). Moreover, $E_1 + E_2$ levels of the E group were significantly higher during treatment than those of the A and the CON groups ($p < 0.01$), but they did not differ from those of the E-A group. At the end of the placebo month, the intact CON group had significantly higher $E_1 + E_2$ levels than the four groups of oophorectomized women, whose levels fell to the lower limit of the assay detectability, indicating that the estrogen administered during Treatment 1 had been completely metabolized. In all cases, $E_1 + E_2$ levels of subjects who received the same drug did not differ when Treatment 1 and Treatment 2 values were compared.

The inter-assay coefficient of variation of plasma T levels was 10%. During both treatment phases, the E-A group had significantly higher T levels than the E, PL, and CON groups ($p < 0.01$) but these did not differ from those of the A group. At the end of the placebo month, T levels in the steroid treated groups also fell to below those of the CON group. The T levels of the A, E and PL groups were significantly lower than both their own baseline values and the CON group values ($p < 0.05$). Once again, T levels of subjects who received the same drug did not differ when group means of the two treatment phases were compared. Furthermore, between group differences in both hormone levels during Treatment 2 were the same as those during Treatment 1.

TABLE III. MEAN PLASMA LEVELS OF TOTAL ESTROGEN ($E_1 + E_2$) AND TESTOSTERONE (T) FOR THE FOUR TEST TIMES

Group	Preoperative baseline	$E_1 + E_2$ (pg.ml) $\pm$ S.E.M.		
		Treatment 1 (72 hr postinjection)	Placebo phase (8 weeks postinjection)	Treatment 2 (72 hr postinjection)
1. E-A ($N = 12$)	67.2 $\pm$ 10.4	243.8 $\pm$ 12.4	7.8 $\pm$ 2.3	236.2 $\pm$ 14.8
2. E ($N = 11$)	49.4 $\pm$ 12.3	301.9 $\pm$ 13.1	14.2 $\pm$ 3.3	289.1 $\pm$ 15.4
3. A ($N = 10$)	42.1 $\pm$ 11.1	107.8 $\pm$ 8.4	9.5 $\pm$ 1.9	98.3 $\pm$ 9.6
4. PL ($N = 10$)	69.4 $\pm$ 8.9	11.2 $\pm$ 3.9	5.8 $\pm$ 3.7	6.2 $\pm$ 2.3
5. CON ($N = 10$)	121.7 $\pm$ 7.4	90.8 $\pm$ 9.4	78.9 $\pm$ 7.8	74.7 $\pm$ 6.6
*Significant differences at the 0.01 level	5 > 1, 2, 3, 4	2 > 3, 4, 5	5 > 1, 2, 3, 4	2 > 3, 4, 5
		T (ng/100 ml) $\pm$ S.E.M.		
		T (ng/100 ml)		T (ng/100 ml)
1. E-A ($N = 12$)	81.1 $\pm$ 5.3	133.1 $\pm$ 12.4	83.2 $\pm$ 4.9	129.2 $\pm$ 11.6
2. E ($N = 11$)	99.6 $\pm$ 4.7	89.4 $\pm$ 3.6	65.3 $\pm$ 3.8	48.4 $\pm$ 2.6
3. A ($N = 10$)	71.9 $\pm$ 10.3	111.1 $\pm$ 6.6	67.9 $\pm$ 2.5	115.3 $\pm$ 6.2
4. PL ($N = 10$)	114.1 $\pm$ 9.6	87.8 $\pm$ 1.6	66.2 $\pm$ 1.7	44.7 $\pm$ 3.2
5. CON ($N = 10$)	90.8 $\pm$ 8.6	99.8 $\pm$ 3.6	89.4 $\pm$ 4.7	88.8 $\pm$ 4.6
*Significant differences at the 0.01 level	N.S.	1 > 2, 4, 5	5 > 2, 3, 4	1 > 2, 4, 5

*Between-group *post hoc* Tukey tests.

Depression

Normative data on the depression scale of the MAACL indicate that the mean score $\pm$ the S.D. for job applicants is 11.1 ± 5.4 and for college students is 13.6 ± 6.9 , whereas normative scores for psychiatric populations range from 16.1 ± 7.4 to 20.8 ± 9.2 . As seen in Figure 1, in all phases of this study, mean group scores fell within the normal range. The ANOVA on depression scores demonstrated a significant group $\times$ time interaction ($p < 0.001$). *Post-hoc* Tukey tests showed that the PL group scores were significantly higher than those of the E-A ($p < 0.05$), A ($p < 0.01$), E ($p < 0.05$), and CON ($p < 0.05$) groups during both treatment phases. At the end of the intervening placebo month, the intact CON group had significantly lower depression scores than the oophorectomized women in the E-A, E, and PL groups ($p < 0.01$), coincident with their higher $E_1 + E_2$ and T levels at that time. Within-group analyses showed that the three steroid treated groups had significantly lower depression scores during both treatment phases compared to both their baseline and their placebo-phase scores ($p < 0.01$). On the other hand, depression scores of the PL group increased consistently and significantly across time compared to their baseline values ($p < 0.01$), in association with the significant decrease in their sex steroid levels postoperatively.

Hostility

Mean hostility score norms $\pm$ S.D. are 6.7 ± 3.3 for job applicants, 7.2 ± 3.8 for college students, and 10.8 ± 4.2 for psychiatric patients (Zuckerman & Lubin, 1965). Figure 2 shows that, during Treatment 2, hostility scores of the A group were significantly higher than those of the E, PL, and CON groups ($p < 0.01$), and A group baseline scores ($p < 0.05$), coincident with their significantly higher T values in each of these comparisons. Moreover, during the second treatment phase, neither hostility scores nor T levels differed significantly in the two groups that received androgen (E-A and A).

Anxiety

There were no differences in anxiety scores among any of the groups across time.

DISCUSSION

Results of this study provide evidence of a covariation between mood and circulating levels of estrogen and T. A preliminary caveat relates to the fairly modest dosage of hormones administered and the nonclinical nature of the population studied; the physiological plasma hormone levels induced and the absence of objective criteria related to the mood changes measured preclude generalization of these findings to clinical populations. These data nevertheless provide interesting information with regard to the effects of sex steroids on affect.

Subsequent to surgery, it was clear that all hormone treated groups and the intact CON group had lower depression scores than the PL group concomitant with their higher circulating levels of both $E_1 + E_2$ and T. Furthermore, when sex steroids were withdrawn during the placebo month, depression scores in the hormone-treated groups increased significantly compared to their scores during both treatment phases. These findings, however, do not allow discrimination of individual effects of the sex steroids on depression scores. Nevertheless, an attempt will be made to examine separately evidence relating to each of the sex steroids and depression.

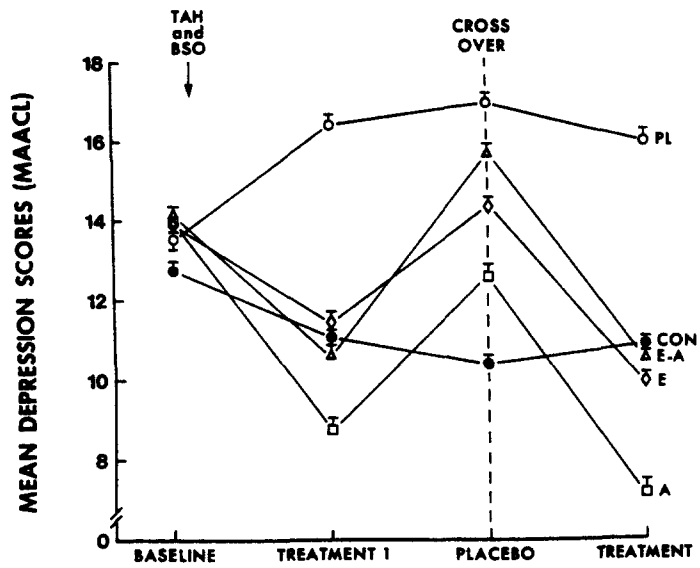


FIG. 1. Mean depression scores $\pm$ S.E.M. The treatment groups are: E-A(Δ), E($\diamond$), A($\square$), PL($\circ$) and hysterectomy CON ($\bullet$).

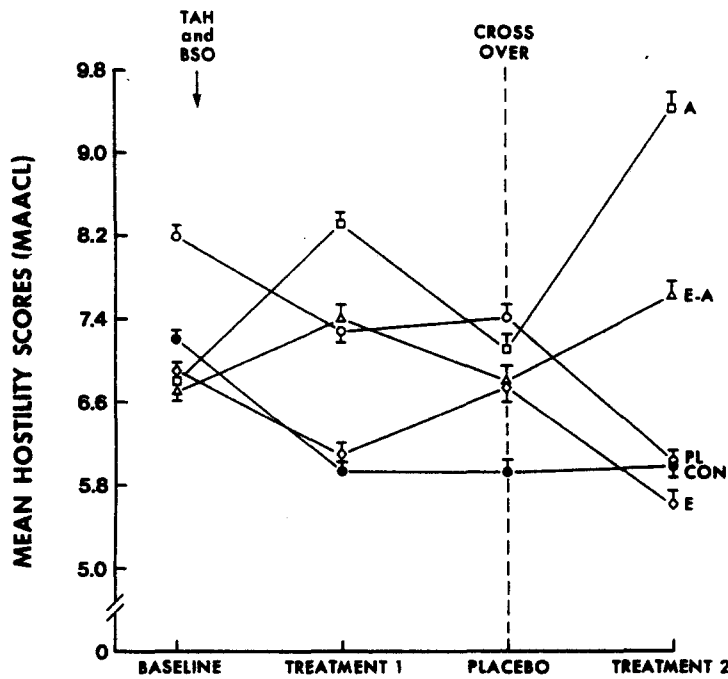


FIG. 2. Mean hostility scores $\pm$ S.E.M. The treatment groups are as in Figure 1.

There is increasing evidence of abnormal indoleamine metabolism in depressed patients, manifested by a reduced level of 5-hydroxytryptamine (5-HT) and 5-hydroxyindole-acetic acid (5-HIAA) in the brain and decreased levels of 5-HIAA in the cerebrospinal fluid (Murphy *et al.*, 1978; Coopen & Wood, 1982). In accordance with Schildkraut's (1965) biogenic amine hypothesis of depression, a decrease in serotonin levels centrally may precipitate depression. Effects of estrogen on neurotransmitter amine levels are twofold. Firstly tryptophan, the precursor of serotonin, is displaced from its binding sites to plasma albumin by estrogens both *in vitro* and *in vivo* (Aylward, 1973), thereby allowing more free tryptophan to be available to the brain, where it is metabolized to serotonin. Aylward (1976) found a significant negative correlation between depression scores and free plasma tryptophan levels and an amelioration in depression scores subsequent to estrogen administration in women who had undergone TAH and BSO. Secondly, it has been demonstrated in the rat that exogenous estrogen decreases monoamine oxidase (MAO) activity in the amygdala and hypothalamus (Luine *et al.*, 1975). Since MAO is the enzyme that catabolizes serotonin, the net effect of estrogen administration would be to maintain higher brain serotonin levels. It is possible that the beneficial effect of estrogen on depression scores found in this study may have resulted from either of these two biochemical changes, although changes in levels of other neurotransmitters and their potential interactions certainly cannot be discounted.

The mechanism of action of androgen on depression scores is less clear. Luine *et al.* (1975) found that testosterone propionate did not cause statistically significant decreases in MAO activity in the hypothalamus, amygdala, and preoptic area in ovariectomized female rats, whereas the same dosage significantly reduced medial + preoptic MAO activity in gonadectomized males. The sex difference in behavioral and neuroendocrine responses to gonadal hormones (Lisk, 1967; McCann *et al.*, 1968) invalidates the extrapolation to females of results from clinical studies on human males that have demonstrated a beneficial effect of exogenous testosterone on depression (Itil, 1976; Klaiber *et al.*, 1976). Several other phenomena, however, may help explain our findings. Androgenic effects may have been reflected in depression scores secondary to their general anabolic (Johnson & O'Shea, 1969) and energizing properties (Rose, 1972). Another possibility is that T may have exerted its effects via aromatization to estrogen in central tissues (Naftolin & Ryan, 1975). The observation that $E_1 + E_2$ levels in the A group were not different from CON group levels during both treatment phases lends support to this hypothesis. That the lower mean depression scores in the A group were not due to alleviation of somatic symptoms was attested to by the observation that exogenous androgen alone was ineffective in relieving hot flushes in these women (Sherwin & Gelfand, 1984). In addition, no side effects of any of the hormonal preparations were either reported or observed; specifically, there were no virilizing effects of exogenous androgen manifested in any of the women during either of the three-month treatment phases.

The finding of an association between heightened hostility scores and T levels in the A group during the second treatment phase does not find support in the menstrual cycle literature. An increase in acts of aggression has been reported in female psychiatric patients (Gregory, 1957) and in prison inmates (Morton *et al.*, 1953) during the premenstrual and menstrual days of the cycle. Plasma T levels peak at mid-cycle and

reach a nadir in the several days preceding menstruation (Bancroft *et al.*, 1983). However there is relatively little variability in plasma T levels throughout the cycle and, not surprisingly, increases in aggression and hostility reported premenstrually have not been found to be positively correlated with T levels, but rather are thought to be related to a decline in estrogen and progesterone at this time (Bäckström & Mattsson, 1975). Also, evidence from studies that have investigated the hypothesized link between circulating T levels and aggression in human males is weak and inconsistent. With the exception of one study (Persky *et al.*, 1971), attempts to relate T levels to pencil-and-paper measures of aggression or hostility have failed to confirm significant hormone – behavior relationships (Kreuz & Rose, 1972; Meyer-Bahlburg *et al.*, 1974; Rada *et al.*, 1976). Although T levels and aggression have been found to correlate in some male prison populations (Kreuz & Rose, 1972; Ehrenkrantz *et al.*, 1974), there remains the possibility that high T levels may be a consequence of aggressiveness rather than its cause.

In contrast to other investigations of T and hostility in which endogenous T levels and behavior were measured concurrently, it is important to consider that, in the present study, fairly drastic hormonal changes were induced in these premenopausal women subsequent to BSO. For several reasons it would seem that this paradigm is not physiologically analogous to those in which the association between endogenous hormone levels and mood have been investigated. Both estrogen and androgen bind to sex hormone-binding globulin (SHBG) in plasma (Mercier-Bodard, 1970). Only the free, unbound portion of circulating T is available to act on target tissues and thus is biologically meaningful. Furthermore, estrogen increases SHBG levels, while androgen reduces them (Anderson, 1974). On the basis of available evidence, it is possible to infer that, in the present study, the administration of androgen alone in the presence of very low levels of endogenous estrogen decreased SHBG levels in these oophorectomized women, which in turn induced an increase in the ratio of free testosterone to free estrogen (Enriori & Reforzo-Membrives, 1984). Then, the percentage of free T would have been greater in the A group relative to the other four groups, as well as to subjects in other studies in which endogenous T levels were measured (Burke & Anderson, 1972; Plymate *et al.*, 1983). Therefore, it is a strong possibility that the significantly higher hostility scores in the group that received androgen alone compared to the scores of the E, PL and CON groups were due not only to their significantly higher levels of total testosterone during the second treatment phase but, more importantly, also to their higher circulating levels of free testosterone. This hypothesis merits testing by replication of this study, including the measurement of SHBG.

The clinical implications of our findings on sex steroids and affect relate to the significant incidence of affective disturbances that follow TAH and BSO. In support of this evidence is our finding that depression scores increased in the PL group post-operatively and remained stable at high levels for the duration of the study. These women were not clinically depressed in the sense that they were experiencing depressive concomitants such as disturbances in sleep and appetite or excessive fatigue and apathy. However, in many cases, the women receiving placebo spontaneously reported feeling 'blue' or 'low'. Our findings suggest that premenopausal women who need to undergo TAH and BSO may be excellent candidates for a combined hormone therapy regimen in an attempt to mitigate symptoms that may be a consequence of their sudden and

drastically altered endocrine status postoperatively. Investigations of the long-term effects of sex steroids on affect in surgically menopausal women will be important in order to confirm these results.

REFERENCES

- Anderson D C (1974) Sex hormone binding globulin. *Clin Endocrinol* 3: 69–72.
- Aylward M (1973) Plasma tryptophan levels and mental depression in postmenopausal subjects: effects of oral piperazine-oestrone sulphate. *IRCS Med Sci* 1: 30–34.
- Aylward M (1976) Estrogens, plasma tryptophan levels in perimenopausal patients. In Campbell S (Ed) *The Management of the Menopause and Post-Menopausal Years*. University Park Press, Baltimore, pp 135–147.
- Bäckström T, Baird D T, Bancroft J *et al.* (1983) Endocrinological aspects of cyclical mood changes during the menstrual cycle or the premenstrual syndrome. *J Psychosom Obstet Gynecol* 2: 8–20.
- Bäckström T, Mattsson B (1975) Correlations of symptoms in premenstrual tension to oestrogen and progesterone concentrations in blood plasma. *Neuropsychobiology* 1: 80–86.
- Bancroft J, Sanders D, Davison D *et al.* (1983) Mood, sexuality, hormones, and the menstrual cycle. III. sexuality and the role of androgens. *Psychosom Med* 45: 509–516.
- Botella Llusà J, Oriol Boosch A, Sanchez Garrido F *et al.* (1980) Testosterone and 17β -oestradiol secretion of the human ovary. II normal postmenopausal women, postmenopausal women with endometrial hyperplasia, and postmenopausal women with adenocarcinoma of the endometrium. *Maturitas* 2: 7–13.
- Burke C W, Anderson D C (1972) Sex-hormone-binding globulin as an oestrogen amplifier. *Nature* 240: 38–40.
- Chakravarti S, Collins W P, Newton J R *et al.* (1977) Endocrine changes and symptomatology after oophorectomy in premenopausal women. *Br J Obstet Gynecol* 84: 769–775.
- Coopen A, Wood K (1982) 5-Hydroxytryptamine in the pathogenesis of affective disorders. In: Ho B T, Schooler J C, Usdin E (Eds) *Serotonin in Biological Psychiatry*. Raven Press, New York, pp 249–258.
- Dennerstein L, Burrows G D, Hyman G J *et al.* (1979) Hormone therapy and affect. *Maturitas* 1: 247–259.
- Dusterberg B, Wendt H (1983) Plasma levels of dehydroepiandrosterone and 17β -estradiol after intramuscular injection of Gynodian-Depot. *Horm Res* 17: 84–89.
- Ehrenkrantz J, Bliss E, Sheard M (1974) Plasma testosterone: correlation with aggressive behavior and social dominance in man. *Psychosom Med* 36: 138–142.
- Enriori C L, Reforzo-Membrives J (1984) Peripheral aromatization as a risk factor for breast and endometrial cancer in postmenopausal women: a review. *Gynecol Oncol* 17: 1–21.
- Eysenck H J, Eysenck S B G (1958) *Eysenck Personality Inventory Manual*. San Diego, California, Educational and Industrial Testing Service.
- Furuhjelm M, Fedor-Freyburgh P (1976) The influence of estrogens on the psyche in climacteric and postmenopausal women. van Keep P A, Greenblatt R B, Albert-Fenet A (Eds) *Consensus on Menopause Research*. MTP Press, Lancaster, pp 84–93.
- George G C W, Beaumont P J V, Beardwood C J (1973) Effects of exogenous estrogens on minor psychiatric symptoms in postmenopausal women. *S Afr Med J* 47: 2337–2344.
- Gregory B A (1957) The menstrual cycle and its disorders in psychiatric patients II clinical studies. *J Psychosom Res* 2: 199–224.
- Itil T M (1976) The neurophysiological models in the development of psychotropic hormones. In: Itil T M, Laudahn G, Herrmann W M (Eds) *The Psychotropic Effect of Hormones*. Spectrum Publications Inc, New York, pp 89–107.
- Johnson L C, O'Shea J P (1969) Anabolic steroids: effects on strength development. *Science* 164: 957–959.
- Klaiber E L, Broverman D M, Vogel W *et al.* (1976) The use of steroids in depression. In: Itil T M, Laudahn G, Herrmann W M (Eds) *The Psychotropic Effect of Hormones*. Spectrum Publications, New York, pp 89–107.
- Kreuz L E, Rose R M (1972) Assessment of aggressive behavior and plasma testosterone in a young criminal population. *Psychosom Med* 34: 321–332.
- Lisk R D (1967) Sexual behavior: hormonal control. In Martini L, Ganong W F (Eds) *Neuroendo-crinology*, Vol 2, Academic Press, New York, pp 197–239.
- Locke H J, Wallace K M (1959) Short marital adjustment and prediction tests. *Marr Fam Liv* 21: 251–258.
- Luine V N, Khylichevskaya R I, McEwen B (1975) Effect of gonadal steroids on activities of monoamine oxidase and choline acetylase in rat brain. *Brain Res* 86: 293–306.
- McCann S M, Dhariwal A P G, Porter J C (1968) Regulation of the adenohypophysis. *Ann Rev Physiol* 30: 589–640.
- Meikle S, Brody H, Pysh F (1977) An investigation into the psychological effects of hysterectomy. *J Nerv Ment Dis* 164: 36–41.

- Mercier-Bodard C, Alfzen A, Beaulieu E E (1970) Sex steroid binding plasma protein (SBP). *Acta Endocrinol* 64: Suppl 147, 204–221.
- Meyer-Bahlburg H, Boon D, Sharma M *et al.* (1974) Aggressiveness and testosterone measures in man. *Psychosom Med* 36: 269–274.
- Morton J H, Additon H, Additon R G *et al.* (1953) A clinical study of premenstrual tension. *Am J Obstet Gynecol* 65: 1182–1191.
- Murphy D L, Campbell I, Costa J L (1978) Current status of the indoleamine hypothesis of affective disorders. In: Lipton M A, DiMascio A, Killam K F (Eds) *Psychopharmacology: A Generation of Progress*. Raven Press, New York, pp 1235–1247.
- Naftolin F, Ryan K G (1975) The metabolism of androgen in central neuroendocrine tissues. *J Steroid Biochem* 6: 993–997.
- Nott P M, Franklin M, Armitage C *et al.* (1976) Hormonal changes and mood in the puerperium. *Br J Psychiatry* 128: 379–383.
- Persky H, Smith K, Basu G (1971) Relation of psychologic measures of aggression and hostility to testosterone production in man. *Psychosom Med* 33: 265–277.
- Pineo P C, Porter J (1967) Occupational prestige in Canada. *Can Rev Sociol* 4: 24–40.
- Plymate S R, Leonard J M, Paulsen C A *et al.* (1983) Sex hormone-binding globulin changes with androgen replacement. *J Clin Endocrinol Metab* 47: 645–648.
- Rada R, Keller R, Winslow W (1976) Plasma testosterone and aggressive behavior. *Psychosom* 17: 128–142.
- Rauramo L, Punnonen R, Kaihola H L *et al.* (1979) Serum oestrone, oestradiol and oestriol concentrations in castrated women during intramuscular oestradiol valerate and oestradiol benzoate therapy. *Maturitas* 2: 53–58.
- Rose R M (1972) The psychological effect of androgens and estrogens: a review. In: Shader R I (Ed) *Psychiatric Complications of Medical Drugs*. Raven Press, New York, pp 251–295.
- Schildkraut J J (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry* 122: 509–522.
- Sherwin B B, Gelfand M M (1984) Effects of parenteral administration of estrogen and androgen on plasma hormone levels and hot flushes in the surgical menopause. *Am J Obstet Gynecol* 148: 552–557.
- Strickler R C, Borth R, Cecutti A *et al.* (1977) The role of estrogen replacement in the climacteric. *Psychol Med* 7: 631–639.
- Studd J W W, Chakravarti S, Collins W P (1978) Plasma hormone profiles after the menopause and bilateral oophorectomy. *Postgrad Med J* 54: 25–30.
- Utian W H (1972) The true clinical features of postmenopause and oophorectomy and their response to oestrogen replacement therapy. *S Afr Med J* 46: 732–737.
- Vanhulle G, Demol R (1976) A double-blind study into the influence of estriol on a number of psychological tests in postmenopausal women. In van Keep P A, Greenblatt R B, Albert-Fernet A (Eds) *Consensus on Menopause Research*. MTP Press, London, pp 106–119.
- Vermeulen A (1976) The hormonal activity of the postmenopausal ovary. *J Clin Endocrinol Metab* 42: 247–253.
- Zuckerman M, Lubin B (1965) *Manual for the Multiple Affect Adjective Checklist*. Educational and Industrial Testing Service, San Diego, Calif.