MOOD AND BEHAVIOR CHANGES IN MENOPAUSAL WOMEN RECEIVING GONADAL HORMONES OR PLACEBO

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ABSTRACT

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Menopausal women with symptoms of hormone depletion underwent a one month baseline period of monitoring by means of a questionnaire completed daily. Questionnaire items dealt with sexual functioning, somatic symptoms, mood, sleep, appetite, energy level, activity level and argument frequency. Then subjects were randomly assigned to either an estrogen-alone group, a combined estrogen-androgen group or to a placebo group. Drug or placebo were administered once a month by injection for three additional months concurrent with daily completion of the questionnaire. Women who received the combined estrogen-androgen drug experienced a significant increase in sleep quality, appetite, energy level, sense of well-being and activity level from baseline to the end of month three of treatment. There were no significant changes on these measures in either the estrogen-alone group or in the placebo group. These findings are consistent with known anabolic effects of androgen. The small sample size (total N = 8) requires that caution be exercised in the interpretation of these findings. Contrary to suggestions in the literature concerning effects of exogenous androgen, no significant changes in sexual functioning were demonstrated. Possible explanations are that the relatively modest dosages of androgen administered in this study may have been too small, the three month duration of hormone therapy may have been insufficient to reveal changes and finally, the androgen-sexuality relationship may involve additional factors.

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Introduction

A considerable body of knowledge has accumulated concerning the biochemical and physiological modes of action of the sex hormones. However, relatively little research has been done on their behavioral and psychological effects, particularly in the human female. The animal literature has been predominantly concerned with studying changes in sexual behavior after castration and subsequent exogenous hormone administration (von Euler & Heller, 1963). Observations of female rodents and primates during various stages of the estrus cycle attest to the importance of concurrent hormonal status relative to sexual behavior (Beach, 1976). Recently, there has been a great deal of interest in the masculinization of genetic female rodents, dogs and primates who had been exposed to androgenic stimulation prenatally (Diamond, 1977). Changes in these animals have been demonstrated in morphological development of the genitalia and in social and sexual behavior. Another fruitful area of investigation of sex hormones has involved intracranial implantation of estrogen and/or androgen in cats and primates (Michael, 1969; Michael, 1971). This procedure generally results in an increase in female sexual behavior, specifically in proceptivity; that is, there is an increase in appetitive activities shown by females in response to stimuli received from males.

It seems likely that the investigation of the effects of gonadal hormones in animals has, to a great extent, focused on sexual behavior because patterns of sexual initiation and response can be fairly accurately observed and because the most convenient subjects

for research have been lower mammals. However, in primates and specifically in humans, with increased mass and organization of the cerebral cortex, the effect of these structures on sexuality becomes of increasing importance. Money (1961) has emphasized the role of cognitive and learned factors in the overt expression of human eroticism. These serve to complicate the study of hormone-behavior relations in the human female. At the same time however, although development of the higher brain centers confounds the study of hormone-behavior relationships, it allows for the investigation of a broader range of behaviors. Studies of the effect of sex hormones in human females therefore, permit the investigation of both sexual as well as non-sexual psychological variables. Human research also allows for the study of non-behavioral measures of sexuality such as sexual thoughts and fantasies. Finally, the use of human females as a subject population permits the testing of hypotheses derived from animal research concerning hormone-behavior relationships in which cognitions are thought to mediate sexuality. The human female therefore, affords an opportunity to investigate the effects of gonadal hormones on more cognitively mediated sexual and non-sexual measures.

The Role of Androgens

Although the ovaries secrete a small amount of androgen, it is the adrenal cortex which is the major source of androgen in the human female. In conjunction with ovarian development at puberty, there is also an increase in the secretion of androgen by the adrenal

cortex, manifested in part, by urinary excretion of 17-ketosteroids, the metabolic end-products of secretions of the adrenal cortex (Rosenthal, 1968). Pubic and axillary hair also develop in the female, in part as a result of stimulation by adrenal androgens. In addition, the clitoris enlarges under the stimulation of androgens from the adrenal gland.

In addition to their influences on sexual development, there are known general effects of androgen. Anabolism refers to the building up of the body substance, the constructive or synthetic chemical reactions included in metabolism. Increased muscular strength and physical vigor result when exogenous androgen is given before puberty or to a young eunuchoid male. As well, a general feeling of well-being prevails (Goodman & Gilman, 1975). Distinct change in the voice is noted and growth (height and weight) is accelerated. Although these anabolic effects are associated with all androgens, the most potent, naturally occurring androgen is testosterone (Eberlein, Winter & Rosenfield, 1967). Papanicolaou and Falk (1938) injected testosterone propionate into female and castrated male guinea pigs. This resulted in pronounced muscular development in both. The large muscles of the male are thought to represent a sexual character dependent upon androgen for its expression. Hypertrophy of the musculature in response to testosterone requires retention of nitrogen and other elements to build protoplasm and in this sense, testosterone exerts an anabolic effect. Therefore, a gain in weight, attributable in part to the protein retained and in part to a retention of sodium chloride, results

from exogenous androgen administration. When used in women, all of the androgens tend to produce dose-related degrees of masculinization. Among the early manifestations are acne, growth of facial hair and deepening of the voice. As well, exogenous androgen administration may result in clitoral hypertrophy. If treatment is discontinued, these side effects slowly subside.

The Role of Estrogen

Although most endocrine glands apparently become functional sometime during fetal life, the ovaries do not become fully active until adolescence (Hamblen, 1949). The influence of higher levels of circulating estrogen at approximately age 11, are reflected in the development of the breasts, in changes in the vagina, uterus and the entire reproductive tract. The major consequence of the increased estrogen production during puberty is its specific stimulating effect for further growth and development of the uterus and vagina. The muscular wall of the uterus enlarges and its glandular lining also develops. The lining of the vagina is extremely sensitive to estrogen and its thickness is proportional to the amount of this hormone present at any given time (Katchadourian & Lunde, 1972). Maintenance of the female reproductive tract in adulthood is thus dependent on the amount of circulating estrogen. Follicle-stimulating hormone (FSH) secreted by the pituitary stimulates the ovaries to produce estrogen. During this first phase of the menstrual cycle, estrogen has its major effect in stimulating regrowth of the endometrium and the maturation of an

ovarian follicle. Estrogen therefore is as well responsible for many features of the normal menstrual cycle.

The Menopausal Syndrome

From the age of 35, the ovaries become less and less efficient. As ovarian failure progresses, ovulation stops and finally the production of estrogen more or less ceases. This loss of estrogen is the decisive factor in the production of the menopausal syndrome. The loss is not absolute and varies with the individual. However symptoms associated with the menopause result from the primary deficiency of estrogen.

Although "menopause" and "climacterium" are often used interchangeably in the literature, the term menopause refers to the cessation of the menses, and climacterium, to the involution of the ovaries and the various processes associated with this involution including menopause (Neugarten & Kraines, 1965). For some women, the so-called menopausal symptoms occur early, before the actual cessation of menses; for other women, symptoms coincide with the menopause; for others, symptoms do not appear until several years later. Still other women seem to remain free of such symptoms altogether.

Deviations from the normal menstrual pattern are usually the first objective signs of the onset of the menopause. Bleeding rarely stops abruptly; intervals between periods usually become irregular and longer and the flow decreases in duration and volume. Eventually, estrogen levels fall below that necessary to stimulate the endometrium and menstruation ceases.

The outstanding symptom of the climacteric is the hot flush

which is a result of vasomotor instability believed to be due to endocrine imbalance. The patient experiences wave-like sensations of heat which may spread over the face, neck and upper chest (Hamblen, 1949). Attacks are usually of short duration but in the severe form, they recur at short intervals both day and night, often interfering with sleep.

Nervous and psychic manifestations of the menopause result from the fact that the central and autonomic nervous systems, being under the influence of estrogen, react to its deficiency (Riley, 1959). As a consequence, the prevalence of nervous manifestations such as irritability, sleeplessness, inability to concentrate and failing memory are common features of the climacteric. Various disturbances in mood such as depression, anxiety and general emotional discomfort are also frequently reported.

Results of a survey of 638 women aged 45 to 54 living in England in 1964-65 indicated that hot flushes and night sweats are clearly associated with the onset of a natural menopause and that they occur in the majority of women (McKinsay & Jeffreys, 1974). Hot flushes were reported to occur more frequently (usually daily) and over more of the body by women whose menstural flow showed evidence of change or cessation, and for 25% of those women whose menses had ceased for at least one year, hot flushes persisted for five years or more. The other six symptoms specified, namely, headaches, dizzy spells, palpitations, sleeplessness, depression and weight increase, showed no direct

relationship to the menopause but tended to occur together, each being reported by approximately 30 to 50% of the respondants with little variation according to menopausal status. Additionally, none of the six sociodemographic variables investigated, i.e. employment status, school leaving age, social class, domestic workload, marital status or parity had any marked association with the reported frequency of symptoms. It is interesting to note that in this sample, despite embarrassment and/or discomfort from hot flushes reported by nearly three-quarters of those experiencing this symptom, only one-fifth had apparently sought medical treatment.

An objective indicant of ovarian functioning is obtained by the pathologic exmination of cells in a vaginal smear. At the time of menopause the smear is frequently hypoestrogenic (Shanklin & Wied, 1973). In the castrate state, more than 50% of cells are basal or parabasal. Administration of exogenous estrogen usually restores vaginal cells to an estrogenic state. However, menopausal symptoms and a hypoestrogenic vaginal smear are associated only 50% of the time. Waxenberg et al., (1960) in a study designed to explore the relationship between vaginal cytology and various aspects of sexual behavior found that in 24 women whose ovaries had been removed, there was no correlation between sexual behavior and hormone levels as reflected by exfoliative vaginal cytology .

There are several consequences of vaginal mucosal atrophy due to estrogen depletion which may profoundly affect sexual functioning.

Loss of tissue elasticity may deny an adequate opening to permit penile penetration; loss of normal secretion may lead to painful intercourse (dyspareunia) and bleeding during and post coitus due to an atrophic membrane (Kantor, 1977).

Effects of Exogenous Androgen Administration

Soon after testosterone propionate had been synthesized in the mid-1930's, physicians started to use it to treat a variety of gynic disturbances such as excessive bleeding at the time of a menstrual period (menorrhagia), excessive tissue proliferation of the breast (cyclomastopathy), painful menstruation (dysmenorrhea) and menopausal symptoms in ovariectomized women (Greenblatt, 1942). One of the earliest studies undertaken to investigate the effects of testosterone was concerned with menopausal women who first received therapeutic doses of estrogen and concomitantly 25-50 mg of testosterone propionate daily. The therapy resulted in the serendipitous finding that libido and sexual response were significantly greater than that experienced with estrogens alone (Shorr, Papanicolaou & Stimmel, 1938). Following this observation, many studies originally undertaken to assess the efficacy of a variety of therapeutic agents for the management of symptoms of the menopause resulted in the almost universal report of increased libido as an effect of the administration of exogenous androgen (Carter, Cohen & Shorr, 1947). Topical application of testosterone ointment to the clitoris produced marked enlargement of the glans and increased libido (Groome, 1939). Thereafter androgens were administered therapeutically

for various endocrinopathic gynecologic disorders either parenterally or by means of testosterone pellet implants. Because androgen dosages varied so widely in the early use of the hormone, differential libido-enhancing effects were observed; with implants of 25 mg, no change in libido was reported whereas an implant of 300 mg increased sexual desire even in older women (Silberman, 1940).

Although the majority of studies of the late 1930's supported the view that exogenous androgen increased sexual desire, some observations were at variance with this conclusion. Their belief was that androgens neutralize the action of estrogens and result in a depression of libido (Abarbanel, 1940). Consequently testosterone propionate was recommended for treatment of nymphomania or the relief of "exaggerated sex urge" (Rubenstein, Shapiro & Freeman, 1940). Mounting evidence to the contrary served to curtail the use of androgens for this purpose within a short time.

Salmon and Geist (1943) analyzed the effects of androgens on libido in a group of 101 women who were being treated for a variety of endocrine disorders such as painful menstruation (dysmenorrhea), abnormal uterine bleeding between menstrual periods (menometorrhagia), bilateral ovariectomy or estrogen deficiency. All but 13 of the 101 women verbally reported some increase in libido subsequent to exogenous androgen administration. In the estrogen deficient cases in which there was "secondary or endocrinopathic frigidity" as a result of menopause or the absence of menstruation (amenorrhea), 9 of the 11

patients treated only with testosterone propionate reported increased libido and increased clitoral sensitivity but did not experience orgasm during intercourse. Twelve patients in this group treated solely with estrogens reported relief of vasomotor symptoms but no appreciable change in libido while 7 of 9 patients who were given estrogens and androgens simultaneously reported both abatement of vasomotor symptoms and increased sexual desire. The optimal therapeutic effect was obtained in those cases in which the vaginal smear revealed a full estrogenic effect with the concurrent administration of 10 or 25 mg of testosterone propionate twice or three times a week. The investigators concluded that androgens have a three-fold action causing a greater intensity of sexual gratification, a heightened susceptibility to psychic stimulation and increased sensitivity of the external genitalia. However they did not present the data on which all of these conclusions are based.

In a study done to evaluate the effect of androgen in women who presented with the complaint of frigidity it was found that effects of exogenous androgen were dependent upon previous sexual functioning (Greenblatt, Mortara & Torpin, 1942). Of seven women who reported "very little or no libido" in the past, four reported a marked increase and three no change in sexual desire after several testosterone propionate pellet implants. However, of 22 patients treated with implants who "had once had libido but lost it", eight reported a moderate increase and 13 a marked increase in libido after treatment. The authors concluded that although it may not be possible to increase libido in some psychologically frigid women who never have experienced sexual desire,

restoration of libido easily occurs following testosterone implantation in those women who at some time had known libido. Information volunteered during the course of treatment constituted the support upon which these conclusions were based. Kupperman and Studdiford (1953) as well have supported the view that administration of androgens for the treatment of various gynecologic disturbances has been frequently associated with an increased libido. They too emphasized that little ameliorating effect from the androgens on frigidity in women who have never experienced libido can be expected.

Due to the increasing controversy regarding the efficacy of various combinations of estrogen and androgen in the treatment of the menopause, an investigation was carried out to assess the differential effects of the hormones (Greenblatt, Garner, Calk & Harrod, 1950). The experiment was double-blind. A total of 102 women with symptoms of the menopause received either an estrogen preparation (Diethylstilbestrol, 0.25 mg), an androgen preparation (Methyltestosterone 5.0 mg) or an estrogen-androgen combination (Diethylstilbestrol 0.25 mg and Methyltestosterone 5.0 mg) or a placebo each for differing periods of time in varying sequence. Satisfactory relief of menopausal symptoms was reported by 96.9% of all patients who received estrogen alone. Therapy with the estrogen-androgen combination gave the same relief of menopausal symptoms in 89.6% of the cases while only 23.5% of those who received the androgen preparation reported satisfactory relief of symptoms. In the placebo condition, 83.8% of patients reported no improvement of symptoms. Most noteworthy, 66.6% of the patients stated

a preference for the estrogen-androgen combination over the estrogen preparation because of increased well-being and libido they experienced while on the combined drug. It should be noted that although all patients were tested in each condition, duration of treatment with any one drug was not held constant across patients. As well, prolonged effects of one course of therapy made retrospective verbal report suspect and comparison difficult because varying rates of drug metabolism had a carry-over effect to the following treatment condition. Information regarding well-being and changes in libido was obtained in brief monthly interviews designed to elicit subjective symptoms during the previous month.

In a series of studies done to evaluate hormone replacement therapy in the postmenopausal woman, it was found that the most efficacious therapeutic preparation was an estrogen-androgen combination with a 1:20 ratio of estrogen dosage (Masters & Magallon, 1950; Masters & Grody, 1953; Masters, 1957). The mean age of the patients was 76 years. They voluntarily reported generally increased well-being and vitality. Objective observations in an associated study (Caldwell & Watson, 1952) showed improved physical capacity, increase in weight and improvement in memory and ability to learn new material as measured by The Wechsler-Bellevue and The Wechsler Memory Scale.

A study of patients who had advanced cases of breast cancer and were treated with massive amounts of testosterone propionate supported the reports of its enhancing effects on the sexual behavior of women.

A considerable increase in sexual desire was recorded in those patients who had shown temporary clinical improvement (Foss, 1951). These were fortuitous findings obtained during the course of regularly scheduled physical examinations.

The role of androgen in human female sexuality became more clearly defined in the course of postoperative evaluation of patients who had had bilateral ovariectomy and adrenalectomy as a result of surgical treatment of malignant neoplastic breast disease (Waxenberg, Drellich & Sutherland, 1959). Following ovariectomy and treatment with exogenous estrogen, no change in sexual desire was shown. However, after adrenalectomy 14 of 17 patients reported the absence of all sexual desire. In a later study, 7 patients had ovariectomy 1 to 5 years before the adrenal glands were ablated. Several patients in this group reported moderate changes in sexual feelings and behavior after their earlier ovariectomies but all seven reported sudden, almost total loss of sexual feelings and responsivity after removal of their adrenal glands (Drellich & Waxenberg, 1966). It was concluded that the loss of endogenous androgen resulting from adrenalectomy was in large part responsible for the observed radical decrease in libido.

Schon and Sutherland (1960) carried out a study designed to evaluate the sexual functioning of women from the time they were faced with the diagnosis of breast cancer through the period covering the various operations related to this disease. Eighty-five per cent of the women retained the same degree of sexual desire and frequency

of activity after mastectomy as before and 75% experienced the same intensity of gratification. The authors concluded therefore, that mastectomy did not appreciably influence sexual behavior. Of six women who underwent subsequent bilateral ovariectomy, sexual desire remained at the same level in four patients, decreased mildly in one and in one it dropped to zero. Sexual activity retained preoperative frequency levels in half the patients and half reported a decrease. Four of the six women experienced the same degree of sexual pleasure, one reported a decrease and one abolition of sensation. Once again, the investigators concluded that ovariectomy appeared to have no appreciable effect on sexual behavior. A statistical evaluation of these data was not done because it was felt that the number of cases was too small. Thirty women who had had a mastectomy and ovariectomy underwent hypophysectomy as a therapeutic measure to check the progress of metastatic breast cancer. None of these patients had been adrenalectomized. Interviews ten months postoperatively revealed that in 87% of the patients, sexual activity was less frequent or absent and in 85%, sexual gratification was reduced or not experienced. Subsequent administration of thyroid hormones and of cortisone had no effect on the sexual status after surgery. It was concluded that absence of the tropic pituitary hormone which activated the adrenal androgens accounted for the observed drastic decline in sexual functioning after removal of the pituitary gland. It should be noted that these patients were unable to be interviewed preoperatively so that the data concerning presurgical

levels of sexual functioning consisted of retrospective verbal reports. In addition, ovarian hormones (estrogen and progesterone) were not administered post-operatively, the assumption being that absence of ovarian hormones does not necessarily influence sexual behavior.

Greenblatt and Leng (1972) administered therapeutic doses of various hormones to a patient complaining of frigidity and reported on the woman's recording of her responses to each of the hormones. Estrogens increased the sexual response to 1+ , in a scale varying from 0-5. Both progestens and a placebo elicited a 0 response on the scale indicating no change in libido. Methyltestosterone administered in 15 mg doses orally elicited a 3+ response; intramuscular injection of testosterone propionate (25 mg/week) resulted in a 4+ response and implantation of two 75 mg pellets of testosterone proved most effective, yielding a 5+ response. Of all the hormone preparations, androgens alone consistently intensified her desire for sexual relations and gratification could be equated with dosage. Information regarding method of data collection, duration and sequence of treatment conditions is lacking. Though the findings are compelling, missing procedural details render them uninterpretable. This report therefore, constitutes an N of one, anecdotal, uncontrolled case study.

Kennedy (1973) studied the effects of exogenous androgen administration in women who had advanced carcinoma of the breast or endometrial carcinoma. Results showed that after several weeks of massive androgen therapy in the female (testosterone enanthate 400 mg three times a week), there may be an increase in libido. It was

found that the incidence of this reaction increases with prolonged therapy. In women with advanced breast cancer, more than 60% of patients noted an increase in libido after six months of continuous treatment. An augmentation in libido was expressed in terms of a heavy feeling in the pelvis, an increase in the frequency of sexual intercourse or a loss of previous frigidity (author's own term). It was noted that a relatively prompt disappearance of the induced libido follows within a short time of discontinuance of treatment. This report is anecdotal in nature; neither the data themselves nor their means of collection were presented.

In summary, early studies of exogenous androgen administration reported increased libido in women who were being treated with a combined estrogen-androgen preparation. On the other hand, there was an absence of heightened sexuality in a similar population of women being treated with estrogen alone. These findings first alerted investigators to the libido-enhancing effect of androgen in the human female. Corroborating data of androgen's behavioral effects appeared in studies of women being treated for carcinoma of the breast. The finding of total loss of libido following adrenalectomy pointed to the loss of endogenous androgen as the critical factor to account for the sudden, drastic decline in sexual behavior. These studies served to solidify the evidence in the literature concerning the role of androgen as the libido-enhancing hormone in human female sexuality.

Effects of Exogenous Estrogen and Progesterone Administration

Several studies have reported effects on libido resulting from the use of exogenous estrogen and/or progesterone in the treatment of menopausal symptoms. Bakke (1965) carried out a double-blind cross-over study using an estrogen preparation, an estrogen-progestin combination and a placebo. The patients' symptoms were recorded in a monthly office call in combination with a Questionnaire which inquired about changes in 12 somatic symptoms as well as mood, feelings of energy, irritability and sexual interests. Results indicated that the six women who enjoyed an increase in libido stated that the progestin-estrogen combination was more potent in this regard than estrogen alone and of the six women who rejected the drug because of an increase in libido, five did so taking the progestin-estrogen combination and only one while taking the estrogen alone. None of the placebo group reported increased libido. In all, 11 women reported increased libido with an estrogen-progestin mixture, while five reported an increase with estrogen alone. These data suggest that exogenous estrogen and progestin supplementation may lead to optimal sexual enjoyment in menopausal women in the absence of exogenous androgen administration. There are several design considerations which should be noted in this study which render the findings equivocal. It was retrospective in nature and did not involved detailed collection of frequency and kind of sexual behavior. Basal level of sexual activity was not assessed so that within subject comparison is not possible and subject variability cannot be accounted for. Nevertheless corroboration of these findings occurs in a report

by Kennedy (1973) who used massive doses of estrogenic hormones in the treatment of carcinoma of the breast in postmenopausal women. It was found that administration of massive oral doses of Diethylstilbestrol in the ranges of 300 to 1000 mg a day was associated with a striking increase in libido comparable to that noted with the androgenic hormones. Although the incidence of this increased libido is not as great as with the androgenic hormones, the degree of change was thought to approach that of the androgens. This report does not provide a data analysis nor does it indicate the method of data collection.

Although there is a great deal of evidence to uphold the now common view that androgen is the libido enhancing hormone in the human female, it must be acknowledged that the strongest support for this notion rests on the findings of the studies in which patients who had advanced carcinoma of the breast were subsequently surgically deprived of endogenous ovarian, adrenal and pituitary hormones in an attempt to arrest the disease (Foss, 1951; Waxenberg et al., 1959; Schon & Sutherland, 1960; Waxenberg et al., 1960). The observed alteration of libido in these patients were fortuitous findings in the form of patients' retrospective verbal report at times specifically but more often serendipitously elicited during the course of treatment of the disease. The authors have taken great care to emphasize both subjective and objective indicants of physical improvement in these patients postoperatively thereby attributing changes in sexual functioning to endogenous androgen depletion. Though improvement in physical status

likely did occur even if for the limited period of time during which sexual functioning was assessed, one can still not overlook the influence of the drastic nature of the surgical procedures themselves as well as the psychological factors inherent in this particular patient population due to the severity of the original disease. Factors such as self-selection, no baseline of sexual functioning, presence of other uncontrolled variables (i.e. surgical procedures, diagnosis of a mortal illness), casual methods of data collection and reliance on retrospective reports lead one to be cautious about the evidence for the role of androgen in human female sexuality.

Adding to the confusion in the literature to date on the role of androgen in human female sexuality are the studies which indicate that ovarian hormones (estrogen and progesterone) have been reported to increase libido in women (Bakke, 1965; Kennedy, 1973). The belief that female sexuality is largely independant of the influence of estrogens needs to be reconsidered in the light of more recent findings. There are studies which indicate that extremely small amounts of estrogen are all that are needed to attain "sexual tuning" of the organism (Kane, Lipton & Ewing, 1969). Michael (1962) implanted micro amounts of estrogen directly into the hypothalamus of the cat and was able to induce in the animal a state of sustained sexual receptivity without any other physiologic signs of estrus. This data would seem to indicate the possibility of a considerable quantitative difference in need for hormones between the hypothalamus and the secondary sexual structures.

In this context it is important to recall that estrogen is secreted in small amounts by the adrenal gland. The possibility emerges, in light of this knowledge, that it is the loss of endogenous estrogen which accounts for the drastic decline in libido after adrenalectomy. This would be consistent with Waxenberg's data which emphasize the critical role of the adrenals in female sexuality in the absence of the ovaries. One might hypothesize that it is the small amount of adrenal estrogen, not adrenal androgen which is the critical factor in the maintenance of female sexual behavior. Finally, another complicating factor which must be taken into consideration regarding the theoretical issue of sex hormone effects on behavior is the fact that biotransformation of these hormones takes place in the body. The ultimate metabolic by-products of the hormones which actually effect the changes being seen or reported may be different from what was originally administered.

The issue of the effect of androgen in human female sexuality is of utmost relevance in the therapeutic management of the menopause. At the present time, clinical decisions regarding which hormone or combination of hormones will be most efficacious in the treatment of the menopausal woman are heavily dependent on the individual physician's clinical judgment regarding the effects of the various hormonal preparations available as well as on their perception of the patient's personality characteristics. Insofar as these decisions are not tied to an empirical base, such clinical judgments are highly variable,

often resulting in trial-and-error type treatment until the proper preparation appears to work both subjectively and objectively with any given patient.

At present there are no studies in the literature which have systematically documented changes in female sexual behavior, mood, or somatic complaints relative to baseline or to a control group as a result of exogenous androgen administration. It was the goal of the current investigation to examine under controlled conditions, the behavioral effects of an estrogen preparation, of an estrogen-androgen combination and of a placebo in menopausal women over the course of four months. It was hypothesized that (1) the estrogen-androgen combination would result in an enhancement of libido manifested by an increase in sexual functioning; (2) the estrogen-androgen combination would result in an increased sense of well-being, energy level, appetite and sleep as compared to the estrogen-alone preparation and (3) the estrogen-alone preparation and the estrogen-androgen combination would be equally effective in alleviating somatic complaints but that there would be no change in these symptoms over time in the control group.

Method

Subjects

Eight patients who complained of menopausal symptoms (hot flushes, fatigue, irritability, insomnia) were recruited from the practice of the head of the Department of Obstetrics and Gynecology, Jewish General Hospital, Montréal, Québec. Three other subjects decided to defer treatment after the initial interview with the experimenter. Three additional subjects failed to comply with the experimental procedure and withdrew from the study after two weeks of completing questionnaires. None of the subjects had ever received hormone replacement therapy in the past nor had they had any previous gynecological surgery. The subjects were all in good health; except for menopausal symptomatology, they had no other somatic complaints. Apart from two subjects who were taking Diazepam 5 mg at bedtime, none of the subjects were receiving any medication at the time of their recruitment into the study. All subjects had intact marriages and all of their husbands were in good general health. The subjects ranged in age between 42 and 53 years with a mean of 49 years.

Experimental Design

A three group pretest-postest design was used. These consisted of an estrogen-alone group, an estrogen-androgen combination group (combined drug group) and a placebo group. After the initial interview with the experimenter, subjects who met criteria of suitability were asked to complete a standard questionnaire daily for a one-

month period to provide baseline data. At the end of one month, each subject was randomly assigned to one of the three treatment groups. There were three subjects in the placebo group, two in the estrogen-alone group and three in the combined drug group. The mean age of subjects was 48.3 years in the placebo group, 49 years in the estrogen-alone group and 49.6 years in the estrogen-androgen combined group. Daily monitoring by means of questionnaire completion by subjects in all groups proceeded for the next three months. Both the experimenter and the physician were blind to the subjects' group assignment. The design as well permitted within group and between group comparisons. Random assignment of subjects to treatment groups precluded the possibility of selection on the part of the physician as a contaminant of mood and behavior change resulting from hormone replacement therapy. The inclusion of a control group permitted an assessment of the contribution of factors such as the effects of self-monitoring, passage of time and expectations of benefits resulting from the administration of a monthly injection.

Materials

Instruction and Consent Form (Appendix A)

Initial Interview Form (Appendix B)

Daily Self-Report Questionnaire (Appendix C)

Estrogen Preparation (Delestrogen, Ayerst)

Estrogen-Androgen Preparation (Climacteron, Merck)

Placebo (Sesame oil)

Daily Self-Report Questionnaire

The Daily Self-Report Questionnaire was the major instrument used to measure change during the course of this study. Some questions had been used previously (Markowitz, 1977) but most were devised especially for this study in order to permit sampling of the specific psychological and somatic areas of interest. Many questions dealt with quantifiable, discrete behaviors such as the number of times a subject left the home per day for business or social purposes (question 13a). Other questionnaire items required the subjects to rate a specific mood or behavior for each previous 24 hour-period on a bipolar rating scale which had a range of one to seven. Each end of every scale had a verbal description of the mood or behavior in question. Subjects were asked to fill out the questionnaire at a convenient but similar time each day to aid in establishing questionnaire completion as a daily routine.

Computation of Drug Dosages

It was necessary to ensure that subjects in both the estrogen-alone group and in the estrogen-androgen combination group would receive equal amounts of estrogen per dose. Different dosages of estrogen could have led to differential alteration of those symptoms directly resulting from estrogen depletion thus confounding the findings. The procedure used was to calculate the molecular weights of the salts to which each of the estrogen preparations was bound and to subtract this sum from the molecular weight of the total compound. The residual represented the

amount of free estradiol in each drug. After the amount of free estradiol in each drug was thus obtained, it was determined that 0.63 ml of the estrogen-alone preparation was equivalent to the amount of unbound estradiol in 1 ml of the estrogen-androgen combination drug (Appendix D). Therefore subjects in the combined group received 1 ml of the estrogen-androgen preparation and subjects in the estrogen-alone group received 0.63 ml of estrogen intramuscularly each month.

Subjects in the placebo group received 1 ml of sesame oil intramuscularly each month. Sesame oil was selected because it is used as the suspension for the estrogen-androgen preparation.

Procedure

During the course of an office visit, the gynecologist determined whether a patient's presenting complaints rendered her a suitable candidate for hormone replacement therapy. If the patient as well met the remaining criteria for recruitment into the study (no previous hormone replacement therapy for at least one year prior to recruitment, intact ovaries, married or availability of a steady partner and partner in state of reasonably good health), she was presented with the Instruction and Consent Form and asked to contact the experimenter. In order to avoid the possibility of unstandardized information being conveyed to the subject prior to recruitment into the study, the physician did not discuss the experimental procedure with the subject. During the initial interview with the experimenter, questions pertaining to the information sheet were discussed and signed consent relating to participation in the study was obtained.

Information concerning socioeconomic status, number of children, health of spouse, history of past illness, date of onset and description of current symptoms, and degree to which symptoms interfered with daily functioning were then elicited (Initial Interview Form). After the information gathering was completed the experimenter gave the following instructions.

"We know that the drugs used to treat symptoms such as yours can be helpful. However, you doctor and I feel that more information is needed concerning their general effects. Therefore before you are started on the drug it will be useful to establish your current level of functioning in several areas. These include your general state of health and well-being, your sexual life and how you are getting along with other people. I am going to ask you to fill in one of these forms at home every morning before 10 A.M. and to mail it to me in the stamped addressed envelopes I will be giving you. This must be done every day for a month after which time you will return to your doctor's office and be started on drug therapy. You will then continue to fill out the forms daily for three additional months while you will be receiving the drug. You may find it hard work at first, but previous experience has shown us that women soon find it easy to do if they do it at the same time each day. Some of the items on the questionnaire may not be pertinent to you. Research has shown that there is a marked individuality of patterns in sexual functioning. What we want to do is establish each person's individual pattern. These questionnaires will be kept

strictly confidential - no one other than myself will have access to them. Let's go over one of the forms together to make sure you understand what is required and so that I may answer any questions you may have about it."

Each subject was then given 30 questionnaires and 30 addressed, stamped envelopes. An appointment was made for the subject to return to the physician's office exactly one month following the initial interview with the experimenter. After this one month period of baseline monitoring, a drug appropriate to the group to which the subject had been randomly assigned was administered intramuscularly by the office nurse and an additional 30 questionnaires and envelopes were supplied. The exact procedure (i.e. visit with office nurse for drug administration, and issuing of a month's supply of questionnaires and envelopes) was repeated once a month for the two following months. Daily questionnaire completion by all of the subjects was maintained by frequent phone calls from the experimenter. Drugs were administered to the subjects free of charge.

Results

In order to assess the reliability of the Self-Report Questionnaire, Pearson product-moment correlation coefficients (r) (Mendenhall and Ramey, 1973) were computed between ratings by all eight subjects on selected items at two points in the baseline period. Sums of scores or ratings from each subject over the seven days of week one and week four on six questionnaire items were used to calculate the correlations; the first and last weeks of the baseline months were chosen in order to permit an assessment of reliability over a two week time span in a period when reasonable stability in scores might have been expected. Pearson correlations of selected items on the Self-Report Questionnaire appear in Table I. As can be seen from this table, correlations ranged from .52 to .93.

Table I

Pearson Correlations Between Week One and Week Four of Baseline for Selected Items on the Self-Report Questionnaire (N 8)

Measure	r
Sense of Well-being	.87
Appetite	.89
Sleep	.92
Level of Activity	.93
Energy Level	.92
Times Left the Home	.52

There were three subjects in the placebo treatment group, two in the estrogen-alone group and three in the estrogen-androgen combined group. The data which were subjected to statistical analysis consisted of mean daily scores for each subject on each variable computed from the month of baseline monitoring and each of the subsequent three months of treatment. The number of days in each month was variable both within and between subjects because subjects were not all run simultaneously nor was it possible to schedule the administration of injections exactly 28 days apart. Therefore means were computed by dividing the total score of the variable in question for one month by the number of days in that particular treatment month for each subject, thus normalizing the data. Group means were computed by summing the mean scores for all subjects in a group and dividing by the number of subjects in that group.

Mean scores for each treatment group for each of the four months were analyzed using a Balanova program for a 3 (Treatment Group) x 4 (Number of Months) mixed model design analysis of variance (ANOVA) for unequal N's. There were therefore three main factors in the design; treatment group (A), time (B) and subjects (S). Subjects were nested in treatment group and crossed with time.

Sexual Functioning

ANOVA Summary Tables for degree of sexual desire, number of sexual thoughts or fantasies, frequency of specific sexual activity, level of sexual arousal and number of orgasms during sexual activity appear in Appendix E. There were no significant effects for treatment

group or time and no significant interaction effects on any of these variables. Tables of treatment group means of these measures appear in Appendix E as well.

Somatic Complaints

ANOVA Summary Tables for headaches and nausea appear in Appendix F. Again, no significant group, time or interaction effects were obtained. Therefore there were no systematic reductions or increases in number of headaches or in ratings of nausea observed over the four months of the study.

Subjects were instructed to record the number of hot flushes they had experienced each day by circling one of the five frequency intervals provided on the questionnaire. The intervals were: None, 1-4, 5-10, 10-20, and over 20. The mean frequency of hot flushes per day was computed by summing the products obtained by multiplying the mean frequency reported by each subject by the midpoint of each interval and then dividing by the number of days in the treatment month. The ANOVA Summary Table for mean frequency of hot flushes appears in Table II.

Table II

Frequency of Hot Flushes: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	13.97	3.48
Subjects	5	4.01	
Time	3	4.02	2.18
Treatment Group x Time	6	9.85	5.34*
Time x Subjects	15	1.84	

* $p < .01$

Table III

Mean Frequency of Hot Flushes:

Summary Table of Post-Hoc Tests of Simple Main Effects

Source	SS	df	F
Time at Placebo Group	2.783	3	.5029
Time at Estrogen Group	3.04	3	.5493
Time at Combined Group	65.32	3	11.803*

* $p < .01$

The graph of these data (figure 1) however, illustrates a large discrepancy between the baseline frequency of hot flushes in the combined drug group (7) and the estrogen-alone and placebo groups (mean frequencies of 0.6 and 0.5 respectively) whose baselines were almost identical. At the end of month three of treatment, the mean daily frequency of hot flushes was nearly the same for each of the three treatment groups. Tukey post-hoc tests (Kirk, 1968) (Table IV) showed that significant decreases occurred only between baseline and each month of treatment ($p < .05$). There were no significant changes between the treatment months themselves.

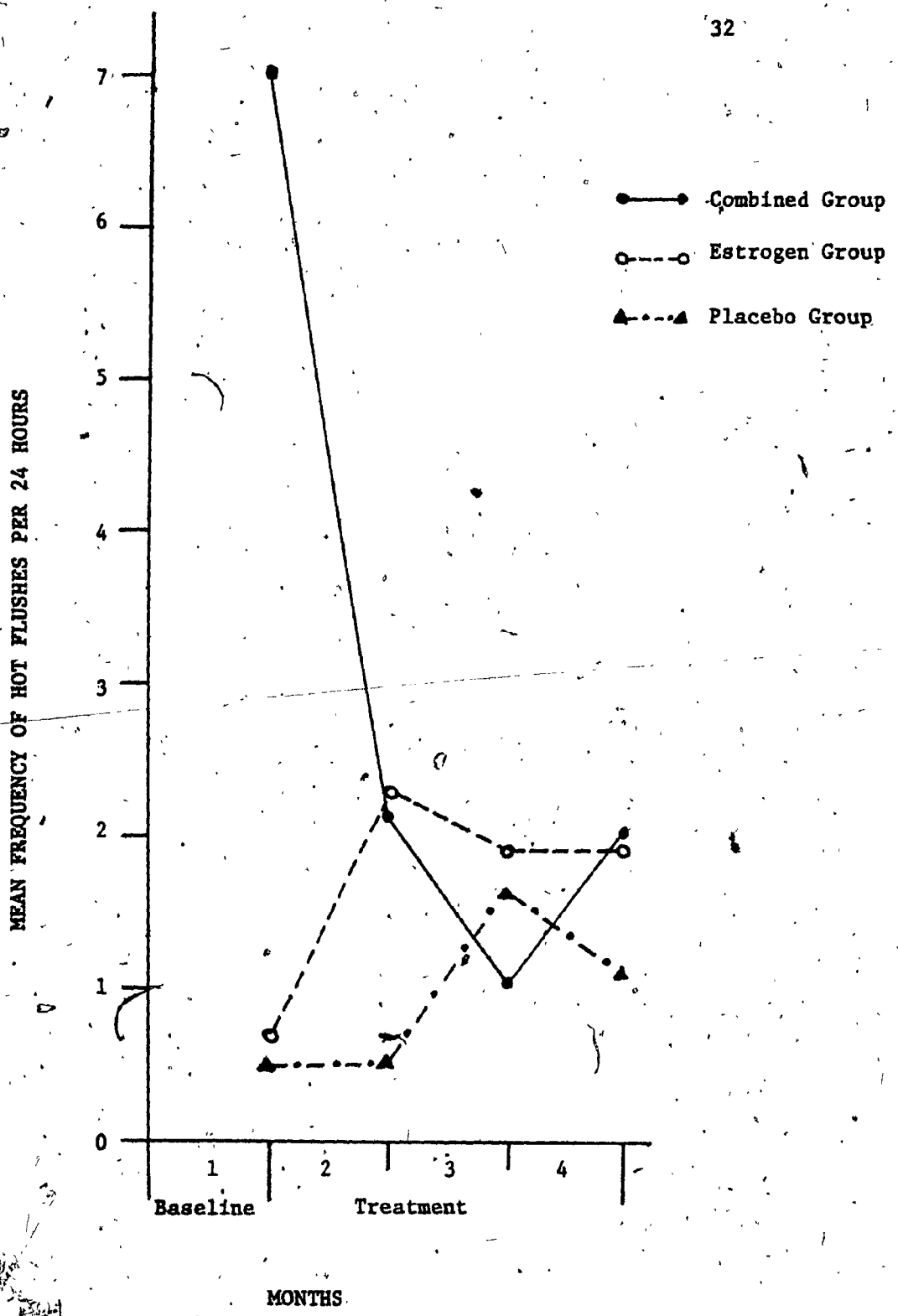

FIGURE 1: FREQUENCY OF HOT FLUSHES

Table IV

Mean Frequency of Hot Flushes:

Post-Hoc Analysis with Tukey Tests Between the Means of Treatment Months

Comparisons	Mean Difference	p
Month 4 - Month 3	1.68 - 1.47	NS
Month 4 - Month 2	1.68 - 1.58	NS
Month 4 - Month 1	1.58 - 2.98	$< .05$
Month 3 - Month 2	1.47 - 1.58	NS
Month 3 - Month 1	1.47 - 2.98	$< .05$
Month 2 - Month 1	1.58 - 1.4	$< .05$

Table V

Sleep: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	6.49	1.60
Subjects	5	4.07	
Time	3	0.57	7.76*
Treatment Group x Time	6	0.59	7.95**
Time x Subjects	15	0.07	

* $p < .01$

** $p < .001$

The ANOVA Summary Table for mean ratings by subjects of their sleep quality appears in Table V. A significant effect for time ($p < .01$) was obtained. There was as well a highly significant group x time interaction ($p < .001$). Post-hoc tests of Simple Main Effects (Table VI) showed that there was a highly significant increase over time in ratings of sleep quality in the combined drug group ($p < .001$) whereas there were no significant changes in either the estrogen-alone or in the placebo groups. A graph of these data appears in Figure 2.

Table VI

Sleep: Summary Table of Post-Hoc Simple Main Effects

Source	SS	df	F
Time at Placebo Group	.011	3	.0045
Time at Estrogen Group	.131	3	.5914
Time at Combined Group	5.095	3	23.0002*

* $p < .001$

Mean ratings of appetite were analyzed by ANOVA (Table VII). There was a significant change in appetite over time ($p < .01$) and as well a significant group x time interaction ($p < .02$). Post-hoc tests of Simple Main Effects (Table VIII) showed that there was a highly significant increase in appetite ratings in the combined drug group across time ($p < .001$). No significant changes were demonstrated on this

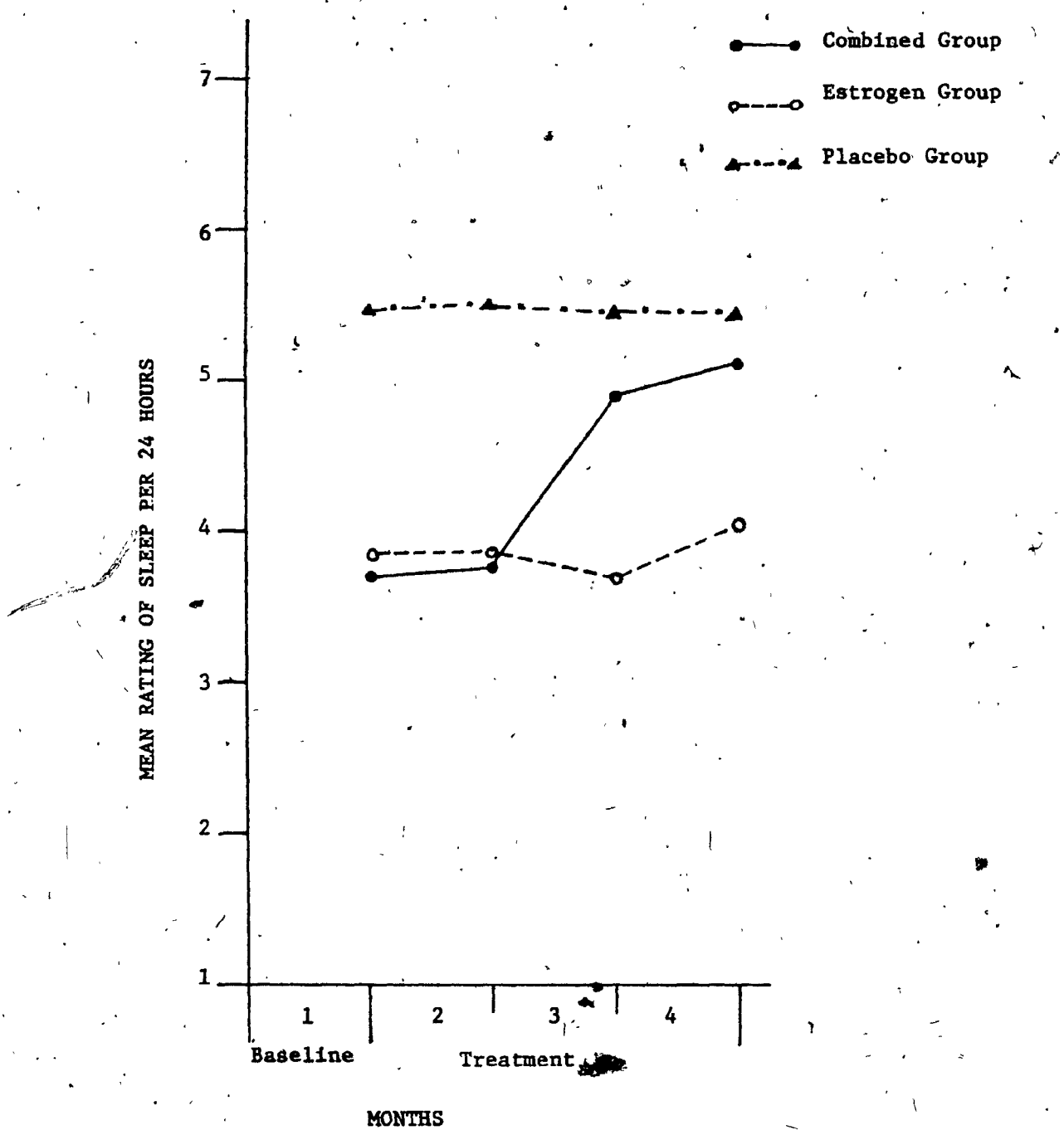

FIGURE 2: QUALITY OF SLEEP

Table VII

Appetite: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	3.52	1.42
Subjects	5	2.48	
Time	3	0.65	6.15**
Treatment Group x Time	6	0.35	3.29*
Time x Subjects	15	0.11	

* $p < .02$

** $p < .01$

measure in either of the other two treatment groups. Stability in appetite ratings across time in the placebo and estrogen-alone groups and increase across time in the combined drug group can be seen in a graph of these data (Figure 3).

Table VIII

Appetite: Summary Table of Post-Hoc Analysis of Simple Main Effects

Source	SS	df	F
Time at Placebo Group	.596	3	1.869
Time at Estrogen Group	.17	3	.533
Time at Combined Group	3.298	3	10.3431*

* $p < .01$

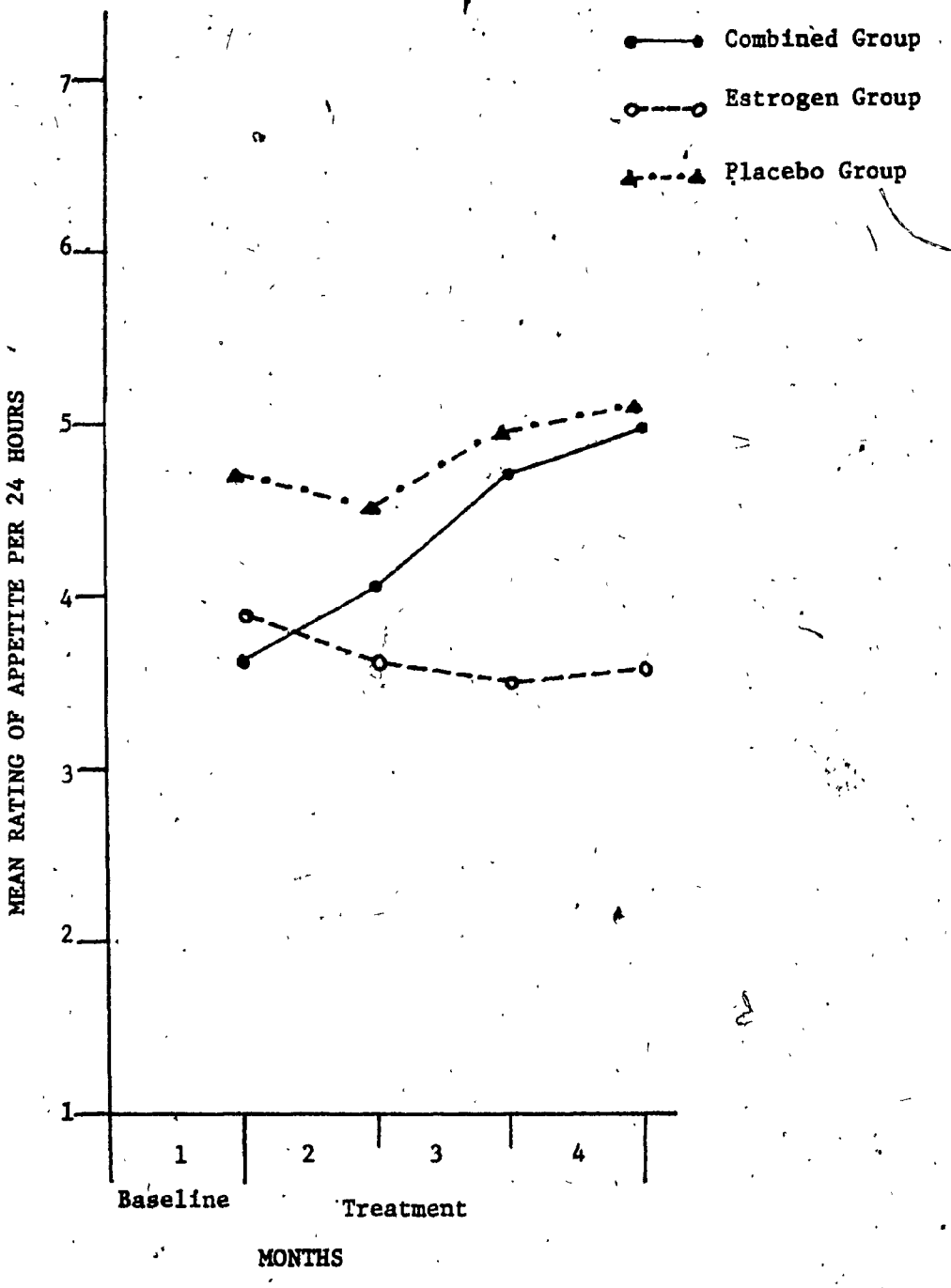

FIGURE 3: QUALITY OF APPETITE

Sense of Well-Being and Mood

The ANOVA Summary Table for ratings of sense of well-being appears in Table IX. There was a significant change in sense of well-being over time ($p < .04$). As well, a group x time interaction was

Table IX

Sense of Well-Being: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	4.77	1.55
Subjects	5	3.08	
Time	3	0.47	3.43 **
Treatment Group x Time	6	0.35	2.60 *
Time x Subjects	15	0.14	

* $p < .06$

** $p < .04$

significant at the .06 level. Post-hoc tests of Simple Main Effects (Table X) revealed that the combined drug group experienced a significant increase in sense of well-being over the four month course of the study ($p < .01$). No significant changes were found in the other two groups. Because the interaction attained only a .06 level of significance, this analysis provides probable evidence for an increment in sense of well-being as a result of the estrogen-androgen combined drug. It might be expected that with a larger sample size, the combined drug would account for a first-order group x time interaction at a conventional significance level.

Table X

Sense of Well-Being:

Summary Table of Post-Hoc Simple Main Effects

Source	SS	df	F
Time at Placebo Group	.498	3	1.217
Time at Estrogen Group	.136	3	.332
Time at Combined Group	2.879	3	7.0799*

* $p < .01$

A graph of these data (figure 4) shows the increase in ratings of sense of well-being in the combined drug group from baseline to the end of month three of treatment.

The ANOVA of the mean daily self-ratings of general mood (Appendix G) showed no significant changes over time for any group. Neither exogenous hormone administration nor placebo significantly affected mood during the four month course of the study.

Energy Level, Level of Activity and Number of Times Left the Home.

Ratings of energy level were analyzed by means of an ANOVA (Table XI). Results showed that there was a significant change across time ($p < .001$) as well as a significant group x time interaction ($p < .003$). Post-hoc tests of Simple Main Effects (Table XII) revealed that subjects in the combined drug group reported a significant increase in energy level

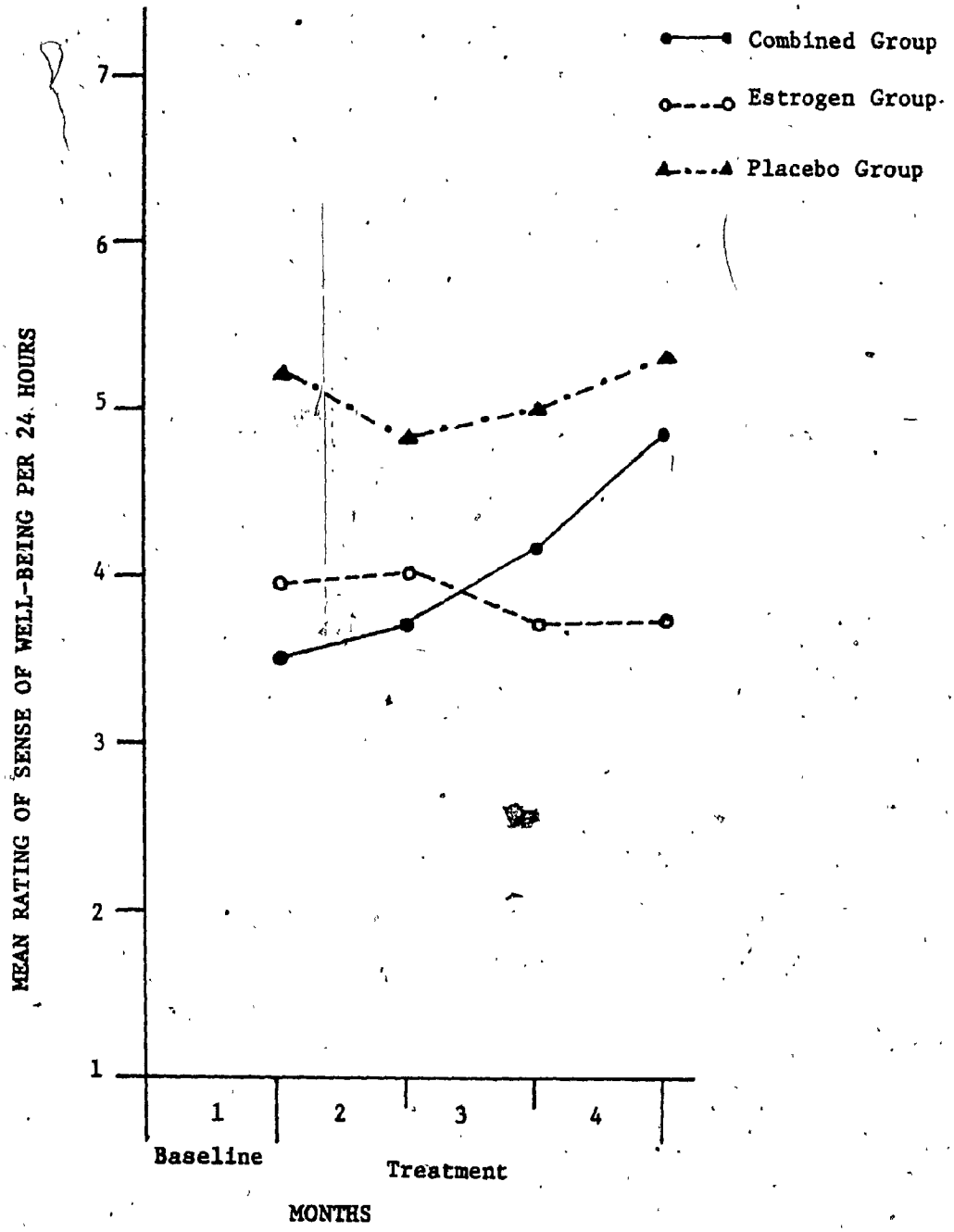

FIGURE 4: SENSE OF WELL-BEING

($p < .001$). There were no significant changes across time in energy ratings for either of the other two groups. A graph of these data are presented in Figure 5.

Table XI

Energy Level: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	6.17	1.73
Subjects	5	3.56	
Time	3	0.71	8.96*
Treatment Group x Time	6	0.44	5.60**
Time x Subjects	15	0.08	

* $p < .001$

** $p < .003$

Table XII

Energy Level:

Summary Table of Post-Hoc Analysis of Simple Main Effects

Source	SS	df	F
Time at Placebo Group	.881	3	3.703
Time at Estrogen Group	.07	3	.882
Time at Combined Group	1.2407	3	15.6437*

* $p < .001$

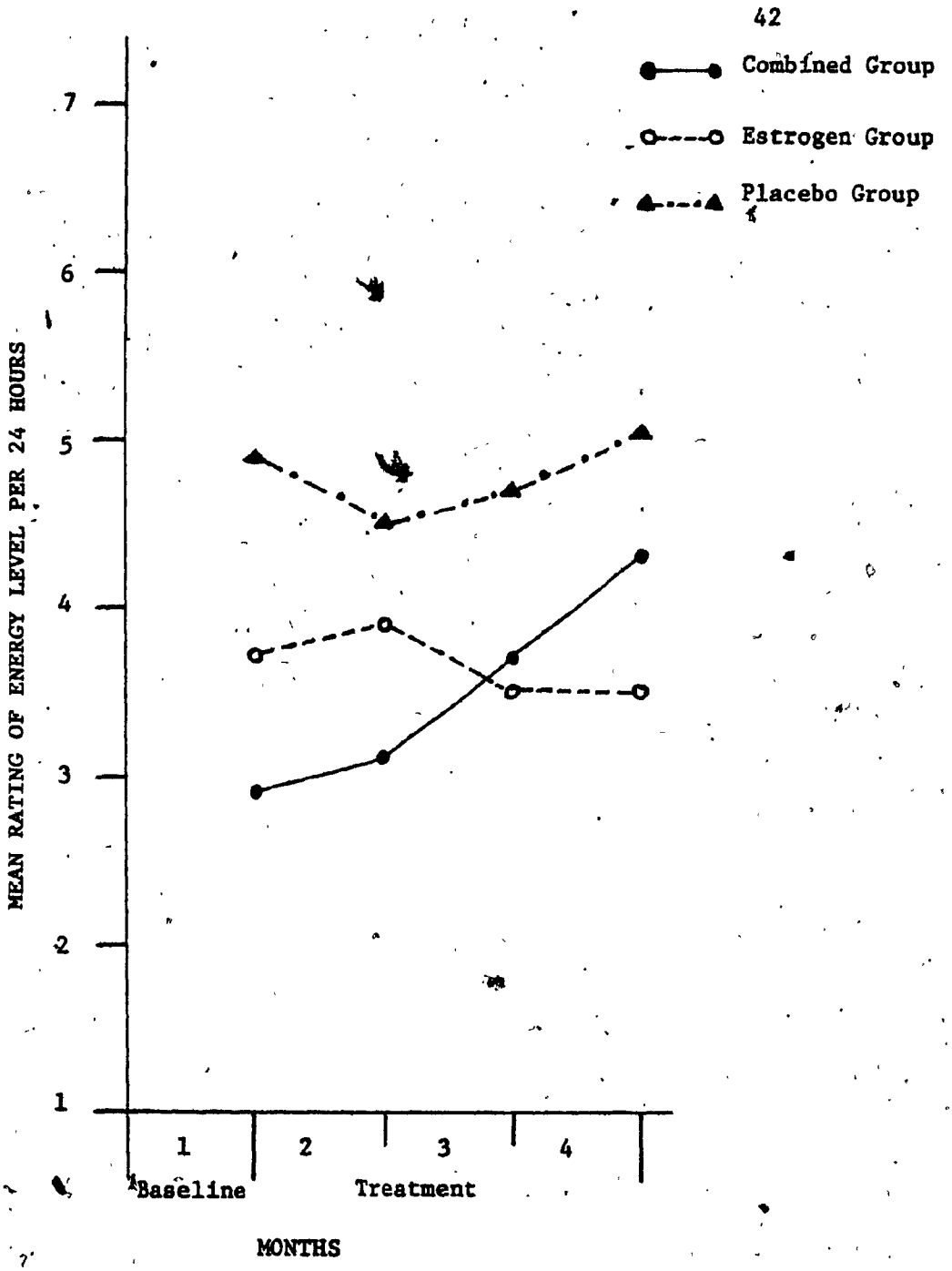

FIGURE 5: ENERGY LEVEL

The ANOVA Summary Table for level of activity (Table XIII) shows that there was a significant change over time ($p < .03$). A group x time interaction, though not significant at the conventional .05 level, attained significance at the .09 level. On this basis, post-hoc tests of Simple Main Effects were carried out (Table XIV). Results

Table XIII

Level of Activity: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	.57	1.53
Subjects	5	1.03	
Time	3	1.23	3.79*
Treatment Group x Time	6	0.74	2.27
Time x Subjects	15	0.32	

* $p < .03$

Table XIV

Level of Activity:

Summary Table for Post-Hoc Analysis of Simple Main Effects

Source	SS	df	F
Time at Placebo Group	1.648	3	1.69
Time at Estrogen Group	.092	3	.325
Time at Combined Group	6.361	3	6.5277*

* $p < .01$

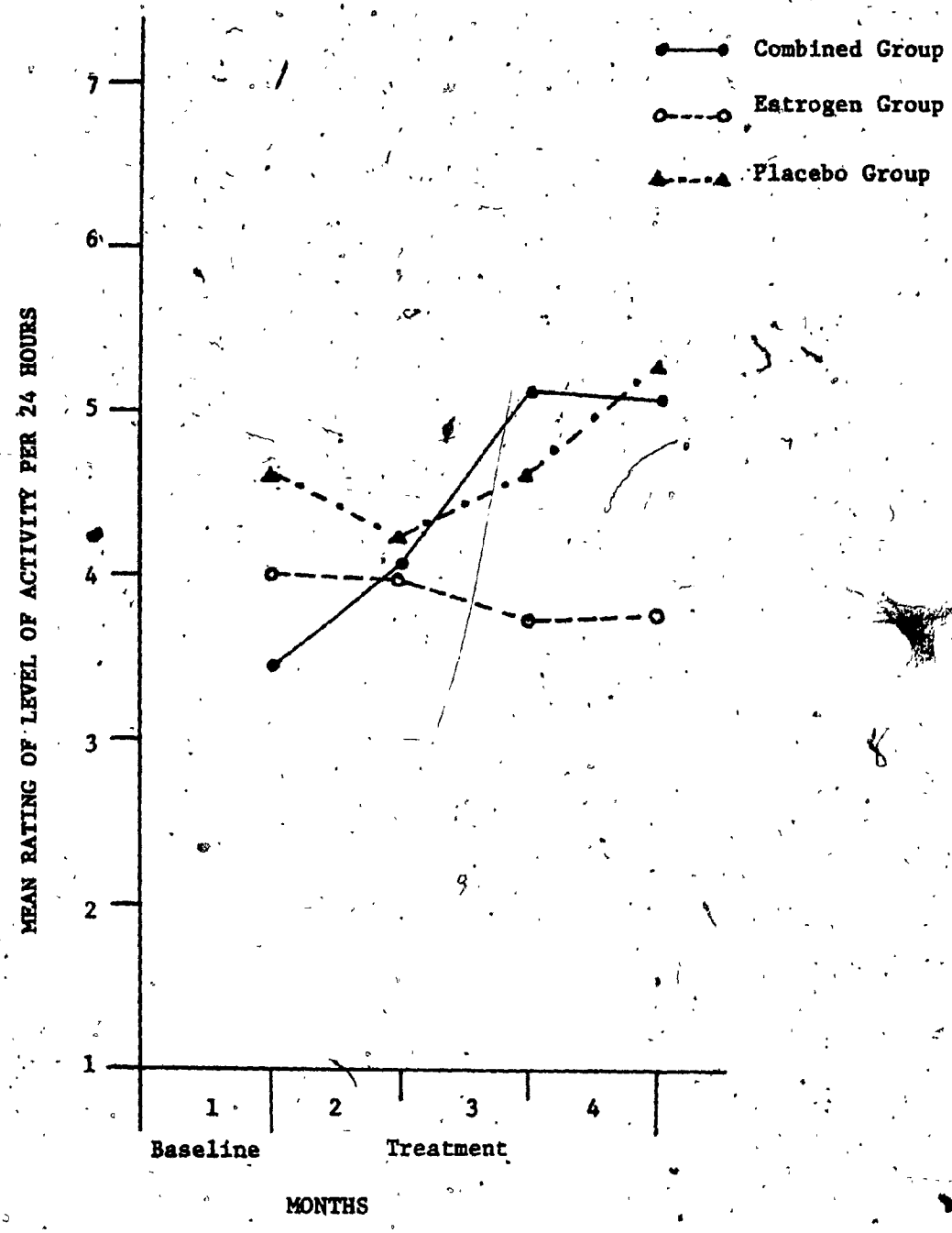

FIGURE 6: LEVEL OF ACTIVITY

showed that there was a significant increase in level of activity in the combined drug group across time ($p < .01$). There were no significant changes in either the estrogen-alone or in the placebo group. These post-hoc analyses provide probable evidence that the combined estrogen-androgen drug caused an increase in level of activity. It may be hypothesized therefore, that with a larger sample size, the combined drug would produce a first-order interaction effect at a conventional level of significance. These data are presented graphically in Figure 6.

Another measure designed to monitor level of activity required subjects to record daily the number of times they left the home for business or social purposes. The ANOVA on reported number of times subjects left home (table XV) showed only a significant interaction between groups and time ($p < .02$). Post-hoc analysis of the Simple

Table XV

Number of Times Left the Home: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	.92	.57
Subjects	5	1.62	
Time	3	.01	.20
Treatment Group x Time	6	.16	3.29*
Time x Subjects	15	.05	

* $p < .02$

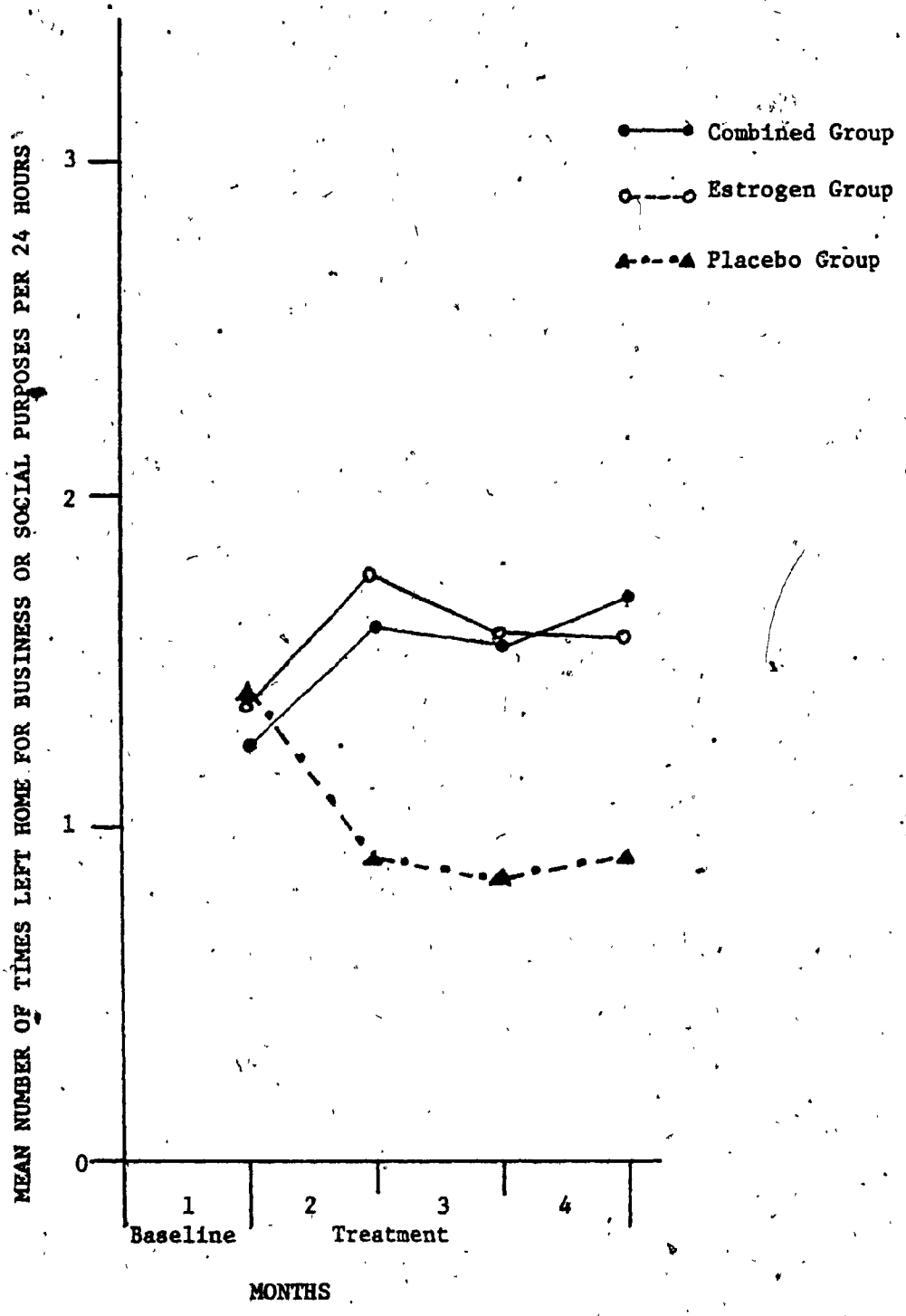

FIGURE 7: NUMBER OF TIMES LEFT HOME FOR BUSINESS OR SOCIAL PURPOSES

Main Effects (Table XVI) showed that there was a significant decrease in the number of times a subject left the home per 24 hours in the placebo group over the four months of the study ($p < .05$). There were no significant changes on this variable in either of the hormone treatment groups. Figure 7 illustrates these data in a graph.

Table XVI

Number of Times Left the House for Business or Social Purposes: Summary Table of Post-Hoc Tests of Simple Main Effects

Source	SS	df	F
Time at Placebo Group	.531	3	3.687*
Time at Estrogen Group	.1455	3	1.0105
Time at Combined Group	.272	3	1.8889

* $p < .05$

Number of Arguments

ANOVA on the mean number of arguments in which subjects had actively engaged per 24 hours showed a significant change over time ($p < .004$) (Table XVII). There was no significant group x time interaction effect on this measure. Thus, treatment group did not have a differential effect on the number of arguments actively engaged in. Decreases on this measure in all three treatment groups over the four month course of the study can be seen in Figure 8.

It is of interest to inspect the graphs of those variables in which post-hoc Simple Main Effects tests isolated significant changes

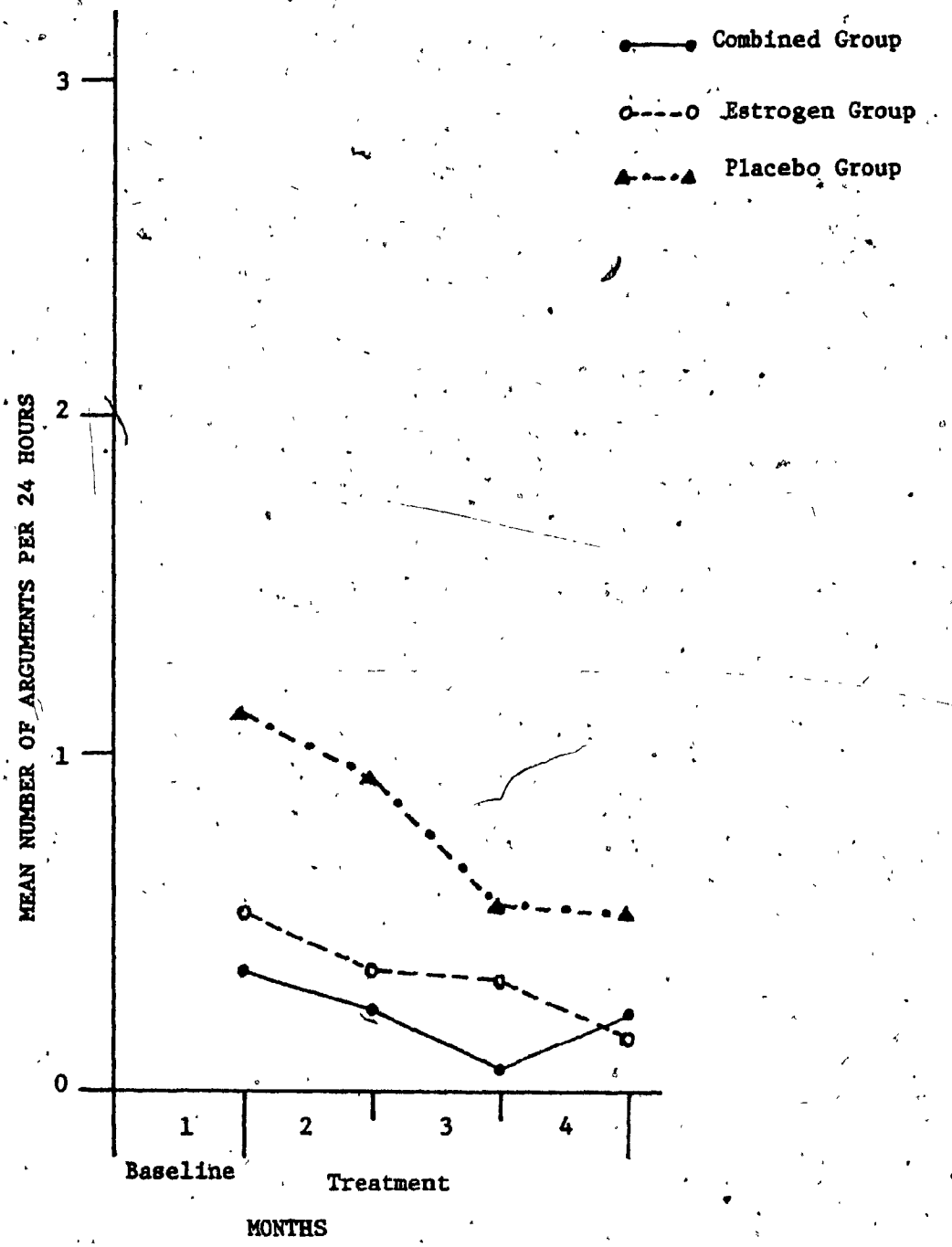

FIGURE 8: NUMBER OF ARGUMENTS

Table XVII

Number of Arguments: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	1.05	1.03
Subjects	5	1.10	
Time	3	.25	6.76*
Treatment Group x Time	6	.04	1.05
Time x Subjects	15	.04	

* $p < .004$

in the combined drug group. The graphs suggest a fairly uniform time course of the combined drug's action. There appears to be no change on any of the mean ratings between baseline and the end of month one of treatment on any of these variables; changes seemed to have occurred only after the second injection had been administered. However, when Tukey procedures were employed to evaluate the observed month to month changes in the treatment phase of the experiment, no significant differences were obtained. Thus, indications that drug effects take place only after the second injection cannot be statistically supported as yet.

Discussion

Several statistical and design considerations should be kept in mind in interpreting the results of this experiment. The number of subjects per treatment group was small; three subjects received placebo, two estrogen-alone and three, the estrogen-androgen combination. Glass and Stanley (1970) point out that statistical analysis of data derived from small samples leads to increased risk of sampling error due to greater variability. Experimental data from small samples are thus disposed to a Type II Error, namely failure to reject the null hypothesis when it is false. The implication for this study is that findings for certain variables of no significant differences between treatment groups are less conclusive than positive results of experimental manipulations. On the other hand, the risk of sampling error in this experiment was reduced by the fact that monthly group means for each variable were calculated from a large number of observations (approximately 30) per subject. Additionally, baseline data in this study provided evidence concerning both within and between group variability.

Graphs depicting the variables which showed significant change demonstrate that the baselines of the two hormone groups are nearly similar in almost all instances. However, mean scores of the placebo group are much higher than the two hormone groups at baseline and show a marked stability over time. This phenomenon occurred despite initial random assignment of subjects to groups. It may be hypothesized that placebo group ratings were artifactually high when one compares them to

baseline scores of the two drug groups and would, with a larger N, approach similar levels at baseline as those of the two drug groups. Nevertheless, even though statistical analysis did show significant change in several variables in the combined drug group, caution must be exercised in interpretation of these findings in the context of all of the data. Results of this study therefore ought to be regarded as preliminary findings which await confirmation with a larger sample size.

The method of data collection in this experiment imposed certain limits on the nature of the population which could be sampled. Because the procedure required subjects to complete a questionnaire daily, only women who were able and willing to comply with this procedure were represented in the study. Results therefore may not be generalizable to other segments of the population. A further caveat concerns drug effects obtained in this study. The changes observed are a result of a three month course of hormone replacement therapy; it is possible that long-term hormone supplementation would result in somewhat different effects on sexual functioning, mood and behavior.

The data of this experiment were derived from self-reports in the form of questionnaires which were completed daily by subjects. Self-report data, as well as being economical to gather, are perhaps one of the best measures of subjective states such as well-being, nausea or sexual feelings. The quality of such evidence however is also a function of the experimental design which has provided it. The presence

in this study of a group receiving placebo whose self-reports could be compared with those of groups receiving two different active drug treatments constituted a rigorous test of drug induced differences. This of course does not deny the worth of objective performance based assessments which could provide additional kinds of information on the effects of exogenous hormones.

The major findings of this study are that the estrogen-androgen combined drug resulted in a significant increase in energy level, appetite and quality of sleep over the four month period of this experiment. There is as well evidence that subjects in the combined drug group experienced a significant increase in sense of well-being and level of activity. These findings are consistent with the known anabolic effects of androgen (Goodman and Gilman, 1975). Subjects who received the estrogen-alone preparation or placebo did not show any significant changes on these same measures. The seemingly logical conclusion that it was the androgen component of the estrogen-androgen combined drug which was responsible for these significant changes in mood and behavior in light of the absence of significant change on these same measures in the estrogen-alone group would be misleading however. Knowledge concerning the metabolism of androgens precludes such a cause and effect statement. Animal studies provide evidence that a number of physiological and behavioral effects of testosterone appear to rely upon its conversion to other metabolic forms. Aromatization of testosterone results in the

formation of estrogens, whereas ring-A reduction results in the formation of androgens that are nonaromatizable, i.e., not metabolized to estrogens (Dorfman and Unger, 1965). Paup, Coniglio, and Clemens (1974) explored the behavioral effects of neonatal administration of either aromatizable or nonaromatizable androgens and of estrogen in female hamsters who were subsequently ovariectomized. The results indicated that the females treated with the aromatizable androgens (androstendione and free testosterone) mounted significantly more than did oil-treated controls. Females treated with nonaromatizable androgens (androsterone or dihydrotestosterone) did not differ from the controls. All estrogen treated females displayed significantly more mounts than the controls. It was concluded that the increased masculine response potential in the female hamster was dependent upon estrogen or androgen changed to estrogen. In light of such evidence for the differential effect of androgens on behavior as a result of their differing biochemical properties, it cannot be concluded that significant changes in mood and behavior in this study as a result of the combined estrogen-androgen drug are due to the androgen alone. The two hormones (estrogen and androgen) may have caused the observed changes by having acted synergistically. Though the biochemical basis of these changes are not clear, this is the first evidence from a controlled experiment of effects of administering an estrogen-androgen combined drug to human females.

It is interesting to note that number of headaches and reports of nausea did not decrease significantly during the study in any of the treatment groups. It is probable that the significant decrease in the mean frequency of hot flushes in the combined estrogen-androgen group from baseline to the end of month one of treatment was due to an elevated baseline in this group, in turn probably an artifact of the small sample size; all groups reported similar rates (range of 1.2 - 2 per day) of hot flushes at the end of the third month of treatment. The findings on nausea, headaches and hot flushes allow the observation that although hormone replacement therapy did not appreciably affect the intensity of certain physical symptoms, it was clear in this investigation that the combined estrogen-androgen drug did promote a general feeling of increased well-being and an improvement in certain parameters of physical functioning in those subjects to whom it was administered.

The menopausal literature provides evidence that vasomotor instability and atrophic vaginitis are a result of estrogen deficiency and are the only two symptoms which have been found to be reliably associated with hormonal changes at the time of menopause (Utian, 1972; Hart and Durno, 1973; Ross and Vande Wiele, 1974). It has already been mentioned that the finding of a significant decrease in hot flushes in the combined drug group does not allow for between group comparison. Caution should be exercised in interpreting the significant change in number of hot flushes in the combined drug group as evidence of a diff-

erential drug effect due to initial group differences at baseline. There was as well no significant decrement in frequency of hot flushes in the estrogen-alone group in this study. Since vasomotor instability is a function of decreased estrogen in menopausal women (Ross and Vande Wiele, 1974) and is said to respond dramatically to exogenous estrogen (Eisdorfer and Raskind, 1975), it was expected that frequency of hot flushes would decrease significantly in the estrogen-alone group over time. The data of this study do not support this expectation; there were no significant changes in the mean frequency of hot flushes in the estrogen-alone group as determined by the post-hoc test of Simple Main Effects. It is possible that the sample size was too small to permit significant change in this symptom to be manifested.

The significant decrease in the number of arguments per 24 hours over time by drug and placebo groups was a puzzling finding. The assumption in menopause literature has been that irritability is a function of estrogen deficiency (Rhoades, 1967). Thus the expectation has been that exogenous estrogen would reduce irritability and constitutes part of the rationale for hormone supplementation during the menopause. However subjects in the placebo group showed the same decreasing trend in number of arguments as those in the two active hormone groups. To the extent that the number of arguments a subject engages in per 24 hours is a measure of irritability, the assumption of the effectiveness of hormone replacement therapy in alleviating this complaint was not substantiated in this study. It is possible that the decrease in the number

of arguments over time irrespective of treatment group is a result of the process of self-monitoring itself. It remains to be seen whether an objective measure of irritability rather than the subjective one used in this study would detect differential effects favouring drug over placebo.

In an attempt to measure changes in physical activity, subjects were asked to record on a daily basis, the number of times they left the home for business or social purposes. The finding of a significant decrease in the number of times subjects in the placebo group left the home and of no significant change on this measure in either of the two hormone groups over time leads to the possible conclusion that hormone treatment acted in some manner to maintain daily life routine. However, it was determined that the stability of this measure was poor. It is likely that numerous situational variables affect the number of times a woman leaves the home per 24 hours and therefore this measure cannot be regarded as a reliable nor a specific index of physical activity.

This investigation provides suggestive evidence for a uniform time course in the action of gonadal hormone administration. It may be recalled that on all of the variables in which the estrogen-androgen group changed significantly, drug effects appeared only after the second injection. This is of potential theoretical and clinical importance. To date, there is little if any information concerning the time course of sex hormone action in humans; knowledge regarding the relationship of optimal blood levels of hormone and manifestations of hormone effects

is scanty. Both physicians' and patients' clinical impressions provide evidence that side effects of hormone supplementation (breast tenderness, weight increase) in the absence of improvements in symptoms or mood early on in treatment seem to predispose to the decision to terminate treatment in some women. In light of the consistent fidning in this study of no significant manifestations of drug effect during the first month of treatment, it may be possible to increase patient compliance with treatment by imparting the information that no change is to be expected at least until the second month of drug therapy. Further research with a larger sample size will clarify this finding.

The experimental hypothesis that the combined estrogen-androgen drug would result in an enhancement of libido manifested by an increase in sexual functioning was not empirically supported. In fact, no significant changes were recorded either in the combined drug group or in the two other treatment groups on any of the measures of sexual functioning over the course of the study. Since the prevailing notion in the literature is that androgen is the libido enhancing hormone in the human female, the finding of no increment in libido as a result of exogenous androgen administration in this study is noteworthy. It is useful to recall that subjects in the combined estrogen-androgen group in this investigation received 150 mg of testosterone enanthate plus 7.5 mg of estradiol dienanthate and 1 mg of estradiol benzoate a month in a single dose by injection. Evidence of androgen's libido enhancing effect in early studies

generally was the result of relatively large doses of androgen. It may be of historical interest to chronologically review dosages administered in previous studies which implicated androgen as the libido enhancing hormone in the human female. Loeser (1940) implanted pellets of testosterone propionate in dosages ranging from 600 to 1,500 mg; Salmon (1941) administered 500 mg of "pure crystalline androgenic substance" per month to menopausal women; Greenblatt et al (1942) implanted testosterone propionate in women in dosages of 200 to 400 mg; 300-400 mg of testosterone propionate was used to treat metastatic breast cancer by Herrman and Adair (1946); Greenblatt (1950) administered 450 mg of testosterone propionate per month to treat menopausal symptoms; Foss (1951) used 200-300 mg of testosterone propionate daily to treat advanced metastases from breast cancer and Kennedy (1973) administered testosterone enanthate in dosages of 1,200 mg a week intramuscularly in an effort to halt the course of the same disease. In summary, reports of increased libido in women in the studies cited were a result of androgen administered in dosages varying from 450 mg to 9,000 mg per month. It is possible that exogenous androgen has an effect on libido only when it is administered in these massive doses. Changes in sexual functioning may therefore not be evident when the dose of androgen is as modest as it was in this investigation. An additional consideration concerning the absence of significant change in sexual functioning in this study relates to the possibility that the dosage of androgen administered would only achieve an effect in a time period exceeding the three months of the study.

It will be recalled from the introduction that evidence for an androgen-sexuality relation based on adrenal ablation (Waxenberg et al, 1959; Waxenberg et al, 1960; Schon and Sutherland, 1960) can be questioned on the basis of the unknown effect of total endogenous depletion of estrogen; adrenalectomy may have its effect on libido by removing the secondary source of estrogens. As well, there are serious difficulties inherent in interpreting findings concerning sexual functioning based on a subject population suffering from advanced metastatic cancer. Another factor which may confound the role of androgen in female sexuality is its anabolic property. Since androgen stimulates metabolism, it may increase sexual feelings secondary to increasing the sense of general well-being. Thus the issue of whether androgen is the critical hormone in the maintenance of female sexual functioning appears still in question. Research methodology which incorporates both spouse reports of sexual functioning and objective measures of sexual arousal in subjects may provide useful data by which to evaluate the effect of androgen on female sexual behavior.

References

Abarbanel, A.R. American Journal of Obstetrics and Gynecology, 1940, 39, 243.

Bakke, J.L. A double-blind study of a progestin-estrogen combination in the management of the menopause. Pacific Medicine and Surgery, 1965, 73, 200-205.

Beach, F.A. Sexual Attractivity, Proceptivity and Receptivity in Female Mammals. Hormones and Behavior, 1976, 7, 105-138.

Caldwell, B.M. and Watson, R. An evaluation of psychologic effects of sex hormone administration in aged women. Journal of Gerontology, 1952, 7, 228-244.

Carter, A.C., Cohen, E.J. and Shorr, E. The use of androgens in women. Vitamins and Hormones, 1947, 5, 317-391.

Diamond, M. Biological Foundations for Social Development. In Human Sexuality in Four Perspectives. F. Beach (Ed.), Baltimore: The Johns Hopkins University Press, 1977.

Dorfman, K. and Unger, F. Metabolism of steroid hormones. New York: Academic Press, 1965.

Drellich, M.G. and Waxenberg, S.E. Erotic and affectional components of female sexuality. In Science and Psychoanalysis, J. Masserman (Ed.) New York: Grune and Stratton, 1966.

Eberlein, W.R., Winter, J. and Rosenfield, R.L. The Androgens. In Hormones in blood. C.H. Gray and A.L. Bacharach (Eds.) 2nd edition, volume 2. New York: Academic Press, 1967.

Eisdorfer, C. and Raskind, M. Aging, Hormones and Human Behavior. In Hormonal correlates of behavior. Volume I B.E. Eleftherion and R.L. Sprott (Eds.) New York: Plenum Press, 1975.

Foss, G.L. The influence of androgens on sexuality in women. Lancet, 1951, 1, 667-669.

Glass, G.V. and Stanley, J.C. Statistical methods in education and psychology. New Jersey: Prentice-Hall Inc., 1970.

Gobdman, L.S. and Gilman, A. (Eds.) The Pharmacological Basis of Therapeutics, Fifth edition. New York: MacMillan Co., 1975.

Greenblatt, R.B. Androgenic therapy in women. Journal of Clinical Endocrinology, 1942, 2, 665-666.

Greenblatt, R.B., Mortara, F. and Torpin, R. Sexual libido in the female. American Journal of Obstetrics and Gynecology, 1942, 44, 658-663.

Greenblatt, R.B., Barfield, W.E., Garner, J.F., Calk, G.L. and Harrod, J.P. Evaluation of an estrogen, androgen, estrogen-androgen combination and a placebo in the treatment of the menopause. Journal of Clinical Endocrinology, 1950, 10, 1547-1558.

Groome, J.R. Lancet, 1939, 2, 722.

Hamblen, E.C. Endocrinology of Women. Springfield, Illinois: Charles C. Thomas, 1949.

Herrmann, J.P. and Adair, F.E. Journal of Clinical Endocrinology, 1946, 6, 769.

Kantor, H.I., Sexual effects of estrogen replacement therapy. Medical Aspects of Human Sexuality, 2, No. 2, February 1977.

Kane, F.J., Lipton, M.A. and Erving, J.A. Hormonal influences in female sexual response. Archives of General Psychiatry, 1969, 20, 202-209.

Kaplan, H.S. The New Sex Therapy. New York: Brunner Mazel, 1974.

Katchadourian, H.A. and Lunde, D.T. Fundamentals of Human Sexuality. New York: Holt, Rinehart and Winston, 1972.

Kirk, R.E. Experimental design: Procedures for the behavioral sciences. Belmont, California: Brooks/Cole Publishing Company, 1968.

Kennedy, B.J. Effects of massive doses of sex hormones on libido. Medical Aspects of Human Sexuality, 1973, 7 (3), 67-75.

Kupperman, H.S. and Studdeford, W.E. Endocrine therapy in gynecologic disorders. Postgraduate Medicine, 1953, 14, 410-425.

Loeser, A.A. British Medical Journal, 1940, 1, 479.

Markowitz, H. Patterns of Sexual Responsiveness within the Menstrual Cycle. M.A. Thesis in progress, Concordia University.

Masters, W.H. and Magallon, D.T. Androgen administration in the post-menopausal woman. Journal of Clinical Endocrinology, 1950, 10, 348-358.

Masters, W.H. and Grody, M.H. Estrogen-androgen substitution in the aged female. II Clinical response. Journal of Obstetrics and Gynecology, 53, 2, 139-147.

Masters, W.H. Sex steroid influence on the aging process. American Journal of Obstetrics and Gynecology, 1957, 74, 733-747.

McEwen, B.S. Interactions between hormones and nerve tissue. Scientific American, July, 1976.

McKinlay, S.M. and Jeffreys, M. The menopausal syndrome. British Journal of Preventive and Social Medicine, 1974, 28, 108-115.

Mendenhall, W. and Ramey, M. Statistics for psychology. Belmont, California: Duxbury Press, 1973.

Michael, R.P. Estrogen sensitive systems in mammalian brain. International Congress Series. Excerpta Medica, 1962, 47, 650-652.

Michael, R.P. In Progress in endocrinology. C Gual (Ed.) Excerpta Medica Foundation, Amsterdam, 1969.

Michael, R.P. In Frontiers in neuroendocrinology. L. Martini and W.F. Ganong (Eds.) London: Oxford University Press, 1971.

Money, J. Sex hormones and other variables in human eroticism. In Sex and Internal Secretions. Young, W.C. and Corner, G.W. (Eds.) Vol. II 3rd Edition, Baltimore: Williams and Wilkins Co., 1961.

Money, J. Sexual dimorphism and homosexual gender identity. Psychological Bulletin, 1970, 74, 6, 425-440.

Neugarten, B.L. and Kraines, R.J. Menopausal symptoms in women of various ages. Psychosomatic Medicine, 1965, 27, 266-273.

Paup, D.C., Coniglio, L.P. and Clemens, L.G. Hormonal determinants in the development of masculine and feminine behavior in the female hamster. Behavioral Biology, 1974, 10, 353-363.

Perloff, W.H. Role of hormones in human sexuality. Psychosomatic Medicine, 1949, 11, 133-139.

Rhoades, F.P. Minimizing the menopause. Journal of American Geriatric Society, 1967, 15, 347.

Riley, G.M. Gynecologic endocrinology. New York: Paul B. Hoeber Inc., 1959.

Rosenthal, I.M. in Textbook of Gynecologic Endocrinology. J.J. Gold (Ed.) New York: Harper and Row, 1968.

Ross, G.T. and Vande Wiele, R.L. The Ovaries. In Textbook of Endocrinology, R.H. Williams (Ed.), Philadelphia: W.R. Saunders, 1974, 368-422.

Rubenstein, H.S., Shapiro, H.D. and Freeman, W. American Journal of Psychiatry, 1940, 97, 703-707.

Salmon, V.J. and Geist, S.H. Effects of androgens upon libido in women. Journal of Clinical Endocrinology, 1943, 3, 235-238.

Schon, M. and Sutherland, A.M. The role of hormones in human behavior. Changes in female sexuality after hypophesectomy. Journal of Clinical Endocrinology and Metabolism, 1960, 20, 833-841.

Shanklin, D.R. and Wied, G.L. (Eds.) The Journal of Reproductive Medicine, December, 1973, 11, 6.

Shorr, E., Papanicolaou, G.N. and Stimmel, B.F. Proceedings of Society of Experimental and Biological Medicine, 1938, 38, 759.

Silberman, D., Radman, H.M. and Abarbanel, A.R. American Journal of Obstetrics and Gynecology, 1940, 39, 332.

Thompson, B, Hart, S.A. and Durno, D. Menopausal age and symptomatology in a general practice. Journal of Biological Science, 1973, 5, 71.

Utian, W.H. The true clinical features of postmenopausal and oophorectomy and their response to estrogen therapy. South African Medical Journal, 1972, 46, 72.

von Euler, V.S. and Heller, H. Comparative endocrinology. Volume I. Glandular hormones. New York: Academic Press, 1963.

Waxenberg, S.E., Drellich, M.G. and Sutherland, A.M. Changes in female sexuality after adrenalectomy. Journal of Clinical Endocrinology, 1959, 19, 193-202.

Waxenberg, S.E., Finkbeiner, J.A., Drellich, M.E. and Sutherland, A.M. The role of hormones in human behavior. Psychosomatic Medicine, 1960, 22, 435-442.

APPENDIX A

INSTRUCTION AND CONSENT FORM

We know that the drugs used to treat symptoms such as yours are helpful but we want to get more information on their general effects and to try and determine which particular drug will be most suitable for you. Therefore we are conducting a study to obtain certain kinds of information which will be useful to both physicians and patients. For example, many people are aware of changes in their sexual functioning at the time of the menopause. Little is known about these changes in menopausal women and this is an area which concerns us. Before I start you on a drug it will be useful to establish your current level of sexual functioning as well as other feelings. I would like you to meet with Barbara Sherwin, a nurse and psychology intern who works with me. She will explain what information we are interested in. One month after you have seen Barbara you will return to my office and be started on one of three preparations - either an estrogen preparation, an estrogen-androgen preparation or a no drug preparation. Both the hormone preparations are in common use. In order to partially compensate you for your trouble in providing the information we need for our study, you will be receiving the drug therapy free of charge. On the basis of what we learn about the drugs and from the records you keep for us, you will later be put on the treatment which is best for you.

I understand that I will be taking part in a study concerning the menopause with Dr. _____ and that I will be receiving one of three possible preparations for the first three months of therapy. In addition I will be receiving the injection free of charge.

Date _____ _____

_____

Witness

APPENDIX B

INITIAL INTERVIEW FORM

NAME _____

ADDRESS _____

TELEPHONE _____

AGE _____

DATE OF MARRIAGE _____

HISTORY OF PAST ILLNESS _____

_____

PRESENTING SYMPTOMS _____

NUMBER OF CHILDREN _____

CURRENT OCCUPATION _____

LEVEL OF EDUCATION _____

HOBBIES _____

SMOKING _____

ALCOHOL CONSUMPTION _____

MEDICATIONS CURRENTLY BEING TAKEN _____

HUSBAND, WORKING, RETIRED, STATE OF HEALTH _____

SLEEPING ARRANGEMENTS _____

ONSET OF CURRENT SYMPTOMS _____

PREVIOUS SEXUAL HISTORY

_____

_____

_____

APPENDIX C

DAILY SELF-REPORT QUESTIONNAIRE

DIRECTIONS

Please note your feelings and activities as you observed them during the past 24 hours only. Indicate your choice by putting a circle around the appropriate number or by filling in the blank spaces with specific information.

For purposes of clarification, masturbation is defined as stimulation of one's own genitals by other parts of one's own body and/or by any other means. Orgasm is defined as an intense peak in sexual excitement or feeling followed by relaxation. It is sometimes accompanied by intense emotional responses such as a subsequent feeling of exhilaration. These are common but not inclusive feelings that some people report.

NAME DATE
TIME FILLED OUT

1. Indicate the degree of your sexual desire during the past 24 hours.

LOW SEXUAL DESIRE	1	2	3	4	5	6	7	HIGH SEXUAL DESIRE

2. Try to estimate how many sexual thoughts or fantasies you have had in the past 24 hours. _____

3. How many times did specifically sexual activity (e.g. intercourse, erotic play) occur with your partner? _____

A) Rate the level of sexual arousal you experienced. If sexual activity occurred more than once, rate each incident separately.

a)

LOW SEXUAL AROUSAL	1	2	3	4	5	6	7	HIGH SEXUAL AROUSAL

b)

LOW SEXUAL AROUSAL	1	2	3	4	5	6	7	HIGH SEXUAL AROUSAL

4. How many times did you reach orgasm during the sexual activity or activities? _____

5. Who initiated the sexual activity? Circle the appropriate item.

SELF PARTNER MUTUAL

6. How many times did you engage in masturbation during the preceding 24 hours? _____

A) Rate the level of sexual arousal you experienced during masturbation.

LOW SEXUAL AROUSAL	1	2	3	4	5	6	7	HIGH SEXUAL AROUSAL

7. How many times did you reach orgasm during masturbation? _____

8. Rate your general energy level during the past 24 hours.

LOW ENERGY LEVEL	1	2	3	4	5	6	7	HIGH ENERGY LEVEL

9. Rate your sense of well-being during the past 24 hours.

FELT VERY POORLY	1	2	3	4	5	6	7	FELT VERY WELL

10. Rate your general mood during the past 24 hours.

FELT DEPRESSED	1	2	3	4	5	6	7	FELT CONTENTED OR HAPPY

11. Indicate the degree to which you experienced the following symptoms during the past 24 hours.

a) HEADACHE:

VERY SLIGHT	0	1	2	3	4	5	6	7	VERY SEVERE

b) NAUSEA:

VERY SLIGHT	0	1	2	3	4	5	6	7	VERY SEVERE

c) VAGINAL BLEEDING:

VERY SLIGHT	0	1	2	3	4	5	6	7	VERY SEVERE

d) FREQUENCY OF HOT FLUSHES:

None	1-4	5-10	10-20	over 20

e) SLEEP:

SLEPT VERY POORLY	1	2	3	4	5	6	7	SLEPT VERY WELL

f) APPETITE:

ATE VERY LITTLE	1	2	3	4	5	6	7	ATE MUCH MORE THAN USUAL

12. How many arguments or disputes have you had in the past 24 hours? Circle the number.

1 2 3 4 5 6 7

Indicate your degree of involvement in the argument.

I WAS NOT PARTICIPATING VERY MUCH	1	2	3	4	5	6	7	I WAS PARTICIPATING VERY ACTIVELY

13. In the past 24 hours I

a) went out (e.g. with friends, family on business),

Circle the number of times

1 2 3 4 5

13b. Rate your level of activity during the past 24 hours.
(physical, social, recreational)

Not very active	1	2	3	4	5	6	7	Extremely active

14. Complete the following sentence:

In the last 24 hours I felt _____

_____

APPENDIX D

COMPUTATION OF DRUG DOSAGE EQUIVALENCE

Drug Groups

a) Estrogen-Androgen Combined Group

Climacteron

Each 1 ml contains:

Testosterone enanthate benzilic acid hydrozone....	150 mg
equivalent to testosterone	69 mg
Estradiol dienanthate	7.5mg
equivalent to estradiol	4.1mg
Estradiol benzoate	1.0mg
equivalent to estradiol	0.7mg

Therefore 1 ml of Climacteron contains 4.8 mg of free estradiol.

b) Estrogen-alone Group

Delestrogen

Each 1 ml contains:

Estradiol valerate	10 mg
equivalent to estradiol (unbound)	7.6 mg

Equivalence of free (unbound) estradiol in the two drugs was established by dividing the amount of unbound estradiol in the estrogen-alone drug (7.6 mg) by the amount of unbound estradiol in the estrogen-androgen combined drug (4.8 mg). It was thus determined that 1 ml of Climacteron and 0.63 ml of Delestrogen contained equivalent amounts of free estradiol.

c) Placebo Group

Sesame oil	1 ml

APPENDIX E

Degree of Sexual Desire per 24 Hours: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	1.03371	.20932
Time	3	.01495	.07686
Treatment Group x Time	6	.32547	1.6724

Degree of Sexual Desire per 24 Hours: Treatment Group Means

	Baseline	Month 1	Month 2	Month 3
Placebo Group	2.23	2.17	1.56	1.63
Estrogen Group	1.72	2.22	2.50	2.34
Combined Group	1.42	1.42	1.62	1.72

Number of Sexual Thoughts or Fantasies per 24 Hours: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	36.9215	.69224
Time	3	4.4783	.69142
Treatment Group x Time	6	6.49762	1.0032

Number of Sexual Thoughts or Fantasies per 24 Hours: Treatment Group Means

	Baseline	Month 1	Month 2	Month 3
Placebo Group	7.31	2.95	1.98	3.01
Estrogen Group	1.29	1.93	2.14	2.03
Combined Group	.06	.20	.27	.71

Number of Sexual Encounters per 24 Hours: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	.0716	.8629
Time	3	.0265	.6175
Treatment Group x Time	6	.0338	.7864

Number of Sexual Encounters per 24 Hours: Treatment Group Means

	Baseline	Month 1	Month 2	Month 3
Placebo Group	.54	.20	.21	.20
Estrogen Group	.14	.13	.13	.11
Combined Group	.15	.15	.20	.26

Level of Sexual Arousal per Encounter: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	23.2507	2.7546
Time	3	.9988	.6410
Treatment Group x Time	6	2.3046	1.4791

Level of Sexual Arousal per Encounter: Treatment Group Means

	Baseline	Month 1	Month 2	Month 3
Placebo Group	3.67	1.71	2.35	2.84
Estrogen Group	3.13	5.59	5.35	5.50
Combined Group	1.56	1.25	2.11	2.37

Number of Orgasms per Encounter: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	.6955	1.8856
Time	3	.1447	1.1452
Treatment Group x Time	6	.1368	1.0825

Number of Orgasms per Encounter: Treatment Group Means

	Baseline	Month 1	Month 2	Month 3
Placebo Group	.58	.13	.26	.40
Estrogen Group	.50	.92	1.00	1.00
Combined Group	.14	.25	.55	.69

APPENDIX F

Headache per 24 Hours: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	.2025	.4107
Time	3	.0117	.1032
Treatment Group x Time	6	.0935	.8254

Nausea per 24 Hours: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	.2205	.457724
Time	3	.0653	1.3441
Treatment Group x Time	6	.0380	.7823

APPENDIX G

General Mood per 24 Hours: ANOVA Summary Table

Source	df	MS	F
Treatment Group	2	2.6936	.9162
Time	3	.4759	1.9983
Treatment Group x Time	6	.3633	1.5256