

# TRANSACTIONS OF THE FORTIETH ANNUAL MEETING OF THE SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

## Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause

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The investigation of estrogen and/or androgen administration on physical and psychological symptoms in the surgical menopause was carried out in a prospective, double-blind, crossover design. When patients who received either a combined estrogen-androgen drug or androgen alone were compared with those who received estrogen alone or placebo, energy level, well-being, and appetite were increased ( $p < 0.01$ ). The androgen-containing preparations also induced lower somatic, psychological, and total scores on the menopausal index. Superior functioning in the androgen-treated groups occurred in association with higher plasma testosterone levels during the treatment phases ( $p < 0.01$ ). These data suggest that reduced levels of circulating testosterone subsequent to bilateral oophorectomy may play an important role in the development of physical and psychological symptoms that are frequent sequelae of this surgical procedure. (AM J OBSTET GYNECOL 1985;151:153-60.)

**Key words:** Surgical menopause, estrogen and androgen, androgen parenteral therapy

The precipitate decline in plasma estrogen levels following bilateral oophorectomy in premenopausal women has been well documented.<sup>1,2</sup> Less frequently acknowledged is the significant decrease in plasma testosterone levels subsequent to removal of both ovaries in this same population.<sup>3</sup> The observation that testosterone levels in ovarian vein blood are greater in early postmenopausal women than in reproductive-aged women<sup>4</sup> implies that patients who need to undergo bilateral oophorectomy are subsequently deprived of an important source of androgen production. Despite

these known endocrine changes and the significant incidence of symptoms following total abdominal hysterectomy and bilateral salpingo-oophorectomy,<sup>5</sup> little evidence is available with regard to the functional role of androgen in the woman.

In order to evaluate possible differential effects of estrogen and androgen on symptoms in surgically menopausal women, a prospective, double-blind, crossover study was undertaken. The objectives of this investigation were twofold: (1) to independently assess the clinical response of somatic and psychological symptoms to exogenous estrogen and androgen administered singly as well as in combination and (2) to address the theoretical issues regarding physical and behavioral effects of the sex steroids in women.

### Material and methods

**Subjects.** The participants in this study were premenopausal women who required a total abdominal hysterectomy and bilateral salpingo-oophorectomy for reasons other than malignant disease. They were re-

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| Treatment groups           | Preoperative baseline |               | Treatment 1 |         |         | Placebo, month 4 |                     | Treatment 2 |         |         |
|----------------------------|-----------------------|---------------|-------------|---------|---------|------------------|---------------------|-------------|---------|---------|
|                            |                       |               | Month 1     | Month 2 | Month 3 |                  |                     | Month 5     | Month 6 | Month 7 |
| Estrogen-androgen combined |                       | S U R G E R Y |             |         |         |                  | C R O S S - O V E R |             |         |         |
| Estrogen alone             |                       |               |             |         |         |                  |                     |             |         |         |
| Androgen alone             |                       |               |             |         |         |                  |                     |             |         |         |
| Placebo                    |                       |               |             |         |         |                  |                     |             |         |         |
| Hysterectomy control       |                       |               |             |         |         |                  |                     |             |         |         |

Fig. 1. Experimental design.

quired to be in a stable heterosexual relationship for at least 2 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 total abdominal hysterectomy but in whom the ovaries were to be retained were recruited to serve as an additional control group. Between September, 1980, and February, 1983, each patient who was scheduled for total abdominal hysterectomy and bilateral salpingo-oophorectomy 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. Before operation, patients were randomly assigned to either a combined estrogen-androgen group, an estrogen-alone group, an androgen-alone group, or a placebo group. The control hysterectomy group 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 bilateral salpingo-oophorectomy (placebo group) and the second to control for changes that may have been due to the surgical procedure itself (control hysterectomy group).

Following 1 month of baseline monitoring, patients underwent operation. Intramuscular injection of a hormonal preparation or placebo was administered monthly for the first 3 months (treatment 1). At the beginning of the fourth postoperative month, all patients received an injection of placebo. Women were then randomly crossed over to one of the four treatments they had not experienced during treatment 1 for an additional 3 months (treatment 2). Therefore, the entire experimental procedure encompassed a total of 8 months per patient. Fig. 1 contains a diagrammatic representation of the experimental design.

**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 was bound were calculated. This sum was then subtracted from the weight of the total compound. With 1 ml of the combined estrogen-androgen drug used as the standard, equivalent doses of the sex steroids contained in the other preparations were computed. Accordingly, it was determined that 0.63 ml of the estrogen-alone drug and 0.48 ml of the androgen-alone drug contained amounts of estradiol and testosterone that were equivalent to amounts of these hormones in 1 ml of the combined preparation. 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. Moreover, it has been shown that other sex steroid depot preparations induce maximal plasma hormone levels 1 to 4 days following injection and that the half-life is 14 days.<sup>6</sup> The estrogen-androgen combined drug (Climacteron), 1 ml, contains testosterone enanthate benzilic acid hydrozone, 150.0 mg; estradiol dienanthate, 7.5 mg; and estradiol benzoate, 1.0 mg. The estrogen drug (Delestrogen), 1 ml, contains estradiol valerate, 10.0 mg. The androgen drug (Delatestryl), 1 ml, contains testosterone enanthate, 200.0 mg. The placebo

consisted of sesame oil, 0.5 ml. After operation, drugs were given 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 9 and 11 AM at four different times during the study. The first sample was taken approximately 1 month before operation; the second and fourth, 72 hours following the third injection in both treatment phases; and the third, on the last day of the placebo month that fell in between. The blood was immediately centrifuged and the plasma stored at  $-20^{\circ}\text{C}$ . Total plasma estrogens were measured by radioimmunoassay with the use of 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 the level of 12.5 pg/ml. Plasma testosterone levels were measured with 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 control hysterectomy group underwent the identical experimental procedure except for the administration of monthly injections.

#### Material

**Daily menopausal rating scale.** Somatic and psychological symptoms were monitored daily by means of the daily menopausal rating scale. This instrument, devised and tested in a previous study,<sup>7</sup> was found to be a reliable and sensitive index of drug effects. Each symptom or behavior appears on an interval rating scale that has a range of 0 to 7. The poles of each scale have a verbal description of the symptom or behavior in question. Measures of energy level, well-being, appetite, and sleep quality reported here were monitored and quantified by means of the scale. Patients were given 30 questionnaires and 30 stamped, self-addressed envelopes at the beginning of each month and were instructed to fill in and mail a questionnaire daily. The 8-month duration of the study, therefore, yielded data on 240 days per patient and 12,720 patient days in all.

**Menopausal index.** The menopausal index, revised by Neugarten and Kraines,<sup>8</sup> was originally published by Blatt et al.<sup>9</sup> It lists 26 symptoms most often reported by clinicians and by women themselves as being typical or frequent complaints at menopause. Symptoms are categorized into three constellations—somatic (nine symptoms), psychosomatic (five symptoms), and psychological (12 symptoms) as seen in Table I. Because the scoring system that assigns differential weights to the various symptoms is not empirically based,<sup>9</sup> in this study, patients were required to rate the frequency and severity of each symptom on a bipolar rating scale that had a range of 0 to 7. The low end of the scale for each

**Table I.** Menopausal index

|                                  |                                       |
|----------------------------------|---------------------------------------|
| <b>A. Somatic symptoms</b>       |                                       |
|                                  | Hot flushes                           |
|                                  | Cold sweats                           |
|                                  | Weight gain                           |
|                                  | Rheumatic pains                       |
|                                  | Cold hands and feet                   |
|                                  | Breast pains                          |
|                                  | Headaches                             |
|                                  | Numbness and tingling                 |
|                                  | Skin crawls                           |
| <b>B. Psychosomatic symptoms</b> |                                       |
|                                  | Feelings of suffocation               |
|                                  | Blind spots before eyes               |
|                                  | Pounding of the heart                 |
|                                  | Dizzy spells                          |
|                                  | Pressure or tightness in head or body |
| <b>C. Psychological symptoms</b> |                                       |
|                                  | Tired feelings                        |
|                                  | Irritable and nervous                 |
|                                  | Feel blue and depressed               |
|                                  | Forgetfulness                         |
|                                  | Trouble sleeping                      |
|                                  | Inability to concentrate              |
|                                  | Crying spells                         |
|                                  | Excitable                             |
|                                  | Attacks of panic                      |
|                                  | Loss of interest in most things       |
|                                  | Feeling tense or wound-up             |
|                                  | Worry needlessly                      |

symptom was described as "almost never" while the extreme end stated "very often." Patients filled out the menopausal index at four points during the study immediately prior to venous blood collection.

**Statistical analyses.** The hormonal and behavioral data were analyzed with the Computer Programs analysis of variance for groups  $\times$  time blocks. For each item on the daily menopausal rating scale, the data analyzed were the mean of the preoperative baseline, the mean of the first 2 weeks of each treatment month, and the mean of the last 2 weeks of the intervening placebo month. In addition, analysis of covariance was also carried out in order to eliminate possible effects of initial group differences in baseline scores. Post hoc pairwise comparisons were performed with use of the Tukey test. Statistical significance reported here is based on results of the latter analyses.

#### Results

**Subject characteristics.** There were 12 patients in the combined estrogen-androgen group, 11 in the estrogen-alone group, 10 in the androgen-alone group, 10 in the placebo group, and 10 in the control hysterectomy group. Pathology reports confirmed that two patients had endometriosis; one was in the estrogen-alone group and the other in the placebo group. The rest of the sample (51 women) underwent operation for benign uterine fibroids. Five subjects who met the selection criteria and who were initially interviewed did

**Table II.** Mean plasma levels of total estrogen (estrone and estradiol) and testosterone at the four test times

|                                          | <i>Estrogen-androgen</i> | <i>Estrogen</i>  | <i>Androgen</i> | <i>Placebo</i>  | <i>Control</i>  | <i>Significant differences*</i> |
|------------------------------------------|--------------------------|------------------|-----------------|-----------------|-----------------|---------------------------------|
| Total estrogen (pg/ml), mean $\pm$ SEM   |                          |                  |                 |                 |                 |                                 |
| Preoperative baseline                    | 67.2 $\pm$ 10.4          | 49.4 $\pm$ 12.3  | 42.1 $\pm$ 11.2 | 69.4 $\pm$ 8.9  | 121.7 $\pm$ 7.4 | $p < 0.01^\dagger$              |
| Treatment 1                              | 243.8 $\pm$ 12.4         | 301.9 $\pm$ 13.1 | 107.8 $\pm$ 8.4 | 11.2 $\pm$ 3.9  | 90.8 $\pm$ 9.4  | $p < 0.01^\ddagger$             |
| Placebo phase                            | 7.8 $\pm$ 2.3            | 14.2 $\pm$ 3.3   | 9.5 $\pm$ 1.9   | 5.8 $\pm$ 3.7   | 78.9 $\pm$ 7.8  | $p < 0.01^\dagger$              |
| Treatment 2                              | 236.2 $\pm$ 14.8         | 289.1 $\pm$ 15.4 | 98.3 $\pm$ 9.6  | 6.2 $\pm$ 2.3   | 74.7 $\pm$ 6.6  | $p < 0.01^\ddagger$             |
| Testosterone (ng/100 ml), mean $\pm$ SEM |                          |                  |                 |                 |                 |                                 |
| Preoperative baseline                    | 81.1 $\pm$ 5.3           | 99.6 $\pm$ 4.7   | 71.9 $\pm$ 10.3 | 114.1 $\pm$ 9.6 | 90.8 $\pm$ 8.6  | NS                              |
| Treatment 1                              | 133.1 $\pm$ 12.4         | 89.4 $\pm$ 3.6   | 111.1 $\pm$ 6.6 | 87.8 $\pm$ 1.6  | 99.8 $\pm$ 3.6  | $p < 0.01^\S$                   |
| Placebo phase                            | 83.2 $\pm$ 4.9           | 65.3 $\pm$ 3.8   | 67.9 $\pm$ 2.5  | 66.2 $\pm$ 1.7  | 89.4 $\pm$ 4.7  | $p < 0.01^\parallel$            |
| Treatment 2                              | 129.2 $\pm$ 11.6         | 48.4 $\pm$ 2.6   | 115.3 $\pm$ 6.2 | 44.7 $\pm$ 3.2  | 88.8 $\pm$ 4.6  | $p < 0.01^\S$                   |

\*Between-group post hoc Tukey tests.

 $^\dagger$ Control hysterectomy versus estrogen-androgen, estrogen alone, androgen alone, and placebo. $^\ddagger$ Estrogen alone versus androgen alone, placebo, and control hysterectomy. $^\S$ Estrogen-androgen versus estrogen alone, placebo, and control hysterectomy. $^\parallel$ Control hysterectomy versus estrogen alone, androgen alone, and placebo.

not continue in the study. Two women decided to defer operation, one refused to comply with the experimental procedure after only 1 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 operation and was thus 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 showed that patients in the control hysterectomy group were significantly younger than those in the four treatment groups ( $36.3 \pm 2.2$  versus  $45.8 \pm 3.3$  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 total abdominal hysterectomy undertaken for benign conditions. Subjects in all five groups were homogeneous with respect to occupational status and years of school. There was, however, a wide range in these variables within groups which increased the generalizability of the findings. All subjects had normal personality profiles<sup>10</sup> and satisfactory marital relationships.<sup>11</sup>

**Total plasma estrogen and testosterone levels.** Mean plasma levels of total estrogen (estrone and estradiol) and testosterone at the four test times appear in Table II. The interassay coefficient of variation of total estrogen was 9%. At baseline the younger control hysterectomy group had significantly higher total estrogen 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, which testifies to the success of the randomization procedure. At 72

hours following injection in both treatment phases, all groups had higher total estrogen levels than the placebo group ( $p < 0.01$ ). Moreover, total estrogen levels of the estrogen-alone group were significantly higher during treatment than those of the androgen-alone and the control hysterectomy groups ( $p < 0.01$ ) but were not different from those of the estrogen-androgen group. At the end of the placebo month, the control hysterectomy group with intact ovaries had significantly higher total estrogen levels than the four groups of women who had undergone oophorectomy. In these latter women the levels fell to the lower limit of assay detectability, which indicates that the estrogen administered during treatment 1 had been completely metabolized. In all cases, total estrogen levels of subjects who received the same drug did not differ when treatment 1 and treatment 2 values were compared.

The interassay coefficient of variation of plasma testosterone levels was 10%. During both treatment phases, the estrogen-androgen group had significantly higher testosterone levels than the estrogen-alone, placebo, and control hysterectomy groups ( $p < 0.01$ ), but values did not differ significantly from those of the androgen-alone group. By 8 weeks after injection, testosterone values in steroid-treated groups also fell to levels below those of the control hysterectomy group and levels of the androgen-alone, estrogen-alone, and placebo groups were significantly lower than both their own baseline values and control hysterectomy group values ( $p < 0.05$ ). Once again, testosterone levels of subjects who received the same drug did not differ when group means of the two treatment phases were compared. Moreover, between-group differences in both hormone levels at treatment 2 were the same as those found during treatment 1.

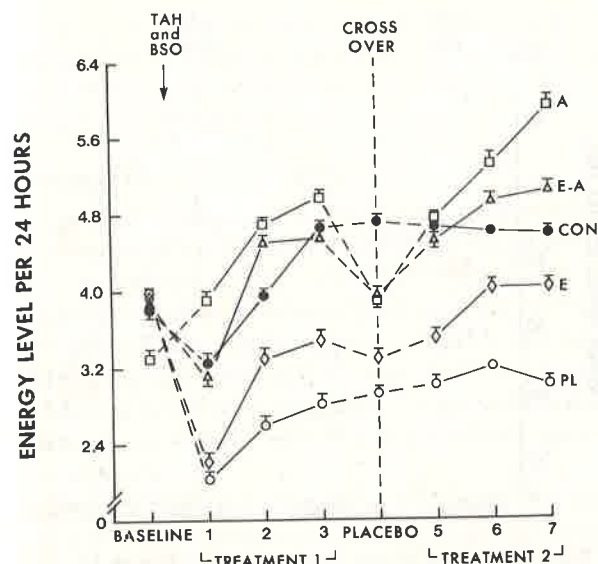


Fig. 2. Energy level for 24 hours. The treatment groups are: Estrogen-androgen group (E-A,  $\Delta$ ), estrogen-alone group (E,  $\diamond$ ), androgen-alone group (A,  $\square$ ), placebo group (PL,  $\circ$ ), and control hysterectomy group (CON,  $\bullet$ ).

**Energy level and well-being.** Hormonal effects on these two measures, thought to reflect how patients were feeling in general, were very similar. In each of the three treatment months of both phases, women in the estrogen-alone and placebo groups reported significantly lower ratings of energy level and well-being than did the control hysterectomy group, with intact ovaries, and those who received either of the androgen-containing preparations ( $p < 0.01$ ). Moreover, in treatment months 1, 3, 5, 6, and 7, estrogen-alone and placebo group scores were lower than those of the other three groups ( $p < 0.01$ ). When hormones were withdrawn during the placebo month, the control hysterectomy group with intact ovaries attained higher scores on both measures than did all women who had undergone oophorectomy ( $p < 0.01$ ) coincident with the higher plasma hormone levels at that time. It can be seen in Figs. 2 and 3 that there was a decrease in energy level and well-being from baseline to the first postoperative month in four groups ( $p < 0.01$ ); only the patients who received androgen alone maintained energy level and well-being ratings in the immediate postoperative period. Furthermore, by the end of the seventh postoperative month, energy level and well-being scores of the control hysterectomy group and both groups that received androgen (estrogen-androgen and androgen alone) exceeded the preoperative baseline scores ( $p < 0.01$ ) whereas scores of the estrogen-alone and placebo groups did not differ significantly from baseline values at that time.

**Appetite.** Analysis of daily ratings of appetite quality shown in Fig. 4 found that in each of the treatment

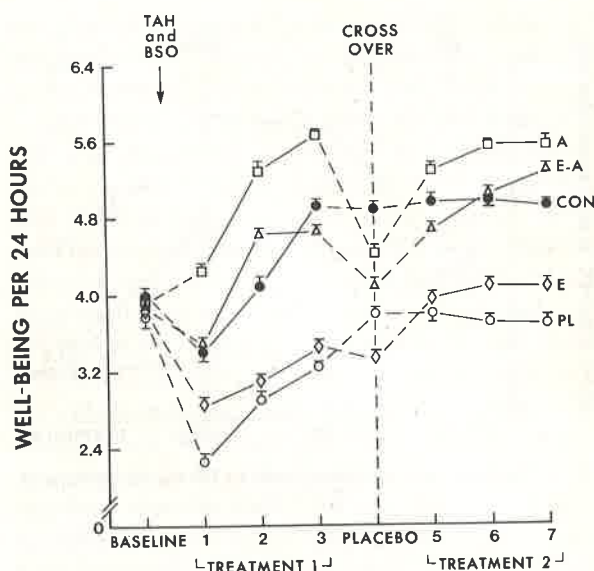


Fig. 3. Well-being per 24 hours. The treatment groups are as in Fig. 2.

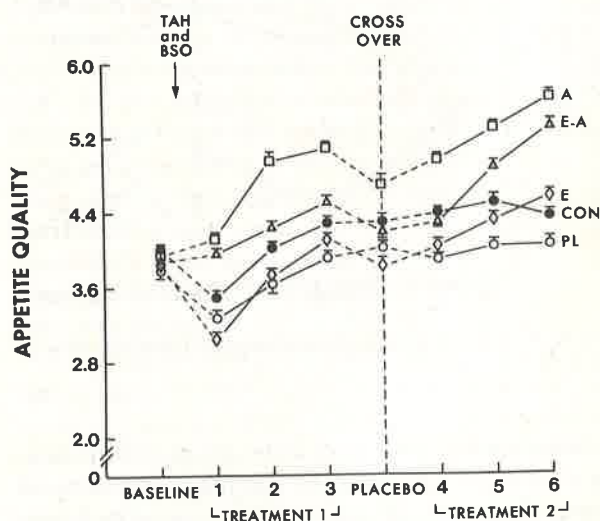


Fig. 4. Appetite quality. Treatment groups as in Fig. 2.

months, scores of the estrogen-alone, placebo, and control hysterectomy groups were significantly lower than those of the androgen-alone group ( $p < 0.01$ ) and lower than those of the estrogen-androgen group as well in months 1, 2, and 7 ( $p < 0.01$ ). The lower estrogen-alone, placebo, and control hysterectomy group appetite ratings occurred in association with their lower testosterone levels in both treatment phases. During the placebo month, scores of the androgen-alone group decreased significantly compared to the treatment values ( $p < 0.01$ ). By the third month in both treatment phases, appetite ratings were higher than preoperative baseline scores in only the estrogen-androgen and the androgen-alone groups ( $p < 0.01$ ).

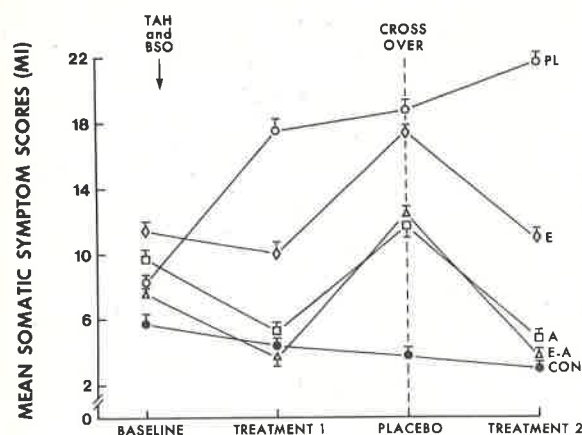


Fig. 5. Mean somatic symptom scores. Treatment groups as in Fig. 2.

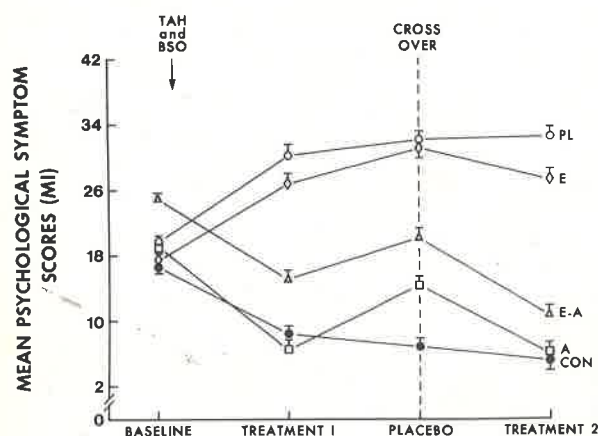


Fig. 6. Mean psychological symptom scores. Treatment groups as in Fig. 2.

**Sleep quality.** Analysis of daily ratings of sleep quality showed that there were no significant differences in any of the groups throughout the course of the investigation.

#### Menopausal index

**Somatic symptoms.** Lower scores on subtests of the menopausal index indicate a lower frequency and severity of symptoms. Fig. 5 shows that during both treatment phases somatic symptom scores of the estrogen-androgen, androgen-alone, and control hysterectomy groups were lower than those of the estrogen-alone and the placebo groups ( $p < 0.01$ ), whereas during the placebo month all women who had undergone oophorectomy reported higher scores than the control hysterectomy group ( $p < 0.01$ ). Furthermore, within-group analyses showed that all steroid-treated groups experienced a significant increase in scores during the placebo month compared to the treatment phase scores. However, scores of patients in the placebo group increased significantly and consistently after operation

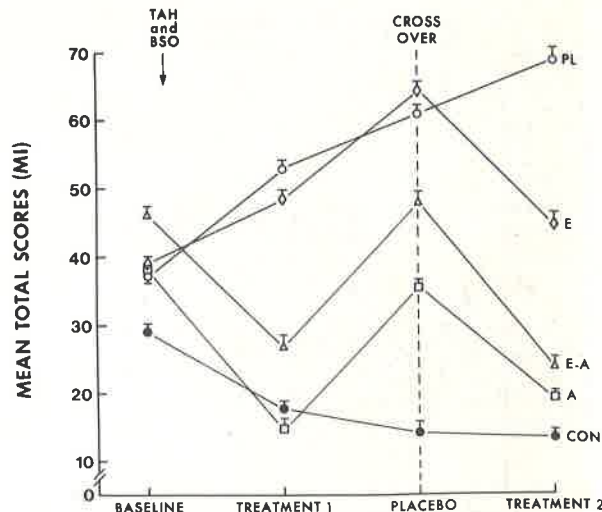


Fig. 7. Mean total scores. Treatment groups as in Fig. 2.

compared to the preoperative baseline values ( $p < 0.01$ ) whereas those of the control hysterectomy group remained stable at low levels throughout the course of the study.

**Psychosomatic symptoms.** There were no significant changes in psychosomatic symptom scores in any of the groups across time.

**Psychological symptoms.** As seen in Fig. 6, psychological symptom scores of the estrogen-alone and placebo groups were significantly higher than those of the estrogen-androgen, androgen-alone, and control hysterectomy groups during both treatment phases ( $p < 0.01$ ). Moreover, during the intervening placebo month, scores of the control hysterectomy group were lower than those reported by the estrogen-androgen group ( $p < 0.05$ ) and by the estrogen-alone and placebo groups ( $p < 0.01$ ). Analysis of within-group changes across time found that baseline psychological symptom scores were lower than treatment phase scores in the estrogen-alone and placebo groups ( $p < 0.01$ ) whereas both androgen groups and the control hysterectomy group attained lower scores during the treatment phases compared to the baseline values ( $p < 0.01$ ).

**Total scores.** Composite scores of all items on the menopausal index appear in Fig. 7. The estrogen-androgen, androgen-alone, and control hysterectomy groups attained lower total scores during both treatment phases than the estrogen-alone and placebo groups ( $p < 0.01$ ). However, during the placebo month, total scores of the control hysterectomy group were lower than those of all women who had undergone bilateral salpingo-oophorectomy ( $p < 0.01$ ). Furthermore, in contrast to the lower scores attained by the estrogen-androgen and androgen-alone groups during treatment compared to the baseline and placebo phase

scores ( $p < 0.01$ ), the estrogen-alone and placebo groups reported higher total scores on this measure at all postoperative testing times compared to the preoperative values ( $p < 0.01$ ).

### Comment

Results of this study unequivocally demonstrated differential responses of physical and psychological symptoms to estrogen and/or androgen administration in surgically menopausal women. In view of the fact that patients in this investigation were generally healthy and functioning well preoperatively, these data also provide interesting information with regard to the incidence of symptoms in treated and untreated surgically menopausal patients.

The postoperative decrease in both total estrogen and testosterone levels in women who have undergone oophorectomy reflected in the placebo phase hormone assays is consistent with data reported previously.<sup>1,3</sup> The single exception was the absence of a statistically significant decline in the testosterone levels of the estrogen-androgen group by the end of the placebo month. It may be that endogenous testosterone levels did not decrease in this group subsequent to operation. However, an alternative hypothesis is that the half-life of the combined preparation is longer than the half-lives of the other drugs, and thus the dose administered had not been completely metabolized by the eighth week following the last injection. Studies on the pharmacodynamics of the combined preparation currently underway will provide a basis for resolving this issue.

Coincident with the observed increases in circulating testosterone levels in the estrogen-androgen and androgen-alone groups during treatment was enhancement of energy level, well-being, and appetite reported by these patients. The androgenic effect on these behaviors was likely a reflection of the anabolic<sup>12</sup> and energizing properties<sup>13</sup> of this steroid. The observation that androgen alone had a more profound effect on energy level, well-being, and appetite relative to the combined drug at several points during treatment can be explained by changes in sex hormone-binding globulin concentrations induced by the sex steroids. It is known that both estrogen and androgen bind to sex hormone-binding globulin in plasma and that only the free unbound portion has potential for biologic activity.<sup>14</sup> Because estrogen increases sex hormone-binding globulin levels and androgen reduces them,<sup>15</sup> it is possible to infer that the administration of androgen alone in the presence of low levels of endogenous estrogen resulted in a higher percentage of circulating free testosterone in the androgen-alone group compared to the estrogen-androgen group. The relative increase in free testosterone in the androgen-alone group may thus have accentuated the androgenic effects on be-

havior observed. This hypothesis merits testing by measurement of sex hormone-binding globulin subsequent to the administration of both of these drugs.

That exogenous estrogen alone was not more effective than placebo on energy level, well-being, and appetite was clearly demonstrated. Moreover, the finding that scores of the younger control hysterectomy group with intact ovaries were higher than their own baseline values by the end of the seventh postoperative month suggests that preoperative scores may have been depressed in all groups because of psychological factors related to impending operation. If this were the case, the stability in estrogen-alone and placebo group scores following operation may be indicative of an actual postoperative deterioration in their functioning. Studies that have reported increased well-being in postmenopausal women as a function of estrogen administration have been single-blind<sup>16</sup> or have used subjects undergoing a natural menopause<sup>17</sup> so that endogenous testosterone levels were likely to be unchanged. Other authors,<sup>18,19</sup> however, have similarly failed to find a difference between effects of estrogen and placebo on well-being in the postmenopause. It is important to note that in this study increased energy level and well-being did not occur secondary to relief of somatic symptoms since it was found that androgen alone and placebo were equally ineffective in alleviating hot flashes in these same women.<sup>20</sup> Moreover, no side effects of exogenous androgen were either observed or reported. Specifically, there were no signs of virilization in the two androgen groups during either of the 3-month treatment phases.

The superior efficacy of the androgen-containing preparations on somatic, psychological, and total scores of the menopausal index may also be related to the anabolic and energizing properties of this sex steroid. Furthermore, the presence of androgen receptors in the hypothalamus, pituitary, and limbic system<sup>21</sup> allows for the possibility that this hormone may have been exerting its effects on behavior centrally. Additional evidence for a causal relation between these symptoms and circulating levels of sex steroids derives first from the observation that, when hormones were withdrawn during the placebo month, scores of all oophorectomized subjects on the three subscales of the menopausal index increased compared to the treatment phase scores. Second, scores of the placebo group increased consistently and significantly during the postoperative course compared to preoperative values in association with a decrease in circulating total estrogen and testosterone levels. In contrast, scores of the intact control hysterectomy group on the menopausal index maintained stability throughout the study concomitant with stability in sex steroid levels across time.

The consistent clinical superiority of the androgen-

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containing drugs in this study strongly implies that reduced levels of circulating testosterone may indeed play a critical functional role in the development of a myriad of disturbances that often arise in premenopausal women subsequent to bilateral salpingo-oophorectomy. The clinical implication of these findings is that administration of both sex steroids to this population may militate against symptoms that are a consequence of the sudden and drastically altered endocrine status induced after operation. These results need to be confirmed both by replication of this study and by investigation of the long-term effects of combined hormone replacement therapy in surgically menopausal women.

These data serve as well to point out a methodologic issue in menopause research. It was noted that the effect of estrogen on hot flushes, the cardinal menopausal symptom, was obscured when it was grouped together with other symptoms, as is the case in the menopausal index. This finding underlines the importance of investigating menopausal symptoms independently until we derive an empirical basis for clustering them.

In summary, results of this study showed that premenopausal women who received androgen alone or a combined estrogen-androgen drug following total abdominal hysterectomy and bilateral salpingo-oophorectomy reported fewer somatic and psychological symptoms than those who received estrogen alone or placebo. Furthermore, the androgen-containing preparations induced levels of functioning that were similar to those of younger women with intact ovaries. Bearing in mind that neither androgen alone nor placebo alleviated hot flushes,<sup>20</sup> the necessity for administering estrogen as well seems clear. These data provide strong support for the conclusion that a combined estrogen-androgen regimen may serve to enhance the quality of life of women who have experienced a surgical menopause.

Finally, it was observed in this study that menopausal symptoms are dissociable, under different hormonal control, and some, such as sleep quality and psychosomatic symptoms, independent of circulating levels of the sex steroids. In order to further investigate the specificity of hormone-behavior relationships, future research in this area ought to focus on the response of individual symptoms to the administration of each of the sex steroids as well as to their combined effect.

## REFERENCES

1. Vermeulen A. Sex hormone status of the postmenopausal woman. *Maturitas* 1980;2:81.
2. Chakravarti S, Collins WP, Newton JR, Studd JWW. Endocrine changes and symptomatology after oophorectomy in premenopausal women. *Br J Obstet Gynaecol* 1977;84:769.
3. Vermeulen A. The hormonal activity of the postmenopausal ovary. *J Clin Endocrinol Metab* 1976;42:247.
4. Botella-Llusia J, Oriol Boosch A, Sánchez Garrido F, Tresguerres JAF. Testosterone and 17 $\beta$ -oestradiol secretion of the human ovary. II. Normal postmenopausal women, postmenopausal women with endometrial hyperplasia, and postmenopausal women with adenocarcinoma of the endometrium. *Maturitas* 1980;2:7.
5. Dennerstein L, Wood C, Hudson B, Burrows G. Clinical features and plasma hormone levels after surgical menopause. *Aust NZ J Obstet Gynecol* 1978;18:202.
6. Dusterberg B, Wendt H. Plasma levels of dehydroepiandrosterone and 17 $\beta$ -estradiol after intramuscular administration of Gynodian-Depot in 3 women. *Horm Res* 1983;17:84.
7. Sherwin BB, Brender W, Gelfand MM. Mood and behavior changes in menopausal women receiving gonadal hormones or placebo. In: Stark-Adamec C, ed. *Sex roles: origins, influences and implications for women*. St. Albans, Vermont: Eden Press, 1980:190.
8. Neugarten B, Kraines RJ. Menopausal symptoms in women of various ages. *Psychosom Med* 1965;27:266.
9. Blatt MGF, Wiesbader Y, Kupperman HS. Vitamin E and climacteric syndrome. *Arch Intern Med* 1953;91:792.
10. Eysenck HJ, Eysenck SBG. *Eysenck personality inventory manual*. San Diego: Educational and Industrial Testing Service, 1958.
11. Locke HJ, Wallace KM. Short marital adjustment and prediction tests. *Marriage Fam Liv* 1959;21:251.
12. Johnson LC, O'Shea JP. Anabolic steroids: effects on strength development. *Science* 1969;164:957.
13. Rose RM. The psychological effect of androgens and estrogens. A review. In: Shader RI, ed. *Psychiatric complications of medical drugs*. New York: Raven Press, 1972:251.
14. Mercier-Bodard C, Alfsen A, Beaulieu EE. Sex steroid binding plasma protein (SBP). *Acta Endocrinol* 1970;64:204.
15. Anderson DCP. Sex hormone binding globulin. *Clin Endocrinol* 1974;3:69.
16. Utian WH. The true clinical features of postmenopause and oophorectomy and their response to oestrogen therapy. *S Afr Med J* 1972;16:732.
17. Campbell S. Double-blind psychometric studies on the effects of natural estrogens on postmenopausal women. In: Campbell S, ed. *The management of the menopause and postmenopausal years*. Baltimore: University Park Press, 1976:149.
18. Thomson J, Oswald I. Effect of oestrogen on the sleep, mood and anxiety of menopausal women. *Br Med J* 1977;2:1317.
19. George GCW, Beaumont PJV, Beardwood CJ. Effects of exogenous estrogens on minor psychiatric symptoms in postmenopausal women. *S Afr Med J* 1973;47:2387.
20. Sherwin BB, Gelfand MM. Effects of parenteral administration of estrogen and androgen on plasma hormone levels and hot flushes in the surgical menopause. *AM J OBSTET GYNECOL* 1984;148:552.
21. McEwen BS. Neural gonadal steroid actions. *Science* 1981;211:1303.