Effects of Estrogen and Androgen on Somatic, Affective, Sexual and Cognitive Functioning in Hysterectomized and Oophorectomized Women

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ABSTRACT

EFFECTS OF ESTROGEN AND ANDROGEN ON SOMATIC, AFFECTIVE, SEXUAL AND COGNITIVE FUNCTIONING IN HYSTERECTOMIZED AND OOPHORECTOMIZED WOMEN

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Thirty-nine women who required a total abdominal hysterectomy and bilateral oophorectomy for reasons other than malignant disease were randomly assigned to one of four treatment groups preoperatively -- a combined estrogen-androgen group (E-A), an estrogen group (E), an androgen group (A), or a placebo group (PL). Nine women who needed to undergo hysterectomy but whose ovaries were retained served as a control group (CON) for effects of the surgical procedure itself. Thus, the experimental design consisted of five groups and three time periods, namely, a preoperative baseline phase, a three month treatment phase followed by a one month placebo phase for all subjects.

A psychological test battery was administered preoperatively, three days after the third injection of hormone, and on the last day of the placebo month concomitant with the drawing of a blood sample to measure plasma levels of total estrogens, testosterone, luteinizing hormone and follicle-stimulating hormone. A Daily Menopausal Rating Scale (DMRS) consisting of items relating to somatic, affecive and sexual functioning was completed daily by each subject throughout the five month course of the study.

Both of the estrogen-containing preparations were effective in alleviating hot flushes. The E group also achieved higher scores on a test of short-term memory.

However, the E-A and the A drugs had an enhancing effect on several parameters of sexual functioning coincident with higher levels of plasma testosterone. To our knowledge, this is the first empirical evidence of a beneficial effect of androgen on female sexuality in which subjects were neither suffering from malignant disease nor sexual dysfunctions. During treatment, the groups that received androgen (E-A and A) also reported lower somatic, psychological, and total scores on the Menopausal Index and had lower depression scores.

Several findings of theoretical and clinical importance emerged from this study. Overall, administration of the combined E-A preparation induced levels of functioning superior to exogenous E alone. Secondly, the demonstration that menopausal symptoms responded differentially to various treatments suggests that they may not have a common hormonal etiology. The concept of a menopausal syndrome, therefore, needs to be reconsidered. Finally, postoperative deterioration in several aspects of functioning in the PL group coincident with an abrupt, drastic decline in their plasma estrogen levels suggests that hormone replacement therapy has an important role during the immediate postoperative period in premenopausally oophorectomized women.

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TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF TABLES

Page

Page

Page

LIST OF APPENDICES

Page

Page

In 1913 Cushing stated that "it is quite probable that the psychopathology of everyday life largely hinges upon the effect of the ductless glands' discharge upon the nervous system." Tucker (1922) observed that specific behaviors were associated with hyperpituitarism and opposite extremes of the same behavior were manifested under conditions of hypofunction of this gland. While the behavioral phenomena these authors noted were crudely measured and defined with respect to current assessment techniques and nosology, they nevertheless served to point out the early observation that certain behaviors were associated with specific endocrine disturbances.

The 1970's have witnessed a renaissance in psychoendocrinology. The renewal of interest can in large part be attributed to technical advances in endocrine biochemistry, hormonal and neuropharmaceutical manipulation, biochemical analysis and psychological assessment. Historically, research efforts had focused on psychological changes associated with the endocrinopathies and were, therefore, concerned with relatively rare pathological conditions and their sequelae. More recently, there has been a great deal of interest in psychological changes associated with naturally-occurring hormonal fluctuations during the human female reproductive cycle. Most of this research has been devoted to the reproductive period of the female life span. Menopause, the end-point of the reproductive cycle has been the subject of relatively little scientific investigation despite the fact that women can now expect to live one-third of their lives beyond cessation of their reproductive capacity (Canadian Census, 1976). It is the physiological and psychological symptoms purported to result from endocrine change at menopause and their treatment which are the subject of this

study.

Female Reproductive Physiology

Three groups of hormones secreted by specific anatomical structures are of crucial importance in the reproductive process. The hypothalamus synthesizes a releasing factor, gonadotrophin-releasing hormone (GnRH), which is a single-chain decapeptide first isolated in 1971 by Amoss, Burgus, Blackwell, Vale, Fellows and Guillemin. The portal vein system carries the GnRH from the median eminence of the hypothalamus to the anterior pituitary (Harris, 1972). This hypothalamic neurosecretory hormone, GnRH, in turn stimulates the anterior pituitary to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These pituitary gonadotrophins have their most important effect on the ovary. Histologically, the ovary is composed of an outer portion called the cortex and an inner portion called the medulla. The cortex is formed essentially of connective tissue cells that constitute the stroma and in which are found the ovarian follicles with their oocytes (Van Campenhout, 1973). The population of human primordial follicles is established between the fourth month of gestation and birth and any which are eliminated cannot be replaced (Baker, 1963). This makes the oocyte one of the longest-lived cells in the body.

Reproduction requires a perfect integration of the neuro-endocrine activities of the hypothalamic-pituitary-ovarian axis. At the beginning of a normal menstrual cycle, the pituitary secretes a moderate quantity of FSH which stimulates growth in a group of follicles. A menstrual or premenstrual rise in LH stimulates increasing secretion of estradiol from one or more of the developing follicles, from one or sometimes both ovaries. The increasing estradiol concentrations in

plasma cause a suppression of FSH secretion via the negative feedback mechanism. The follicle which is destined to ovulate is able to continue growth and maturation, and appears to sensitize itself to the falling levels of FSH by formation of more FSH receptors. The remainder of the follicles are unable to maintain further growth and undergo atresia (retrogression) (Fraser, 1979). The preovulatory Graafian follicle secretes large amounts of estradiol so that high plasma levels are maintained for 24-36 hours. This high and prolonged peak of estradiol triggers the massive pre-ovulatory release of LH by the so-called positive feedback mechanism. It is likely that the massive LH surge is due to a combination of increased GnRH secretion and increased sensitivity of the pituitary to GnRH (Diczfalusy and Landgren, 1977). The LH peak as well triggers the sequence of events that lead to ovulation. Following ovulation, formation of the corpus luteum leads to increased estradiol and progesterone secretion. Plasma LH and FSH fall to their lowest levels of the cycle during the luteal phase due to the combined negative feedback effect of estradiol and progesterone (Jones and Wentz, 1976). If fertilization and implantation do not occur, the corpus luteum undergoes regression, the mechanism of which is not fully understood. The subsequent fall in estradiol and progesterone withdraws hormonal support from the endometrium (lining of the uterus) and menstruation follows. The fall in estradiol and progesterone is probably also responsible, by removal of negative feedback inhibition, for the rise in FSH and LH which initiates the next cycle (Vande Wiele, Boogumil, Dyrenfurth, Ferin, Jeweleivicz, Warren, Ritzkallah, and Mikhail, 1970). The hypothalamic-pituitary-ovarian feedback mechanism, therefore, regulates the cyclicity of female reproductive function.

Ovarian Steroidogenesis

The relatively nonspecific formation of all steroid hormones is underlined by the fact that they are produced in similar fashion in the testis, the ovary and the adrenal (Kistner, 1979). The androgens -- testosterone, androstenedione and dehydroepiandrosterone -- are formed in the adrenal, the follicle, the corpus luteum and the stroma. Of these androgens, only testosterone has significant biological androgenic activity. The other compounds can be converted to testosterone peripherally (Mahesh and Greenblatt, 1975). The major androgen secreted by the ovary is androstenedione (Villee, 1975).

The three major naturally occurring estrogens in the human female are estrone, estradiol and estriol. 17-beta estradiol is the main biologically active estrogen in women during the reproductive years and is virtually a specific secretory product of the developing follicle and corpus luteum (Baird and Fraser, 1974). The mature Graafian follicle secretes over 95% of the circulating estradiol as well as significant amounts of estrone, androstenedione and 17 alpha-hydroxyprogesterone (Ryan and Petro, 1966). Estrogens can also be readily formed from androstenedione or testosterone via a several-step aromatization reaction (Naftolin, Ryan, Davies, Reddy, Flores, Petro, Kuhn, White and Takaoka, 1975). Estradiol appears to be derived from testosterone and estrone from androstenedione although once formed, estradiol and estrone are interconvertible via a soluble steroid dehydrogenase present in many tissues of the body (Kistner, 1979).

The biological activity of estradiol and testosterone is exerted by the unbound fraction in plasma which probably represents only one to three percent of the total concentration (Slaunwhite, Lockie, Buck and Sandberg, 1962). The plasma proteins that bind testosterone and estradiol include sex-hormone binding globulin (SHBG) which

has a high affinity for both of the sex steroids, and albumin, which has a low affinity, (Mercier-Bodard, 1970). Although testosterone and estradiol bind to the same site on SHBG, testosterone is thought to bind more strongly than estradiol (Mercier-Bodard, 1970). Changes in SHBG concentration may, therefore, alter the relative binding of the two steroids. It is known that an increase in estrogen levels raises SHBG concentrations while an increase in androgens reduces it (Vermulen, Verdonck, van der Straeten and Orie, 1969). Consequently, an estrogen induced rise in SHBG might tip the balance between testosterone and estradiol in favor of estradiol, by preferentially binding testosterone. Conversely, an androgen induced fall in SHBG might tip the balance in favour of testosterone by causing a greater proportional rise in unbound testosterone than in unbound estradiol (Burke and Anderson, 1972).

Recently, it has been demonstrated that serum levels of adrenal androgens are lower in oophorectomized than in ovulating women of comparable age (Cumming, Rebar, Hooper and Yen, 1980). These findings seem to imply that either estrogen and/or normal ovarian function are important for the maintenance of premenopausal levels of adrenal androgens in plasma. Lobo, Gooebelsmann, Brenner and Mishell (1982) corroborated these findings and suggested that the effect may be due in part to a decrease in enzymatic activity in the adrenal gland itself. The ACTH-stimulated adrenal secretion of androgens also decreased in comparison to that in ovulating women. After treatment of the oophorectomized women with estrogen, basal adrenal steroid levels increased in a dose-related fashion. Even though the administration of Premarin 2.5 mg (conjugated equine estrogen) was associated with a doubling of SHBG, the unbound testosterone level increased. Since a fall in testosterone would have been predicted because more of the hormone was being bound to SHBG, this finding

implied that the production of testosterone must have increased also. These data suggested that treatment of oophorectomized women with estrogen can successfully replace that part of ovarian function which may be responsible for maintaining normal serum levels of adrenal androgens.

End-Organ Actions of Sex Steroids

Sex steroids have a wide range of action on many body tissues in the human female. The most obvious actions are on the genital tract, but more subtle changes can also be demonstrated on the breast, cardiovascular system, brain, blood, bone, skin, hair, hepatic function, carbohydrate tolerance and renal sodium excretion (Fraser, 1976). Only those of relevance to reproductive function will be discussed here.

The biological effects of sex steroids are mediated by specific receptors located in the target tissues. The receptors are complex proteins with high affinity and specificity for their trophic hormones (Clarke and Hardin, 1977). Estrogens and androgens have the capacity to stimulate many cellular events which lead to growth of the tissue. It is also known that different estrogens have different affinities and binding times to receptor sites, which at least partially explains differences in biological activity (Taylor, 1976). Further complexities can occur with extensive interconversion of hormones such as estrone and estradiol within the target tissue.

With respect to estrogen, the target tissues in which specific binding have been identified are the ovary, the endometrium , the vaginal epithelium, the vulva, the cervix, and the breast (Littge and Whalen, 1970). Thus, estrogens stimulate the growth of tissue of the entire

reproductive tract and are thereby responsible for its integrity of structure and function.

The Menopause

The term menopause specifically refers to cessation of the menses. Because the pattern of menstrual periods becomes irregular before the menses cease completely, menopause is an event which can only be confirmed retrospectively (Jaszmann, 1976). The climacteric, a commonly used term in the literature, has been defined as a transitory stage in the human female between the ages of reproductive and non-reproductive ability (Utian and Serr, 1976). The period preceding the menopause is called pre-menopause and that following it, the post-menopause. More recently, "perimenopause" has been defined as that time immediately prior to the menopause during which ovarian function is sufficiently decreased to cause clinical changes (Jones, 1980).

Epidemiological studies have found the average age of menopause to range from 49.1 to 50.8 years (Bengtsson, Lindquist and Redvall, 1979; Frommer, 1964; McKinlay, Jeffreys and Thompson, 1972). It is currently accepted that the median age of menopause in industrial societies is 50 years (Gray, 1976).

A) Natural Menopause

Natural or spontaneous menopause is thought to occur as a result of aging of the ovary manifested by a progressive loss and finally, a depletion of ovarian follicles (Jones, 1975). Anatomical changes in the menopausal ovary consist mainly of an atrophy of the ovarian cortex, the repository of the follicles or oocytes (Costoff, 1974). There is also hyperplasia (rapid growth

of cells) of the ovarian medulla which contains stromal cells, thought to be a possible source of androgens (Rice and Savard, 1966).

Of critical importance with respect to physiological effects and symptom formation are the endocrine changes that occur as a result of aging at menopause. During the reproductive years, the main source of estradiol is direct secretion by the ovaries which accounts for over 90% of the total body production (Mishell, Nakamura and Grosignani, 1971). Estrone is almost equally produced by glandular secretion and by peripheral conversion of estradiol and of two androgens, androstenedione and testosterone. Androstenedione is produced by both the ovaries and the adrenals. It has been estimated that 40% of testosterone production is made up of ovarian and adrenal components and peripheral conversion of androstenedione accounts for the remaining 60% (Mikhail, 1970).

It has been found that in women between the ages of 34 to 39 years, FSH levels began to rise despite the fact that no change could be detected in mean estradiol or LH level (Reyes, Winter and Faiman, 1977). This event coincides in time with the decline in the average number of large follicles (Block, 1952). Some time after the FSH level increases, there is a concomitant increase in serum LH levels, usually at age 45 to 50 (Sherman & Korenman, 1975). The reason for an increase in FSH in the presence of normal levels of estradiol in premenopausal women is hypothesized to be due to an age-related change in the hypothalamo-pituitary sensitivity to feedback inhibition by ovarian steroids, but has not yet been demonstrated. After the menopause, there is a 14-fold increase of FSH and over a three-fold increase of LH as compared to the premenopausal state (Coble, Koohler, Cargille and Ross, 1969). Clinically, the significant increase in FSH is in

itself regarded as a diagnostic criterion of menopause (Utian, 1980). The FSH and LH values, following their peak at about three years postmenopause, gradually decline over the next 30 years to values of 40 to 50 percent of these maximal levels (Chakravarti, Collins and Forecast, 1976). Following spontaneous menopause, the level of estradiol drops to approximately one-fifth of premenopausal levels (Thyssen and Longcope, 1976). The plasma levels of estrone drops a relatively lesser extent (approximately 15%) because the rate of conversion of precursor androstenedione to estrone increases (Judd, Judd, Lucas and Yen, 1974).

Consequences of an altered endocrine status in the perimenopause were studied by Chakravarti, Collins, Thorn and Studd (1979). They attempted to correlate the occurrence of various symptoms with hormonal state in women who were experiencing a natural menopause. Eighty-two premenopausal women with a range of complaints were recruited into the study. Vasomotor disturbances were absent in 42 subjects (Group 1) and present in 40 (Group 2). Symptoms were recorded and estradiol, testosterone, LH and FSH were measured at baseline and at the end of three and six months of treatment with Premarin, 1.25 mg. At baseline, headaches, insomnia and dyspareunia were the most common additional complaints among women who were experiencing vasomotor symptoms whereas loss of libido, and depression were more prevalent in women in Group 1. It was found that plasma levels of estradiol, T, FSH and LH in women in Group 1 did not differ significantly from those found in younger, regularly menstruating women whereas estradiol levels of women in Group 2 were significantly lower than values during the follicular phase of the normal menstrual cycle even though these women were still menstruating. Their plasma FSH and LH values were comparable to those of postmenopausal women but testosterone levels of the two groups were not

significantly different from each other. Following six months of estrogen treatment, estradiol levels showed a 2.1-fold increase and testosterone a 1.9-fold increase. Plasma FSH and LH were reduced to 39 percent and 66 percent of pretreatment values respectively although the values remained higher than those found in younger women. Hot flushes, headaches, dyspareunia and insomnia were "noticeably improved" with estrogen treatment. Initial complaints of loss of libido and depression underwent no significant change in response to the estrogen treatment in either group. The authors concluded that in premenopausal women, vasomotor disturbances and a high FSH plasma level are the best criteria on which to select patients who might benefit from estrogen therapy. It should be noted that the behavioral data in this study consisted of self-reports at three times during the study and were not subjected to a statistical analysis.

B) Surgical Menopause

Surgical menopause ensues when both ovaries are removed before the natural menopause has occurred. Although it is unusual for salpingo-oophorectomy (bilateral removal of ovaries and fallopian tubes -- BSO) to be undertaken without total abdominal hysterectomy (TAH), the converse is not true (Hunter, 1976). In premenopausal women, the surgical removal of normal ovaries at the time of total abdominal hysterectomy for benign conditions is a controversial subject in modern gynecology (Utian, 1980). Among the arguments for oophorectomy at the time of hysterectomy is as prophylaxis against the later development of ovarian carcinoma. It has been documented that between four and eight percent of women who develop ovarian carcinoma have previously undergone hysterectomy (Mattingly and Huang, 1969). For the number of women who

have undergone hysterectomy and who later develop ovarian carcinoma, the risk appears to be one in 1000 (Terz, Baiber and Brunschwig, 1967). Secondly, the incidence of conserved ovaries becoming cystic and/or giving rise to pelvic pain in posthysterectomy patients has been reported to be as many as five percent of women (Grogan and Duncan, 1955). The third argument for removing ovaries at the time of hysterectomy is the belief that they soon cease to function. However, there is evidence to show that ovaries do continue to function after hysterectomy until the time of expected menopause (Beavis, Brown and Smith, 1969; Ranney and Aber-Ghazalch, 1977). More recently, Vermulen (1980) has demonstrated that in early postmenopause (less than four years), direct ovarian secretion contributes to plasma estrogen levels whereas later in the postmenopause (greater than four years), plasma estrogen levels are no greater than those in oophorectomized women of the same age. The postmenopausal ovary appears, however, to be responsible for about 50% of plasma testosterone and 30% of androstenedione levels (Vermulen, 1976). The clinical criterion most commonly used in the decision to conserve or remove normal-looking ovaries at the time of abdominal hysterectomy is age of the patient; ovaries are frequently conserved in premenopausal women under the age of 45 years and are removed in those over 45 years. Premenopausal women whose ovaries are removed thereafter suffer an abrupt surgical menopause, whereas those whose ovaries are conserved show only a transient drop of plasma estradiol on the third postoperative day; levels return to normal within two to three weeks (Stone, Dickey and Mickol, 1975).

Several investigators attempted to document the sequelae of a surgical menopause. The incidence of a range of symptoms was studied in 100 patients who had undergone hysterectomy and oophorectomy one to 31 years earlier (Chakravarti, Collins, Newton, Oram & Studd, 1977). Women

were interviewed at least six months following surgery in order to determine symptom incidence. Thirty-four percent of the sample were found to be asymptomatic; only one of 11 subjects in the first postoperative year was symptom free. However, the number of asymptomatic women increased with the number of years since surgery. Hot flushes were reported by 28 percent of women, depression by 68 percent, insomnia by 48 percent, loss of libido by 46 percent, dypareunia by 38 percent and irritability by 36 percent. Ninety-four percent of women recalled experiencing hot flushes within six weeks following surgery. Ten of the 11 subjects within the first year of their operation were suffering from hot flushes but only two subjects afer eight years and one after 14 years were still experiencing this symptom. Furthermore, the highest incidence of depression and irritability was in women four to six years after oophorectomy following which there was a gradual decline. Psychological symptoms failed to show any correlation with the levels of circulating hormones. Data on symptom incidence were collected during a single interview and consisted of global estimates by the subject. The large variation among subjects in the study as well as the fact that six percent of the subjects were receiving estrogen therapy are confounds which limit interpretation of these findings.

Utian (1980) reported on changes in plasma hormones and gonadotrophins in 11 oophorectomized women given different dosages of conjugated equine estrogens (Premarin). Estradiol levels fell precipitously after the operation and were significantly lower than baseline by the first postoperative day. The administration of estrogen in dosages of 0.625 and 1.25 mg. were associated with plasma estradiol concentrations similar to the preoperative levels whereas a dosage of 0.03 mg failed to produce any significant change. FSH and LH values rose gradually

following surgery. In only one instance did exogenous estrogen succeed in reducing FSH to premenopausal levels and that was at a dosage of 2.5 mg., at which time the estradiol level was higher than the premenopausal value. LH was never reduced to a premenopausal level. The author concluded that administering estrogen in usual dosages following oophorectomy does not restore the reproductive hormone profile to a premenopausal status. Associated changes in symptoms were not examined in this study.

The Menopausal Syndrome

Three symptoms constellations -- somatic, psychosomatic, and psychological -- are commonly considered to comprise the menopausal syndrome.

Somatic symptoms generally are associated with the effects of low levels of endogenous estrogen on target tissues. One consequence of this endocrine change is atrophic vaginitis, a loss of vaginal folds and increased vulnerability of the vaginal epithelium. Although atrophy occurs at every level of the reproductive tract, it is clinically most strikingly recognized in the vagina, in which the loss of estrogen results in a thinned and easily traumatized epithelium. Hutton, Jacobs, Munay and James (1978) showed that postmenopausal women complaining of vaginal dryness and dypareunia (painful intercourse) had siginficantly lower mean concentrations of plasma estradiol, but not of estrone, compared to symptomless women. The other somatic symptom that frequently occurs with the cessation of ovarian function is the hot flush. This symptom, reported by 75 to 80 percent of menopausal women (Fink, 1980; McKinlay and Jeffreys, 1974) seems to be related to altered endocrine function, but the exact pathophysiological explanation is still unknown. It has recently been demonstrated, however, that there is a significant positive correlation between plasma LH and

finger temperature elevations in menopausal women reporting hot flushes (Tatryn, Meldrum, Lu, Frumar & Judd, 1979). Furthermore, the temporal relationship between pulsatile release of LH and hot flashes was demonstrated by Casper, Yen and Wildes (1979). They found that although LH pulses were not always accompanied by hot flushes, a flush was never seen to occur in the absence of an LH pulse. The finding that hot flushes occur in hypophysectomized women (Mulley, Mitchell & Tattarsall, 1977) suggests that a suprapituitary mechanism, most likely LHRH release by the hypothalamus, initiates the release of LH which is associated with hot flush episodes. Subjectively, the hot flush is experienced as a wave-like sensation of heat usually originating in the neck, head and/or scalp and spreading to the upper torso, occasionally including the arms. Intensity varies from mild to severe correlating with a duration ranging from 30 seconds to two to three minutes in length (Voda, 1981). The fact that hot flushes are reliably relieved by estrogen replacement therapy (Coope, 1976; Cope, 1976; Dewhurst, 1976; Utian, 1977) strongly suggests that they are the consequence of hormonal changes. In one investigation, however, in which 16 premenopausal women who underwent bilateral oophorectomy were studied in the immediate postoperative period, it was found that only 37.5 percent developed hot flushes. Furthermore, there were no significant differences in total serum estrogens, in FSH or in LH concentrations found between those who developed hot flushes and those who did not (Aksel, Schoomberg, Tyrey and Hammond, 1976).

A myriad of psychosomatic and psychological disturbances is commonly reported at the time of menopause (Blatt, Wiesbader and Kupperman, 1953; Greenblatt, 1955; Greene, 1976). Symptoms classified as psychosomatic include insomnia, palpitations, fatigue, headache, joint pains and dizziness. Common psychological symptoms are

nervousness, irritability, crying spells, depression, anxiety, loss of libido, inability to concentrate, apathy, and poor memory (Christie Brown and Christie Brown, 1976; Dewhurst, 1976; Green, 1976; Lauritzen and van Keep, 1978). It is clear now that these symptoms arise for complex reasons and that no single factor can account for their occurrence.

Within the past decade, evidence with regard to the biochemical basis of the effect of estrogen on depression has become available. The catecholamine-deficiency hypothesis of affective disorders implies that depression involves an impairment of central biogenic amines such that reduced amine levels may cause depression (Schildkraut, 1965). Brain typtophan, the precursor of the neurotransmitter serotonin, is derived from plasma tryptophan and serotonin levels fluctuate in relation to plasma typtophan concentrations (Klaiber, Kobayashi, Broverman & Hall, 1971). It is also known that changes in the levels of monoamine oxidase (MAO), an enzyme involved in the metabolism of serotonin, controls the levels of this neurotransmitter in the central nervous system (Coulam, 1981). Thus, a decrease in free plasma typtophan or an increase in MAO levels would act to induce depression by lowering serotonin levels. Consistent with this hypothesis, it was found that postmenopausal depressed women had significantly lower plasma typtophan levels than nondepressed women (Aylward, 1973). Furthermore, it is known that typtophan is displaced from its binding sites to plasma albumin by natural estrogens. In a well-controlled study, women treated with estrogen showed a marked increase in both plasma estrogen and free plasma typtophan and an improvement in depression. The placebo treated group did not show significant improvement in these measures (Aylward, 1976).

Additional evidence of the relationship between estrogen and depression was provided by the finding that levels of MAO correlate negatively with levels of plasma estrogens (Mason & Schirch, 1961). In order to investigate the role of MAO activity and estrogen administration in depression, Klaiber, Broverman, Vogel and Kobayashi (1979) carried out a double-blind study. All subjects were severely and chronically depressed inpatients whose depression had not responded to electroshock, antidepressants or to psychotherapy. Patients, both pre and postmenopausal women, were randomly assigned to an estrogen group (Premarin, 15 to 25 mg per day) or to a placebo group for three months. The estrogen-treated group showed significantly lower plasma MAO levels and lower depression scores as measured by the Hamilton Rating Scale for Depression. These findings further supported the biochemical hypothesis with regard to estrogen and depression.

The climacteric, a period of time between the ages of 45 to 60 years, also coincides with what is commonly understood to be middle-age. This phase in the female life-cycle is marked by the termination of many traditional, instrumental (work) and expressive (interpersonal) roles and with the stress of redirecting productive and fulfilling interests (Bart, 1967; Notman, 1980). Yet another group of writers have proposed that only women with an inadequate or maladaptive personality development, who have a previous history of psychiatric disorder will manifest psychological disturbance in the face of the losses, the stress, and the hormonal changes associated with the menopause (Ballinger, 1976; Donovan, 1951; Fessler, 1950; Stern and Prados, 1946). Sociocultural attitudes about aging and about the menopause have also been found to influence the experience of this biological event and to affect the frequency and intensity

of psychological and psychosomatic symptoms (Flint, 19755; Maoz, Antonousky and Wijsenbeek, 1970). Epidemological studies have failed to demonstrate an association between menopausal status and psychological and psychosomatic symptoms (Greene, 1976; McKinlay and Jeffreys, 1974; Neugarten and Kraines, 1965; Thompson, Hart and Durno, 1973). Winokur (1973) concluded that women were not at greater risk for psychotic depression during the menopause than during other times in the life span, Schneider and Brotherton (1979) found that although depressed and non-depressed menopausal women could be differentiated on the basis of psychological and social stresses they were experiencing, they did not differ significantly in terms of physical symptomatology. These findings, taken as a whole, suggest that cultural, individual psychological, and situational stresses, as well as endocrine changes affect the well-being of women during this phase of life.

Estrogen Replacement Therapy Studies

The advent of estrogen synthesis in the late 1930's allowed for the testing of biological theories of menopausal symptomatology. The underlying assumption in hormone replacement research has been that whatever symptoms are alleviated by the administration of estrogen to estrogen-deficient women could be directly attributed to endocrine changes at the time of menopause. It followed that unresponsive complaints were not "true menopausal symptoms" (Kupperman and Studdiford, 1953).

Although there are a large number of hormone replacement studies in the literature, most of the reports of the 1950's and 1960's were based on unsystematic clinical observation. Few experimentally controlled studies were done at that time. From 1970 onward, many researchers attempted to carry out more carefully designed

studies, but to date, the majority are flawed by methodological problems that render their interpretation difficult. Many studies were retrospective and few provided baseline measures against which to compare symptomatic changes as a consequence of estrogen administration. Others used inappropriate control groups or neglected to include comparison groups at all. Population samples were often heterogeneous with respect to the time that had elapsed since surgery (hysterectomy and bilateral oophorectomy); in some cases the interval between surgery and testing varied from one to 31 years thus confounding the effects of estrogen with aging. Not infrequently, two or more dosages of estrogen were used in a single study, while all data were analyzed together. Methods of data collection ranged from casual assessment of symptoms by a non-blind investigator during a regular office visit to the use of psychometric instruments with known reliability and validity administered within the context of a double-blind design. Since much of this research has been carried out in Holland, Finland, Sweden, Switzerland and Israel, the measuring instruments used preclude comparability between studies. Statistical analyses of the data were, at times, not presented at all; in other cases, inappropriately liberal statistical techniques were applied to small sample sizes. In summary, the literature assessing the responsiveness of menopausal symptoms to the administration of estrogen is generally poorly controlled and, not surprisingly, often contradictory. A likely explanation of the research difficulties that have pervaded this area is its multidisciplinary nature; researchers of various scientific disciplines who have carried out investigations in this area rarely controlled for all of the potential confounds within the context of a single study. It is this tendancy on the part of investigators to ignore intervening variables not directly associated with their area of

expertise which may account for the inconsistencies in this literature.

Estrogen replacement studies have for the most part focused on changes in somatic, affective, cognitive and sexual functioning in respons to estrogen administration. Although all four parameters were frequently investigated in the same study, an attempt will be made here to separately analyze findings relevant to each of these areas of functioning.

A) Somatic Symptoms

Utian (1972), in a single-blind study, investigated the response of somatic symptoms to estrogen administration. Treatment groups included an immediate, a six month, and a two year post TAH and BSO groups and a two year post TAH group with conserved ovaries. Symptoms were graded by the investigator as being absent, slight, moderate or severe at the time of visits scheduled two to three months apart. Subjects received estradiol valerate 4 mg per day for four months, a placebo for three months and conjugated equine estrogen 5 mg per day for one additional month. Hot flushes, perspiration, and atrophic vaginitis were reported significantly more often in the oophorectomized than in the nonoophorectomized women. These symptoms were alleviated by both forms of estrogen but increased again during treatment with a placebo. It was concluded that these symptoms resulted from low levels of circulating estrogens.

In a study by George, Beaumont & Beardwood (1973), 13 women who had undergone TAH and BSO were given Premarin 1.25 mg for one month. Following that seven were given placebo, and six Premarin 2.5 mg for the next month. In the third month, all subjects were crossed-over to the

preparation they had not received during the previous drug phase. A symptom checklist completed by subjects daily showed that hot flushes were relieved by both estrogen preparations and recurred with a significant frequency during the placebo month.

The efficacy of estrogen in the alleviation of hot flushes was confirmed in a study by Rhoades (1974). Eighty-eight menopausal women received ethinyl estradiol and an equal number were given estrogen in association with progesterone. After two years, 95 percent of subjects experienced relief of hot flushes and headache with both estrogen preparations. The method used to collect these data was not reported and there was no control group to provide a basis for comparison.

Coope, Thompson and Poller (1975) carried out a double-blind crossover study of 30 women of varying endocrine status whose mean age was 52 years. Four subjects were still menstruating regularly, ten had experienced a natural menopause between one and ten years previously, 11 had undergone TAH and four had had TAH and BSO. Half the subjects were randomly assigned to an estrogen group (Premarin, 1.25 mg per day) and half to a placebo group for three months following which they were crossed over to the other treatment group for a further three months. The Menopausal Index (Kupperman, Blatt & Wiesbader, 1953) was used to measure changes in symptoms. Hot flushes were significantly reduced in both groups during the first three months. Following the cross-over, hot flushes increased significantly in the group that had received estrogen first whereas there was no significant change in this symptom in the other group when they were given estrogen following placebo.

In a double-blind, cross-over trial carried out by

Campbell (1976), a significant effect of placebo treatment was found for vaginal dryness and urinary frequency irrespective of treatment order but beneficial effects of estrogen (Premarin 1.25 mg) over placebo were observed for hot flushes and insomnia. These findings were confirmed in a study of similar experimental design reported by Coope (1976). There was a significant proportional reduction of hot flushes due to estrogen administration compared to placebo over the course of the study even though there had been a significant reduction in frequency of hot flushes under placebo treatment during the first treatment phase. Both these studies investigated a heterogeneous population of women ranging in age from 41 to 60 years.

Durst and Maoz (1980), in a single-blind study, investigated changes in somatic symptoms in a group of 80 menopausal women. All subjects received placebo initially and were switched to estrogen therapy when they reported an increase in menopausal symptoms. They were then given .65 mg of a conjugated estrogen. Those who continued to complain had the dosage increased to 1.25 mg the following month. Forty women (Group A) completed the study and the other 40 (Group B) dropped out after one to three months. After one year, both groups reported a significant reduction in hot flushes, cold sweats and headaches compared to their pretreatment scores. These findings imply that somatic symptoms improve without treatment over time. However, data based on two different dosages of estrogen were analyzed together making it difficult to interpret the hormone effects.

Townsend, Whitehead, McQueen, Minardi and Campbell (1980) randomly assigned 56 women with "moderate" menopausal complaints to an estrogen group or to a placebo group for six months following which they were crossed-over to the other treatment for a further six months.

Self-assessment of physical symptoms was carried out by means of Graphic Rating Scales. Compared to baseline scores, estrogen exerted beneficial effects over placebo on hot flushes and vaginal dryness.

In summary, these findings indicate that estrogen administration reliably alleviates hot flushes and vaginal dryness in menopausal women. Furthermore, they suggest that hot flushes occur most frequently immediately following estrogen withdrawl, and that their frequency tends to decrease across time in untreated women.

B) Affective Symptoms

Many affective or psychological symptoms have come to be associated with the menopause. The most frequently investigated symptoms in this group have been depression, irritability, nervousness, and fatigue. Utian (1972) found that irritability and depression were significantly improved both by estrogen (Premarin, 5 mg per day) and by placebo. He concluded that both the active hormone and placebo have a "mental tonic effect" in menopausal women as measured by the investigator's ratings. Results of the George et al. (1973) study in which known psychometric instruments were used are at variance with those of Utian. Using a modified form of the Beck Depression Inventory (BDI), George et al. observed no significant change in either an estrogen (Premarin, 1.25 mg per day) or in a placebo group. Furthermore, other psychological symptoms measured by means of a symptom checklist completed daily showed no significant differences within or between groups. It was concluded that estrogen administration did not have any effect on "minor psychiatric symptoms" (author's term). This study as well, was single-blind. Coope et al.'s (1975) double-blind cross-over study, however, similarly failed to demonstrate differences in depression and

nervousness as measured by the Blatt Menopausal Index, although in this investigation these symptoms were significantly reduced in both the estrogen and in the placebo condition.

Rauramo, Lagerspeitz, Engblom and Punnonen (1975) investigated several aspects of psychological functioning in three groups of women. One group that had just undergone TAH and BSO were administered estradiol valerate 2 mg per day. The second group underwent the same surgery, but was untreated, and the third group had had a TAH with ovaries conserved. Subjective estimates of mood obtained by means of Graphic Rating Scales showed that all groups experienced a decrease in nervousness, fatigue, unhappiness and irritability from preoperative baseline to the end of month one of treatment. The authors interpreted this general improvement to the relief of preoperative stress. Six months postoperatively, however, the untreated oophorectomy group rated themselves significantly higher in nervousness, tiredness and tenseness than the hysterectomy-only group. Mean anxiety scores did not differ significantly either between groups or within groups over time.

Corroboration of differences between estrogen-treated and untreated oophorectomized women across time was provided by Furuhjelm and Fedor-Freybergh (1976). They investigated three groups of subjects. One group of 27 women with irregular menstration and recent onset of vasomotor and psychosomatic symptoms was given estradiol valerate 1 mg per day. A second group of 26 postmenopausal women complaining of the same symptoms as Group 1 was treated with 2 mg of estradiol valerate. Group 3 consisted of 25 postmenopausal women, 12 of whom were given placebo (Group 3A) and 13 treated with 2 mg estradiol valerate for three months (Group 3B). Scores of the estrogen-treated

groups on the Hamilton Depression Scale and the Sabbatsberg Depression Self-Rating Scale both revealed a significant decrease in depression after one, three, and six months of treatment as compared to baseline scores. There were no changes in the placebo group on either of these measures. The single-blind nature of this study and the heterogeneity of the subject sample suggest cautious interpretation of these findings.

Fedor-Freybergh (1976) reported findings on the Eysenck Personality Inventory (EPI) administered during the above study. Women in Group 3A, who were administered 2 mg estradiol valerate per day, showed a decreased neuroticism score and an increased extroversion score on the EPI, whereas Group 3B (placebo) showed the reverse after three months of treatment. It was concluded that estrogen therapy can both improve and reverse deleterious changes in psychological functioning in menopausal women.

The Beck Depression Inventory was administered to 20 postmenopausal women before and following one month of treatment with Premarin 1.25 in a study by Schneider, Brotherton & Hailes (1977). Improvement on the BDI was inversely related to the initial severity of the depression. Thus, of 10 depressed subjects with scores of less than 18, nine showed improvement. However, of 10 patients with scores over 20, six were more depressed after treatment. This suggests that estrogen may improve mild (nonclinical) depression associated with the menopause but that it is ineffective, at least in the doses used, in the treatment of clinical depression. Interestingly, interview data revealed a significantly greater number of perceived psychological and environmental stresses by the depressed as compared to the nondepressed women.

Dennerstein, Burrows, Hyman and Sharpe (1979)

investigated a group of 49 women who had undergone TAH and BSO six months to 27 years previously. Either ethinyl estradiol, a progestogen, a combination of the two hormones or a placebo were administered to three groups of women. Scores on the Hamilton Depression Scale showed beneficial effects of ethinyl estradiol over the other treatment groups. These findings are complicated by the fact that 14 per cent of the sample had received previous psychiatric treatment and 33 per cent had previously been given psychotropic medication. In addition, 21 of the 49 women dropped out of the study and it was not reported what proportion of these subjects had received previous psychiatric treatment. The omission of this information renders these findings uninterpretable.

The results of a well-controlled investigation of psychological symptoms by Stickler, Borth, Cecutti, Cookson, Harper, Potvin, Riffel, Sorbara and Woolever (1977) were discrepant with all of the above findings. Twenty women who had menopausal complaints were randomly assigned either to an estrogen group (Premarin, 1.25 mg) or to a placebo group. Subjects were crossed-over to the other treatment for three month periods over the course of the following year. During an interview at the end of each treatment phase, all subjects reported improvement after taking either estrogen or placebo. Scores on the Minnesota Multiphasic Personality Inventory and the Sixteen Personality Factor Questionnaire showed no consistent differences between placebo and estrogen periods. It should be noted that menopausal status of the subject sample was heterogeneous; nine women were having irregular menses while the other 11 were two to 13 years postmenopausal.

These inconsistencies in the research findings that bear on the relation between estrogen levels and

psychological symptoms, are likely due to the methodological problems described. It can be said, however, that to date there is no clear evidence to support the idea that the administration of estrogen, in doses used to treat menopausal symptoms, significantly affects the parameters of psychological functioning that have been investigated.

C) Cognitive Functioning

Because disturbances in memory and inability to concentrate are prominant complaints at the time of menopause, investigators have attempted to empirically determine changes in these aspects of intellectual abilities as a function of estrogen administration. Rauramo et al. (1975) reported that there were no differences in memory scores as measured by the Integration Memory Test between a group of surgically menopausal women who received estradiol valerate 2 mg per day, a group who were untreated, and a group who had had hysterectomy only. Additionally, no between-group differences were found in logical thinking measured by Raven's Progressive Matrices, or in reaction time, determined in a key-pressing task. These findings are consistent with those of Van Hulle and Demol (1976) who reported no differences between an estrogen-treated group (4 mg of estriol per day) and a placebo group of menopausal women in memory (measured by the Benton Visual Retention Test and by the Digit Span subtest of the Wechsler Adult Intelligence Scale), in concentration (the sub-test of arithmetic calculations of the Groninger Intelligence Test), in learning ability (the Manual Labyrinth of Rey) and in tempo of work and attention (the Spot Pattern Test of Bourdon-Wiersma).

Changes in cognitive functioning in four groups of menopausal women were assessed by Fedor-Freybergh (1977).

Two groups of women received 1 mg estradiol valerate, and another, 2 mg per day. A fourth group was administered placebo. Following six months of treatment, women in the estrogen groups had significantly increased scores compared to baseline in choice reaction time (button-pressing in response to visual and auditory stimuli), in a modification of the Stroop color-word test, in the Konzentrations Verlaufs Test which measures changes in concentration on a serial perceptual sorting task, and in an attention test (VSTM) which measures short-term memory and simple forms of reasoning ability. The placebo group showed no changes on these measures from baseline to the end of treatment. The author suggested that the inconsistency between these findings and those of Raumaro et al. (1975) and of Van Hulle and Demol (1976) may be explained by the multidimentional nature of complex processes such as memory and attention. Since all three studies used different measures, it was implied that some may be more sensitive than others in detecting deficits or improvements in information processing areas as a function of circulating estrogens. It seems likely that some of the discrepancies in these studies may be due to the fact that different forms of estrogen in differing dosages were used. In the latter study, two of the estrogen-treated groups received different dosages of estrogen although all data were analyzed together. These confounds complicate interpretation of these data.

D) Sexual Functioning

Decreased libido following both a surgical and natural menopause is commonly reported by clinicians and patients. However, several investigators have found no changes in libido (undefined) as a function of estrogen administration. Utian (1972) reported a 25 to 44 per cent incidence of decreased libido in women who underwent

hysterectomy irrespective of whether their ovaries were conserved or not. Neither estrogen nor placebo had any effect on decreased or absent libido. Changes in libido were measured by means of the investigator's subjective ratings. Likewise, Coope et al. (1975) found no changes in libido as measured by the Blatt Menopausal Index between an estrogen and a placebo group.

Other investigators studied changes in various aspects of sexual functioning with differing results. Estrogen-treated menopausal women did not differ from a control group in masturbation, orgasm, frequency of coitus and coital satisfaction, although they did report a significant improvement in vaginal dryness (Campbell, 1976). Parameters of sexual functioning were measured by Graphic Rating Scales. These findings were confirmed in a retrospective study of 89 women who had undergone hysterectomy and bilateral oophorectomy six months to five years previously (Dennerstein, Wood & Burrows, 1977). In semi-structured interviews, 37 percent of women reported that sexual relations had deteriorated, 30 percent reported improvement and 29 percent reported no change compared to their preoperative status. When exogenous estrogen was being taken continuously (70 percent of the sample), there was significantly less dyspareunia than when it was being taken sporadically (17 percent) or not at all (12 percent). Moreover, no association was found between administration of estrogen and sexual desire, sexual enjoyment, ability to reach orgasm and ease of vaginal lubrication although dyspareunia was alleviated. Of clinical importance was the finding that preoperative expectations of sexual alteration were significantly associated with loss of desire for sexual intercourse. Furthermore, lack of sexual desire in these patients was found to be unrelated to their reported feelings of physical and mental well-being. The retrospective

uncontrolled nature of this study as well as the varying hormonal status of the subjects preclude firm conclusions based on these findings.

The results of a fourth study on the effect of estrogen administration on sexual functioning in menopausal women likewise found no effects of hormone (Maoz and Durst, 1980). There were no differences in frequency of sexual intercourse or in sexual satisfaction between a group of 40 menopausal women who received conjugated estrogens and a group who remained untreated for nine months. Once again, the estrogen-treated group reported a significant decrease in dyspareunia compared to pretreatment levels. Information concerning sexual functioning was obtained in two semi-structured interviews, one at baseline, and another following nine months of drug (or no drug) treatment. These data, therefore, were in accord with those of Utian (1972), Coope et al.(1975), Campbell(1976) and Dennerstein et al. (1977). One investigator has reported positive effects of estrogen on sexual functioning (Fedor-Freybergh, 1977). Women who received either 1 or 2 mg of estradiol valerate per day reported significant increases in libido, sexual activity, sexual satisfaction, sexual fantasies and orgasm capacity after three months of treatment, whereas there were no changes in any of these measures in a placebo group. The various aspects of sexual functioning were assessed by means of the Sabbatsberg Sexual Self Rating Scale which was completed by each subject at baseline and following three months of treatment. The varying doses of hormone, the heterogeneity of the sample with respect to their menopausal status and the single-blind nature of this study suggests that these findings be interpreted cautiously. The consistency of the evidence from other studies supports the conclusion that although estrogen adminstration is effective in alleviating dyspareunia in menopausal women, it seems to be of no

benefit in the treatment of lack of sexual desire, sexual satisfaction and orgasmic ability.

The Role of Androgens

The two major sources of androgens in the human female are the adrenal cortex and the ovary. 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 adrenal cortex steroid activity (Rosenthal, 1968). Peripherally, pubic and axillary hair develop in the female in part as a result of stimulation by adrenal androgens. Abraham (1974), using dexamethasone to suppress adrenal function in reproductive-age women determined that adrenal contribution to serum estradiol was negligible -- almost 100 percent of estradiol therefore is produced by the ovary. The adrenal, however, made major contributions to both the testosterone (T) and the androstenedione serum levels. The adrenal contribution to serum T was 0.2 ng/ml, whereas the ovarian contribution during the follicular and luteal phase was only 0.1 ng/ml. At ovulation, this rose to 0.28 ng/ml. Adrenal androstenedione was 0.6 ng/ml whereas the ovarian contribution during the follicular and luteal phases was 0.5 ng/ml with an increment at mid-cycle to 1.5 ng/ml. Clearly, the ovarian contribution to serum T and androstenedione levels in reproductive-age women is significant.

In addition to their influences on sexual development, there are known general anabolic effects of androgen. Anabolism refers to the building up of the body substance, the constructive or synthetic chemical reactions included in metabolism. These effects may be manifested by muscle

hypertrophy, weight gain, increased oxygen uptake ability and nitrogen retention by the blood (Johnson and O'Shea, 1969). It is also known that androgens may stimulate the appetite and impart a sense of well-being (Prader, 1967). When administered to females, androgens tend to produce dose-related degrees of masculinization. Among the early manifestatiions are acne, hirsutism (growth of facial hair), deepening of the voice, and clitoral hypertrophy. Most of these side effects do not become troublesome unless the dosage of testosterone reaches 300 mg. per month (Kistner, 1979).

In animal studies, the localization of steriod-sensitive neurons by means of tritium-labeled steroids has aided immeasurably in the study of some of the behavioral actions of gonadal steroids in the brain and has allowed for hypothesizing and testing these behavioral phenomena in humans as a function of hormonal status. Androgen sensitive neurons are difficult to map owing to the fact that testosterone is extensively converted to estradiol as well as 5 -dihydrotestosterone (DHT) in the brain (Naftolin & Ryan, 1975). However, androgen-sensitive receptor sites in female rat brain have been identified in the pituitary, the preoptic area, the basomedial hypothalamus, the corticomedial amygdala, the septum, the hippocampus and the parietal cerebral cortex (McEwen, 1981).

Psychotropic Effects of Androgens

The menopause literature contains no studies that tested the effects of exogenous androgen on affect, on physical symptoms, or on cognitive functioning. Several investigators, however, have provided information concerning the effects of this sex steroid on behavior. In a review article, Herrmann and Beach (1976) concluded that

the psychotropic effects of androgens can be demonstrated in a number of areas of psychological functioning including aggression, psychomotor function, mental performance, mood changes and sexuality. Kruez and Rose (1971) found no relation between adult aggressiveness and testosterone levels in a study of criminals but those with high testosterone levels were found to have been more aggressive during their adolescence than those with lower levels. Persky, Smith and Basu (1971) reported that there was a significant correlation between testosterone production rate and hostility and aggression scores (measured by the Buss-Durkee Hostility Inventory) in a group of younger men whose mean age was 22 years. However in an older group of men (mean age 45 years), age rather than aggression was the important determinant of testosterone production. In a study of 20 normal males tested every second day for two months, there was no significant correlation between plasma testosterone levels and hostility as measured by the Buss-Durkee Hostility Inventory (Doering, Brodie, Kraemer, Becker & Hamburg, 1974). However, there was a significant positive relationship between testosterone and hostility as measured by the Multiple Affect Adjective Checklist (MAACL). The inconsistencies in these findings preclude conclusive statements regarding the relationship between hostility and testosterone levels in the human male.

The notion that androgens have energizing properties is supported by the observation that boys and girls with excess androgen have high energy levles, increased motor activity and increased assertiveness (Rose, 1972). Additionally, Itil, Cora, Akpinar, Herrmann and Patterson (1974) found that depressed patients who received exogenous androgen showed an increase in physical activation. Androgens have also been shown to improve coordination (Herrmann, McDonald and Bozak, 1976).

Performance in various cognitive tests has been found to improve after the administration of androgen. Vogel, Broverman, Klaiber, Abraham and Cone (1971) reported that subjects who received exogenous testosterone showed significantly less deterioration with time than did a control group on serial subtraction problems. Herrmann et al. (1976) demonstrated significantly improved performance on the part of androgen-treated males in arithmetic tests of varying complexity. It was concluded that androgens have effects comparable to psychostimulants. Moreover, several authors have reported that the administration of androgens to depressed males caused a decrease in depressive mood, sadness and feelings of inadequacy (Itil, 1976; Klaiber, Broverman, Vogel and Kobayashi, 1976). It should be noted that without exception, all of the studies which investigated changes in psychomotor, psychological and cognitive functioning utilized male subjects exclusively.

Effects of Androgen on Libido

Evidence concerning the libido-enhancing effects of androgen in the human female comes from three major sources; (1) early reports of androgen administration to treat a variety of gynecological disturbances, including menopausal symptoms, (2) studies in which androgen was administered in an attempt to treat breast cancer and, (3) investigations in which endogenous androgens were totally depleted surgically as a therapeutic measure to halt the course of metastatic breast cancer. Despite the serious methodological shortcomings in each of the three areas, these reports constitute the only evidence in the literature for the effect of androgen on human female sexual functioning and will therefore be reviewed here.

Soon after testosterone proprionate had been

synthesized in the mid 1930's, it was used to treat a variety of gynecological disturbances such as menorrhagia (excessive bleeding at the time of a menstrual period), cyclomastopathy (excessive tissue proliferation of the breast), dysmenorrhea (painful menstruation) and menopausal symptoms in oophorectomized women (Greenblatt, 1942). One of the earliest studies undertaken to investigate the effects of testosterone reported on menopausal women who received therapeutic doses of estrogen and concomitantly 25 to 50 mg. of testosterone propionate daily. The therapy resulted in the serendipitous finding that sexual appetite and response were significantly greater than that experienced with estrogens alone (Shorr, Papapanicolaou and Stimmel, 1938). Following this observation, many studies originally undertaken to assess the efficacy of various therapeutic agents for the management of menopausal symptoms almost universally reported increased libido as an effect of exogenous androgen (Carter, Cohen and Shorr, 1947; Groome, 1939; Silberman, 1940). Several investigators reported, however, that the effects of androgen adminstration on libido were dependant upon previous sexual functioning; women who described "very little or no libido" in the past reported no change in sexual desire following testosterone pellet implants whereas those who "had once had libido but lost it", reported a marked increase after treatment (Greenblatt, Mortara and Torpin, 1942; Kupperman and Studdiford, 1953).

Greenblatt, Garner, Calk and Harrod (1950) carried out a double-blind study to assess the relative efficacy of hormones administered singly or in combination to menopausal women. Satisfactory relief of all symptoms was reported by 96.9 percent of patients who received estrogen alone, and by 89.6 percent who received an estrogen-androgen combination (diethylstilbestrol .25 mg and methyltestosterone 5 mg per day). Only 23.5 percent of

those who received androgen alone reported symptom relief, while 83.3 percent of the subjects in the placebo group reported no improvement of symptoms. Most noteworthy, 66.6 percent of the patients stated a preference for the estrogen-androgen combination because of increased well-being and libido they experienced while on this regime. These findings were confirmed in a study by Caldwell and Watson (1952) in which it was found that postmenopausal women who received a combined estrogen-androgen preparation showed improved physical capacity, increase in weight and improvement in memory and in ability to learn new material. Despite the consistency of the findings of these early studies, it should be noted that they lacked control groups, used unsystematic methods of data collection, and many were often anecdotal in nature.

Greenberg and Leng (1972) administered various doses of a number of hormones to a woman complaining of frigidity and collected her self-reports of changes. Estrogens increased sexual response to 1+, on a scale varying from zero to five whereas both progestens and placebo elicited a zero response. However, methyltestosterone administered in 15 mg doses orally elicited a 3+ response, intramusculaar injection of testosterone propronate 25 mg per 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 sexual desire, and degree of sexual gratification was found to be dose-related. Information regarding exact method of data collection, duration and sequence of treatment connditions was not presented. Though these findings are interesting, missing procedural details in this uncontrolled study render them inconclusive.

A second, though somewhat weak source of support for the libido-enhancing effects of androgen comes from the clinical reports of its administration in the treatment of estrogen-dependant breast cancers (Foss, 1951; Kenhedy, 1973). This treatment was based on the belief that large doses of androgen would oppose the effects of estrogen and thus halt spread of the disease. These women spontaneously reported increased libido as a result of the hormone therapy. However, the massive doses of testosterone propionate used in these cases (1200 mg per week), the confounds inherent in this gravely ill subject sample, and the uncontrolled nature of the reports, detract from the meaningfulness of these findings.

A third series of studies undertaken in the late 1950's and early 1960's concerned women who underwent several surgical procedures in an effort to halt the continuing spread of metastatic breast cancer. Following the administration of estrogen after mastectomy and oophorectomy, no change in sexual desire was obvious (Waxenberg, Drellich & Sutherland, 1959). However, following adrenalectomy, carried out because of progression of the malignant disease, 14 out of 17 patients reported the sudden absence of all sexual desire. In a later study of seven patients who had oophorectomy one to seven years before the adrenals were removed all reported almost total loss of sexual feelings and responsivity after adrenalectomy (Drellich & Waxenberg, 1966). A few of these patients had reported only moderate changes in sexual feelings and response after their earlier oophorectomies. It was concluded that the total loss of endogenous androgen as a result of adrenal ablation was in large part responsible for the observed radical decrease in libido in these patients.

Schon and Sutherland (1960) evaluated the sexual

functioning of women from the time they were faced with the diagnosis of breast cancer though the period covering the various surgical procedures related to its treatment. Eighty-five percent of the women retained the same degree of sexual desire and frequency after mastectomy as before and 75 percent experienced the same intensity of gratification. It was therefore concluded that mastectomy did not appreciably influence sexual behavior. Of six women who underwent subsequent bilateral oophorectomy, sexual desire remained at the same level in four patients, decreased mildly in one and in one other, it dropped to zero. Half the patients reported that sexual activity remained at preoperative levels, while half reported a decrease. Once again, the authors concluded that oophorectomy appeared to have no appreciable effect on sexual functionintg. Statistical evaluation of these data was not undertaken because of the small sample size. Subsequently, 30 women who had had mastectomies and oophorectomies underwent hypophysectomy (removal of the pituitary) as a therapeutic measure to check the progress of metastatic breast cancer. None of these patients had been adrenalectomized. Interviews done ten months postoperatively revealed that in 87 percent of patients, sexual activity was less frequent or totally absent, and in 85 percent, sexual gratification was reduced or not experienced. The administration of thyroid hormone and cortisone had no effect on sexual behavior. It was concluded that the absence of the tropic pituitary hormone that activitates the adrenal production of androgens accounted for the observed drastic decline in sexual functioning following surgical removal of the pituitary. In this study, data concerning presurgical levels of sexual functioning consisted of retrospective verbal reports. A more critical caveat with regard to all of these findings relates to the nature of the population that was studied; assessment of parameters of sexual functioning in women who

required three major surgical procedures in an attempt to halt progress of a malignant disease seriously brings into question the meaningfulness of these observations. Nevertheless, these reports remain the most frequently cited as evidence of androgen's libido enhancing properties in women.

In a review article, McCauley and Ehrhardt (1980) provided guidelines with respect to future research on androgen and human female sexuality during the menopause. They suggested that behavioral data be detailed and accurate, that hormone measurements be undertaken, and that social and cultural circumstances and somatic symptoms be evaluated in menopausal women in order to separate possible influences of these variables on sexuality from the effects of hormones.

The Present Study

The menopause literature contains few studies which have focused on hormone-behavior relations during this phase of life. More complete information on which of the behavioral symptoms commonly reported at the time of menopause are directly attributable to endocrine changes and which are due to concurrent aging and associated mid-life changes (Notman, 1979) would have important theoretical and clinical implications. Such research would add significantly to our knowledge of gonadal hormone-behavior relations in women and could lead to more precisely focused clinical treatment strategies.

Hysterectomized and oophorectomized women provide a unique opportunity for studying hormone-behavior relationships because of the abrupt endocrine changes that result as a consequence of the surgery. Additionally, the commonly accepted clinical practice of administering sex

steroids, singly or in combination, to premenopausal women who have undergone oophorectomy, permits the study of the physical and psychological effects of gonadal hormones under controlled conditions. Differential response of the three menopausal symptom constellations to the administration of estrogen and/or androgen to oophorectomized women would imply varying etiolgies requiring different treatment strategies.

This research project was undertaken in order to assess the effects of sex steroids on mood, on physical symptoms, and on cognitive and sexual functioning in menopausal women. The study was designed to control for as many intervening variables as possible. Several features of the experimental design increased the probability that behavior changes accompanying hormonal manipulations were in fact attributable to hormonal effects per se. This prospective study investigated a homogenoeous population of women with respect to age, endocrine status and general health. Assessment instruments in common usage, having known reliability, validity and established norms, were employed to assess changes in psychological functioning. Dosages of the various hormonal preparations were equated and drugs were administered parenterally thereby minimizing confounding influences of various dosages of hormone and eliminating the issue of compliance. Random assignment of subjects to treatment groups and the double-blind nature of the design served to preclude experimenter and subject biases. Plasma hormone and gonadotrophin levels sampled immediately following psychological assessment provided a rigorous test of the possible associations between circulating hormone levels and psychological and physical functioning. Completion of written self-reports daily throughout the entire course of the study allowed consistent monitoring of the vairables of interest. Finally, the inclusion of two control groups -- one which

served as a control for any placebo effects of the sex steroids adminstered, and one to control for the impact of the specific surgical procedure itself -- provided critical bases of comparison against which to evaluate changes in the hormone treatment groups.

Although estrogen is the hormone most crucially implicated with respect to symptom formation at the time of menopause, there is a paucity of studies that have investigated the effects of androgen, a normal secretory product of the adrenals and ovaries. Surprisingly, the role of this steroid with regard to female psychological and physical health is largely unknown. It was therefore a specific goal of this experiment to investigate the effects of androgen, administered alone or in combination with estrogens, on parameters of psychological and physical functioning in oophorectomized women. To date, no well-controlled study could be located that had attempted to assess empirically the effects of androgen administration in menopausal women.

To summarize, the objectives of this experiment were to (1) assess the effects of estrogen and androgen, administered individually and in combination, on sexual, psychological, somatic, and cognitive functioning in oophorectomized women within the context of a well-controlled experimental design; (2) to provide guidelines with respect to the type of hormonal preparation which effectively alleviates specific menopausal symptoms and (3) to address the theoretical issues with regard to the effects of estrogen and androgen on mood and behavior in the human female.

METHOD

Subjects and Subject Selection

A) Subjects

Forty-seven women were recruited from the practice of the Chairman of a Department of Obstetics and Gynecology at a university teaching hospital in Montreal, Canada. At the time of an office visit when it was determined that the patient needed to undergo surgery, the gynecologist evaluated her suitability for inclusion in the study according to a list of selection criteria described below. Women who agreed to meet with the experimenter for purposes of an explanation of the goals and procedure of the study were then referred. Subjects were interviewed between January, 1980 and October 1981 in the order that they were seen in the gynecologists' office. Eight subjects who met the selection criteria and who were initially interviewed and tested did not continue in the study; two women decided to defer surgery, one refused to comply with the self-monitoring procedure after one week and one was eliminated after the first post-operative month because she declined to accept random assignment to drug groups. In addition, one subject was found to have an unsuspected carcinoma of the ovary at the time of surgery which precluded her participation in the study. In three cases, the random assignment code had to be broken because subjects were experiencing distressing frequencies of hot flushes. On this basis, two subjects were eliminated from the study at the end of the first treatment month; one had received placebo and the other, androgen-alone. The third subject, who as well had been given androgen-alone, was eliminated from the study at the end of the second treatment month. The remaining 39 women comprised the pool of subjects who were assigned at random to the experimental groups. Subjects ranged in age from 29 to 52 years with a mean age of 45.1 years.

B) Subject Selection Criteria

In order to maximize the ability to attribute somatic

and behavioral changes to the experimental manipulations, the attempt was made to secure a subject sample which was as homogeneous as possible. Thus several criteria were adhered to in selecting subjects for this study. Firstly, subjects had to be premenopausal women who required a TAH and BSO for reasons other than treatment of malignant disease; if the pathology report indicated the presence of an unsuspected malignancy, the patient was eliminated from the study. It was required that subjects be married or associated with a steady partner for at least two years and that the partner be in a state of good general health. Likewise, subjects had to be in a state of good general health aside from the symptoms necessitating the surgery. An additional requirement was the absence of a recent (five years) or current history of serious psychological problems for which treatment was obtained. Current treatment with any medications for physical or psychological symptoms precluded participation in the study. Finally, subjects had to be willing to comply with the experimental procedure.

In order to avoid the possibility of unstandardized information being conveyed to the subject prior to recruitment into the study, the gynecologist did not discuss the experimental procedure with the subject. Women who fulfilled the selection criteria met with the experimenter for an initial interview. The Information and Consent Form was presented to the subject at that time (Appendix A). This form was designed both to explain the procedure and goals of the study and to emphasize the voluntary nature of participation. Subjects signed the consent portion of the form at the time of the initial interview with the experimenter to indicate their understanding of these issues and their desire to participate in the study.

Design and Procedure

A) Treatment Groups

Subjects were randomly assigned to one of four drug treatment groups at baseline. All drugs were given intramuscularly once a month for the first four postoperative months. The method and rationale for determining drug dosages of the individual preparations appear below. The treatment groups consisted of an estrogen-androgen (E-A) combined drug (Climacteron, Merck-Frosst), an estrogen alone (E) drug (Delestrogen, Squibb), an androgen alone (A) drug (Delatestryl, Squibb), and a placebo (PL) preparation (Sesame oil). The inclusion of the PL group was intended to control for possible changes in symptoms and behavior as a result of the endocrine changes attendant upon bilateral oophorectomy. Moreover, data generated by premenopausal women who had undergone TAH and BSO and who were not receiving exogenous hormones would provide information concerning the incidence and severity of symptoms as a function of their altered endocrine status.

B) Hysterectomy Control Group

Nine women who required a total abdominal hysterectomy (TAH) without bilateral salpingo-oophorectomy (BSO) were recruited to serve as a control group for the nonspecific effects of TAH in the absence of endocrine changes. Save for the retention of their ovaries at the time of surgery, these subjects met the same selection criteria as those in the treatment groups and underwent an identical experimental procedure except for the administration of hormones. These subjects ranged in age from 30 to 40 years with a mean age of 36.3 years.

C) Computation of Drug Dosages

It was necessary to ensure that subjects in the hormone treatment groups would receive equal amounts of estrogen and androgen per dose. Different dosages of hormones could have led to differential effects on somatic symptoms and on other variables of interest, thus confounding the findings. The procedure used to equalize the dosages was to calculate the molecular weights of the salts to which each of the estrogen and androgen preparations were bound. This sum was then subtracted from the weight of the total compound. The residual represented the amount of free estradiol and/or testosterone in each drug. After the amount of free hormone in each drug was thus obtained, it was determined that 0.63 ml of the estrogen-alone (E) preparation (Delestrogen) was equivalent to the amount of unbound estradiol in 1 ml of the estrogen-androgen (E-A) preparation (Climacteron). In the same manner, it was also determined that 0.48 ml of the androgen-alone (A) drug (Delatestryl) was equivalent to the amount of unbound testosterone in the combined drug. Subjects in the placebo group (PL) received 0.5 ml of sesame oil monthly which was selected because it is used as the suspension for the E-A combined drug. The composition of the three hormonal preparations and the dose equivalence calculations are found in Appendix A.

Design Overview

Two experimental designs that differed only with regard to the number of time periods involved were used in this study. The basic design was a five (treatment groups) x five (time periods) factorial with repeated measures on the second factor. This design pertained to variables measured by means of a daily questionnaire. A five (treatment group) x three (time periods) factorial with repeated measures on the second factor was used with regard to measures that comprised a psychological test battery.

Figure 1 is a diagramatic representation of the experimental design.

Time Periods

A) Injection Times

At the time of referral, subjects were assigned a number in the order in which they were recruited into the study. The sequential numbers corresponded to a previously devised random assignment list of subjects to treatment groups. The random assignment list was in the possession of a staff gynecologist who was not otherwise collaborating in the study. The double-blind nature of the investigation was thus assured; neither the experimenter nor the subjects were aware of group assignment.

Subjects in the four treatment groups each received a total of four injections during the course of the study. The first injection was administered on the third postoperative day by the ward nurse. The drug order for this injection was written by the staff gynecologist who was in possession of the random assignment list. Subjects returned to the hospital three times at monthly intervals to receive injections that were given by the office nurse. The first three injections (one administered after surgery, and two as outpatients) contained the same hormonal preparation for each individual subject; this three month series of injections, therefore, constituted the drug treatment phase.

The fourth injection, adminisitered on the first day of the fourth postoperative month to subjects in all four treatment groups, was a placebo. This design feature was intended to determine whether mean scores on the variables measured would change when hormones were withdrawn. Such within-group changes, if they occurred, would provide supportive evidence of hormonal effects on the behaviors

PREOPERATIVE		SURGERY	POST OPERATIVE			
TREATMENT GROUPS	BASELINE		MONTH 1	MONTH 2	MONTH 3	PLACEBO
ESTROGEN-ANDROGEN						
ESTROGEN						
ANDROGEN						
PLACEBO						
HYSTERECTOMY CONTROL						

Figure 1. Experimental Design

tested. In addition, the magnitude of the within-group changes from the treatment phase to the end of the placebo month would provide information concerning the effect of an abrupt change in endocrine status on behavior with the PL group scores serving as a basis for comparison. The time interval between injections for all subjects ranged from 26 to 32 days (mean = 29.7 days).

B) Test Times

This study involved two testing procedures for all subjects. The first procedure consisted of daily monitoring of symptoms and behaviors throughout the approximate five month course of the study by means of a questionnaire. Thus, mean scores for each of the five months comprised the five (treatment group) x five (time period) repeated measures design.

The second testing procedure consisted of three test sessions at different points in the study during which a psychological test battery was administered. The first test session occurred at the time of the initial preoperative interview; the second was carried out on the third day following the third injection, and the final test session took place on the last day of the placebo month. Venous blood samples were obtained immediately following each of the three test sessions in order to measure plasma levels of total estrogens, testosterone, LH, and FSH. Thus, mean scores on the measures in the psychological test battery administered at these three times constituted the five (treatment group) x three (time periods) repeated measures factorial design of the second testing procedure.

The attempt to investigate the relation between the dependent variables and plasma hormone and gonadotrophin levels guided the choice of the three test sessions. At

baseline, mean scores on the measures reflected levels of functioning associated with endogenous levels of hormone for each individual subject. The timing of the second test session was intended to coincide with either a peak or a stable maximal level of plasma hormones during the third treatment month. Since dose-response data with respect to the specific drugs used in this study were not available, the time of testing could not be determined empirically. Clinical report and evidence from pharmacological studies, however, indicated that maximal plasma levels of hormone occurred one to five days following injections of other estrogen preparations (Rauramo, Punnonen, Kaihola & Gronroos, 1979; Yen, Martin, Burnier, Czekola, Greaney & Callantine, 1975). Accordingly, subjects underwent a test session and had a blood sample drawn on the third day following their third injection. The last day of the placebo month was chosen as the third test session in order to maximize the likelihood that the hormones administered during the treatment phase had been completely metabolized thereby minimizing any effect of exogenous hormone on the measures.

To summarize, each subject underwent a test session and had a blood sample taken preoperatively. Subjects were then given 30 questionnaires and envelopes and instructed to fill out and mail one form each day until their admission to the hospital. On the third postoperative day, each subject was given an injection of hormone or placebo by the ward nurse. At the same time, they received 30 questionnaires and envelopes. Following their hospital discharge after surgery, subjects returned to the hospital on five occasions during the course of the study -- three times to receive an injection and a monthly supply of questionnaires and twice for psychological test sessions coincident with the drawing of a blood sample. The sequence of testing is shown in Figure 2.

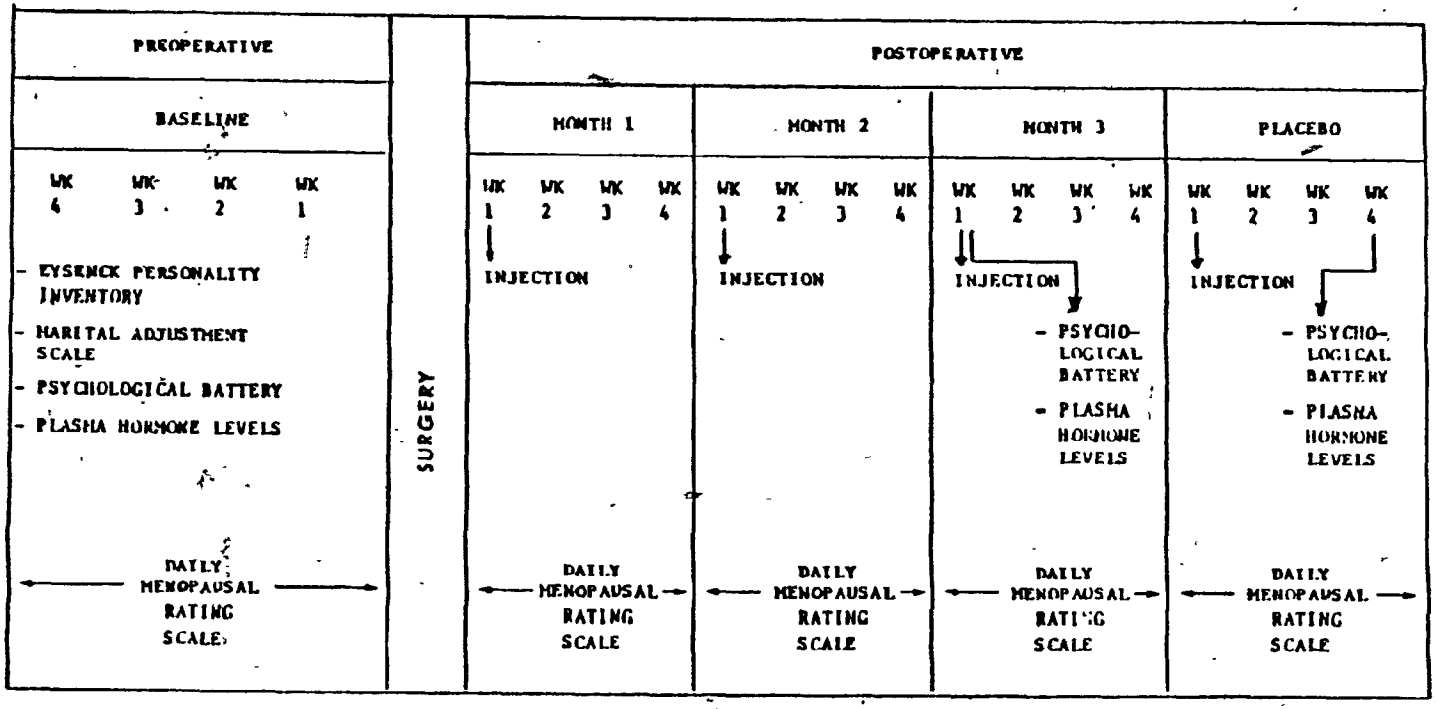

Figure 2. Sequence of Testing

Materials

A) Preoperative Baseline Period

Several measures were administered only during the preoperative baseline test period in order to gather data relating to a variety of subject characteristics. An Initial Interview Form (Appendix A) was used to elicit information pertaining to sociodemographic data, previous medical history, past and current gynecological history and health of the partner. The Marital Adjustment Scale (Locke & Wallace, 1959) was administered because of the possibility that extreme marital disharmony might have confounded any effect of drug on mood, somatic symptoms and sexual functioning. It is a 15-item self-report inventory which requires the subject to rate various aspects of married life. The test has demonstrated good test-retest reliability (Kimmel & Van der Veen, 1974). It is also the most frequently reported measure of marital satisfaction (Burgess, Locke & Thomes, 1971; Weiss, Hops & Patterson, 1973; Wills, Weiss & Patterson, 1974) and thus, provides a basis for comparison with other studies. The standard cut-off score of 100 as recommended by Burgess et al. (1971) was used to distinguish between unsatisfactory and satisfactory marital relationships.

The third instrument used only at baseline was the Eysenck Personality Inventory (EPI). It is a short, reliable and valid measure of two dimensions of personality -- extraversion-introversion and neuroticism-stability (Eysenck, 1962; Eysenck, 1963; Kramer, 1965). It has been determined that this measure is of use in any study where it may be suspected that personality and individual differences are likely to have an effect on the dependent variables (Eysenck & Eysenck, 1968).

B) Daily Menopausal Rating Scale (DMRS)

The DMRS (Appendix B) was the instrument used to measure daily changes in somatic, affective, and sexual functioning during the study. It is a 17-item self-report questionnaire which proved to be a reliable and fairly sensitive index of drug effects in a previous study (Sherwin, Brender and Gelfand, 1980). Many questions dealt with quantifiable, discrete behaviors such as the number of arguments engaged in per day (question 5). Other 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. The poles 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. At the beginning of each month, subjects were given 30 questionnaires and 30 stamped, self-addressed envelopes. They were asked to complete and mail a questionnaire daily.

C) The Psychological Test Battery

The Psychological Test Battery, administered at three points in time during the course of the study, included measures of somatic, affective, and cognitive functioning.

i) The Menopausal Index (MI). The MI, revised by Neugarten and Kraines (1965) was originally published by Blatt, Wiesbader and Kupperman (1953). It lists 28 symptoms most often reported by clinicians and by women themselves as being typical or frequent complaints at menopause. Symptoms were divided, on an intuitive basis, into three subgroups--somatic (12 symptoms), psychosomatic (five

symptoms), and psychological (11 symptoms) (Blatt et al., 1953). The score reflected the total number of symptoms reported by the subject. Three subscores are also derived which represent the number of symptoms reported under the three categories. This scoring method thus yields information about the incidence of symptoms in menopausal women although not about the intensity of these symptoms which is known to be highly variable (McKinlay and Jefferys, 1974). The scoring system of Blatt et al. (1953) provided a weighted numerical index of 11 menopausal symptoms which does take into account both incidence and severity. However, the authors of this instrument based their weighting of these symptoms on what they termed "presumed diagnostic significance". Thus, vasomotor symptoms were scored as four, parasthesia (listed as numbness and tingling), insomnia and nervousness as three and other symptoms such as depression, dizzy spells and fatigue as one. Because this numerical weighting method seemed somewhat arbitrary, it was decided in this study to require each subject to rate the severity of each of 26 symptoms adapted from Neugarten and Kraines (1966) on a bipolar rating scale which had a range of one to seven. The low end of the scale for each symptom was described as "almost never" while the extreme end stated "very often". The subject was instructed to circle the number which best represented the severity with which they were currently experiencing each symptom. In accordance with Blatt et al. (1953), nine symptoms were categorized as being somatic, five as being psychosomatic and 12 as being psychological (Appendix B).

ii) The Multiple Affect Adjective Checklist (MAACL). The MAACL is a self-administered inventory which measures three affects -- anxiety, depression and hostility (Zuckerman and Lubin, 1965). The "Today Form", used in this study, is a sensitive, valid and reliable instrument which measures

current levels of the affect dimensions and was specifically designed for use in repeated measures studies (Hankoff, Rudorfer & Paley, 1962; Tolor & Mabli, 1965; Winter, Ferriera & Ransom, 1963; Zuckerman, 1962). Subjects were required to select from a list of 132 adjectives those which described how they felt at the time of test administration. This instrument has been frequently used in hormone-behavior studies in order to provide measures of affect as they relate to different hormonal states (Lubin, Gardner and Roth, 1965; Persky, Smith and Basu, 1971; Zuckerman, Nurnberger, Vandieveer, Barett and den Breeiyen, 1963).

Three tests, included in the Psychological Test Battery, were given in order to assess the effects of hormonal changes on different aspects of intellectual functioning.

iii) Digit Span. The Digit Span, a subtest of the Wechsler Memory Scale (Wechsler & Stone, 1945), was used as a measure of short-term memory. Three comparable tests were devised, based on the items in the manual (Wechsler & Stone, 1965), one for use in each of the three test sessions, with order counterbalanced across subjects. The instructions given to the subjects and the three sets of stimuli appear in Appendix B.

iv) Abstract Reasoning (AR). AR, a subtest of the Differential Apptitude Test (DAT) (Bernett, Seashore & Wesman, 1974) is intended as a non-verbal measure of a persons' reasoning ability. It involves the ability to perceive relationships in abstract figure patterns. The series presented in each problem requires the perception of an operating principle in the changing diagrams. In each instance, the subject had to discover the principle or

principles governing the change of the figures and give evidence of her understanding by designating the diagram which should logically follow by choosing one of the four options presented. The first 25 items of Form S, the second 25 items of Form S and the first 25 items of the alternate Form T were administered respectively, at each of the three testing sessions. The order of testing was counterbalanced across subjects. Subjects were allowed 12.5 minutes to complete the task.

v) Clerical Speed and Accuracy (CSA). CSA, another subtest of the DAT is intended to measure speed of response in a simple perceptual task. For each item, the subject had first to select the combination of numbers and/or letters which is underlined in a sequence of numbers or letters underlined in the test booklet, then bear it in mind while seeking the same combination in a group of similar combinations on a separate answer sheet. The objective is to measure speed of perception, momentary retention, and speed of response. The first and second halves of Form S (50 items) and the first half of Form T constituted the three tests administered at the three testing sessions during the study with order counterbalanced across subjects.

Plasma Hormone Assays

Venous blood was drawn in four 10 ml Vacutainer tubes containing 143 U.S.P units of sodium heparin. The tubes were immediately placed in chipped ice and were centrifuged in a Sorvall RC-3 automatic refrigerated centrifuge for ten minutes at 2000 r.p.m. The plasma was then aliquoted into four glass culture tubes, covered with parafilm, labelled and stored at -70 degrees Celcius. All samples from each subject were measured in the same assay at the conclusion of the study. Assays were performed in the laboratory of

Dr. H. Guyda, Chief, Department of Endocrinology, Montreal Childrens' Hospital, Montreal, Canada.

(A) Total Plasma Estrogens

Total plasma estrogens (estrone and estradiol) were measured by means of radioimmunoassay. The extraction of protein before the addition of antiserum ensured that both free and previously bound hormone were being assayed. Endocrine Sciences antiserum No. E17-94 (Endocrine Sciences Technical Bulletin, 1972) was used. A standard curve of percent binding and pg/ml was derived for each assay.

(B) Testosterone

Plasma testosterone was measured using the Covalent-Coat Radioimmunoassay Kit (Bio-RIA, Montreal, Canada). The Testosterone (125 I) Assay detects the total unconjugated form of this steroid. It does not distinguish true free testosterone from protein (albumin and SHBG) bound testosterone.

Data Analysis

Huck and McLean (1975) have advanced a number of arguments concerning the appropriate statistical procedures for a pretest-posttest design. Their contention is that, since treatment effects only influence the post test data, a repeated-measures ANOVA applied to this design will yield an F test for the main effect of treatments that is too conservative. In this study, although all the subjects were premenopausal, their ages ranged from 29 to 50 years indicating, a priori, that their plasma levels of endogenous hormones were likely dissimilar. To the extent that hormonal status does affect the variables studied, the

possibility existed that subjects might differ on the psychological and physical measures at baseline even though no treatment had been administered. This information would have been of great interest and it was for this reason that the data were analyzed using a repeated-measures ANOVA computer program.

The problem of choosing a particular posteriori multiple-comparison procedure to apply to a particular set of experimental data has never been properly resolved (Ferguson, 1981). In terms of per-comparison Type I error, multiple comparison procedures may be ordered from low to high as follows: Scheffé, Tukey, Newman-Keuls and Duncan. Historically, the Scheffe method was preferred for unequal sample sizes because it is based on the sampling distribution of F and thus is not dependent upon equal variances of the means nor consequently upon equal sample sizes for its validity (Scheffé, 1959). The Tukey test, based on the studentized range statistic (Tukey, 1953), was derived under the restriction that the variances of the sample means are equal, and therefore the number of observations per sample must be equal. Recently, however, modifications have been developed that relate to the validity of using the Tukey test with data obtained in actual research settings which often fail to satisfy the requirements of the derivation (Keselman & Rogan, 1976). Several authors have recommended the modification of replacing the group size with the harmonic mean of the unequal group sizes (Kirk, 1968; Winer, 1971).

The issue of how large a disparity between group sizes is permissible in the use of the Tukey test with the harmonic mean modification has been addressed by several investigators. Petrinovich and Hardyck (1969) compared the several methods used for paired comparisons among all group means following analysis of variance for sensitivity to

violation of stated requirements. No appreciable change in Type I error rates was found between the Scheffé and modified Tukey test when sample sizes differed by a ratio of 3:1. They concluded that such conditions as unequal sample size, unequal variances, nonnormal populations etc. seem to make little difference to the Tukey and Scheffé methods. The appropriateness of the use of either test on any data appropriate for analysis of variance was supported.

Smith (1971) investigated the effects of the magnitude of differences in group sizes, average group sizes, and number of groups in the comparison using the modified Tukey procedure. It was concluded that the studentized range technique is insensitive to violation of the assumption of equal group size. Even under severe conditions of unequal group sizes (3:1), the test was robust. These findings were confirmed by Keselman and Toothaker (1974) who tested both methods using combinations of unequal sample sizes and unequal variances. These authors likewise concluded that the modified Tukey method is as robust a statistic as the Scheffé method not withstanding the 2:1 disparity in both sample sizes and in variances used in their study.

Keselman, Murray and Rogan (1976) further investigated the effect of the magnitude of the disparity between unequal sample sizes on Type I error probabilities using the modified Tukey test. They demonstrated that for a disparity between two groups of 1.9 :1, the Type I experimentwise probability was .012 at the .01 nominal alpha level. With four groups having a disparity of 1:1:2.1:2.1, the Type I experimentwise probability was .013 at the .01 nominal alpha level. Furthermore, the empirical Type I error probabilities rarely exceeded their nominal significance levels by more than one percent even when the groups differed by 40:1. They recommended, however, that

the Behrens-Fisher modification rather than the harmonic mean be used when the disparity between sample sizes was so extreme. The authors concluded that the Tukey test need not be restricted to comparisons in which sample means are based on an equal number of observations and, once again, emphasized the appropriateness of using the modified Tukey method for pairwise comparisons among unequal sample sizes.

In the present study, the largest disparity between sample sizes was 1.7:1. In accordance with the evidence reviewed, this difference permitted the use of the Tukey method incorporating the harmonic mean modification for the post hoc analysis of pairwise compairsons.

The Tukey test with the harmonic mean modification was used to separately analyze pairwise comparisons on columns (within group) and rows (between group). It was therefore necessary to compute a pooled error term for the between group comparisons (Winer, 1971). In each instance this procedure increased the size of the error term for the between group comparisons thereby making these statistical analyses more conservative.

RESULTS

Subject Characteristics

There were 12 subjects in the E-A group, 12 in the E group, seven in the A group, eight in the PL group and nine in the hysterectomy CON group.

Statistical analyses were carried out on several socioeconomic and personality parameters of the subjects in order to assess whether subjects in the five treatment groups were homogeneous with respect to these characteristics at baseline.. Occupational status was determined according to the scale devised by Pineo and Porter (1967). Forty-one of the 48 subjects (85.4 percent)

worked outside of the home. The occupational status of the remaining seven women was calculated according to the husbands' occupational status.

A series of one-way analyses of variance (ANOVAS) were carried out on the means of the five treatment groups for the variables on age, years of scolarity, occupational status, the neuroticism and extraversion scores of the Eysenck Personality Inventory and on the Marital Adjustment Scale score. All ANOVA Summary Tables appear in Appendix C. The ANOVA on age demonstrated a significant main effect for group, $F,(4,43)=5.05$, $p < .01$. Post hoc Tukey tests demonstrated that subjects in the hysterectomy CON group were significantly younger than those in the other four treatment groups. There were no significant differences among the groups with regard to the means of the other variables analyzed. This information is summarized in Table 1. Since it was only the mean for age which differed between the hysterectomy CON group and the four treatment groups, the two means presented in Table 1 represent the grand mean of the four treatment groups and the mean of the hysterectomy CON group.

The Daily Menopausal Rating Scale (DMRS)

The data which were subjected to statistical analysis consisted of mean daily scores for each subject on each variable on the DMRS. The mean number of preoperative baseline days per subject was 15 (range = 11 to 26 days). The mean of the first two weeks of each treatment month for each subject on each variable was computed and used as the mean score for that month for any given variable. This procedure was employed in order to maximize the probability of finding a drug effect; since dose-response data is not available for the hormonal preparations used in this study, the mean of the first two weeks following drug

Table 1: Subject Characteristics

	Treatment Groups	Hysterectomy Control Group
Age	45.3	36.3*
Years of Scolarity	10.8	11.2
Occupational Status	44.7	50.5
Eysenck Personality Inventory		
-Neuroticism	11.8	10.4
-Extraversion	10.4	10,81
Marital Adjustment Scale	118.0	129.2

* $p < .01$

administration was thought to encompass the time period during which plasma hormone levels would have been stable at some maximal level. Therefore, the means of the treatment months were computed by dividing the total score for the variable in question by 14 (days) for each subject for each treatment month.

Similarly, for the placebo month, an attempt was made to maximize the likelihood that the hormonal preparation administered in the prior drug treatment month had been completely metabolized. Accordingly, the mean of the last two weeks of the placebo month for each variable was computed and represented the individual subjects' score for that month. Therefore, the DMRS data for each subject were the daily means of the preoperative baseline scores, the daily means of the first two weeks of each of the three treatment months and the daily means of the last two weeks of the placebo month.

Mean scores for each subject for the five months were analyzed using Analysis of Variance for Repeated Measures. This was a five (Treatment Groups) x five (Time periods) mixed model design ANOVA for unequal N's. There were therefore three main factors in the design; treatment group, time and subjects. Subjects were nested in treatment groups and crossed with time.

Somatic Symptoms (DMRS)

A) Hot Flushes

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. A score of zero to four was assigned to each interval respectively. The mean relative frequency of hot flushes

for each time period was computed by summing the interval scores for each subject and dividing by the number of days in that time period.

The ANOVA Summary Table for mean number of hot flushes demonstrated a significant main effect for Group, $F(4,43)=5.71$, $p < .001$; for Time, $F(4,172)=12.98$, $p < .0001$ and a significant Time x Group interaction, $F(4,172)=3.97$, $p < .0001$. A graph of the group means of hot flush frequencies is found in Figure 3. Tukey post-hoc tests (Table 2) showed that the PL group and the A group both reported a significant increase in the mean frequency of hot flushes from baseline to month three of treatment whereas there were no significant increases in the E-A, the E or the CON groups. Additionally, all four treatment groups reported a significant increase in frequency of hot flushes from baseline to the end of the placebo month. The CON group however, reported no significant changes in hot flush frequency throughout the entire course of the study, having maintained a stable, very low frequency of this symptom. Between group post-hoc tests show that although there were no significant differences at baseline, by the second month of treatment, the PL group and the A group were reporting significantly increased frequencies of hot flushes compared to the two groups who received estrogen (E-A and E). The latter groups did not differ significantly in hot flush frequency from the hysterectomy CON group during treatment. At the placebo phase, all four treatment groups reported a significantly increased frequency of hot flushes compared to the hysterectomy CON group.

B) Headaches, Nausea, Sleep Quality, Appetite Quality

The ANOVA showed no significant main or interaction effects for nausea.

Table 2

Mean Frequency of Hot Flushes Per 24 Hours:
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$.11^{a,A}$	$.25^{a,A}$	$.18^{a,A}$	$.13^{a,A}$	$.09^{a,A}$
Month 1	$.34^{ab,B}$	$.26^{a,B}$	$.61^{ab,B}$	$.77^{b,A}$	$.09^{a,B}$
Month 2	$.27^{ab,B}$	$.17^{a,B}$	$1.08^{b,A}$	$1.29^{b,A}$	$.11^{a,B}$
Month 3	$.30^{ab,B}$	$.38^{a,B}$	$1.04^{b,A}$	$.86^{b,A}$	$.05^{a,B}$
Placebo	$.74^{b,A}$	$1.38^{b,A}$	$1.08^{b,A}$	$.85^{b,A}$	$.05^{a,B}$

Note. Means with the same superscript do not differ significantly.
a,b, Within group Tukey tests
A,B, Between group Tukey tests

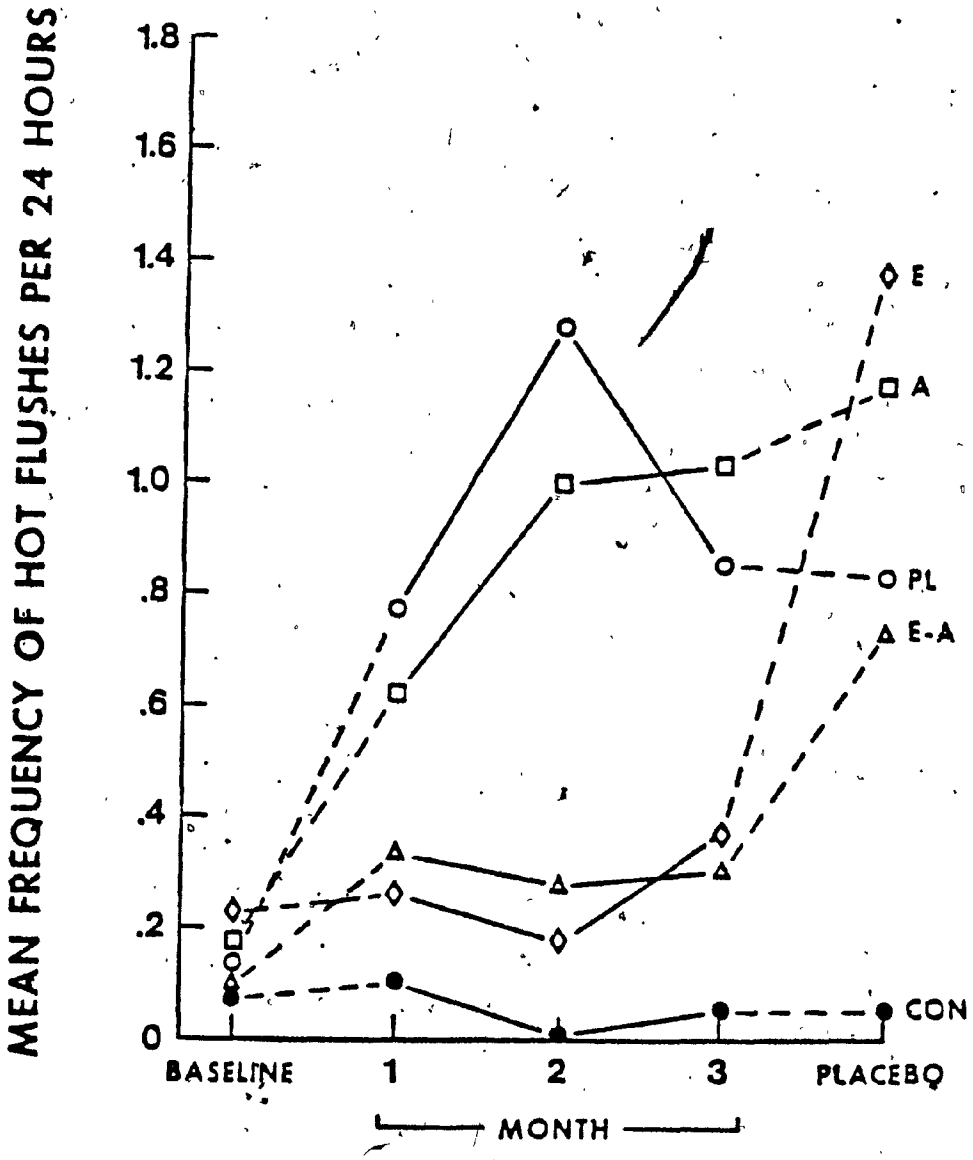

Figure 3. Hot Flushes

There was a significant main effect for Time in the analysis of headache frequency, $F(4,172)=2.36$, $p < .05$. Tukey post-hoc tests between the row means of each time period (Table 3) showed that the only significant change that occurred was an increase in the mean number of headaches from month three of treatment compared to the end of the placebo phase.

The ANOVA for sleep quality likewise showed a significant main effect for Time, $F(4,172)=3.27$, $p < .01$. There was a significant increase in sleep quality during the postoperative period irrespective of group (Table 4).

Ratings of appetite analyzed by means of an ANOVA, similarly showed only a significant main effect for Time, $F(4,172)=11.14$, $p < .0001$. Post-hoc Tukey tests on the row means for quality of appetite (Table 5) demonstrated a consistent, significant increase in appetite from the first postoperative month to the end of the placebo phase. This change in appetite occurred across groups.

Sexual Functioning

A) Sexual Desire

Figure 4 indicates changes in the mean level of sexual desire in graphic form. The ANOVA on this measure demonstrated a significant main effect for Group, $F(4,43)=4.92$, $p < .01$; for Time, $F(4,172)=11.96$, $p < .0001$; and a significant Group x Time interaction, $F(4,172)=2.30$, $p < .001$. Within and between group Tukey tests are found in Table 6. All groups except for those receiving androgen (E-A and A) reported a significant decrease in mean level of sexual desire from baseline to month one of treatment. Moreover, the E-A group alone reported a decrease in sexual desire from the third treatment month to the end of the

Table 3

Mean Number of Headaches Per 24 Hours:
Tukey Post Hoc Tests Between the Row Means

Time Periods	Treatment Groups				Hysterectomy	Row
	E-A	E	A	PL	CON	Means
Baseline	1.27	1.38	.80	.66	.67	1.01^{ab}
Month 1	.82	1.01	.80	.48	.41	$.73^{ab}$
Month 2	.50	.81	.38	.27	.65	$.72^{ab}$
Month 3	.85	.88	.30	.73	.59	$.71^{a}$
Placebo	1.24	1.54	.63	1.58	.18	1.09^{b}

Note: Means with the same superscript do not differ significantly

Table 4

Quality of Sleep:
Tukey Post Hoc Tests Between the Row Means

Time Period	Treatment Groups				Hysterectomy	Row
	E-A	E	A	PL	CON	Means
Baseline	3.80	4.19	4.81	3.77	4.92	4.25^{ab}
Month 1	4.22	3.44	4.22	3.27	4.33	3.89^{a}
Month 2	4.82	3.95	4.88	3.67	4.55	4.36^{b}
Month 3	4.42	4.15	5.16	4.07	4.90	4.49^{b}
Placebo	4.49	3.95	5.98	3.85	4.66	4.37^{b}

Note: Means with the same superscripts do not differ significantly

Table 5

Appetite:
Tukey Post Hoc Tests Between the Row Means

Time Period	Treatment Groups				Hysterectomy	Row
	E-A	E	A	PL	CON	Means
Baseline	3.98	3.84	4.21	4.09	4.50	4.09^{*}
Month 1	3.87	8.46	4.37	3.76	3.87	3.82^{a}
Month 2	4.38	4.11	5.14	4.27	4.38	4.41^{b}
Month 3	4.60	4.28	5.25	4.67	4.49	4.61^{b}
Placebo	4.53	4.03	4.84	4.43	4.04	4.85^{b}

Note: Means with the same superscripts do not differ significantly

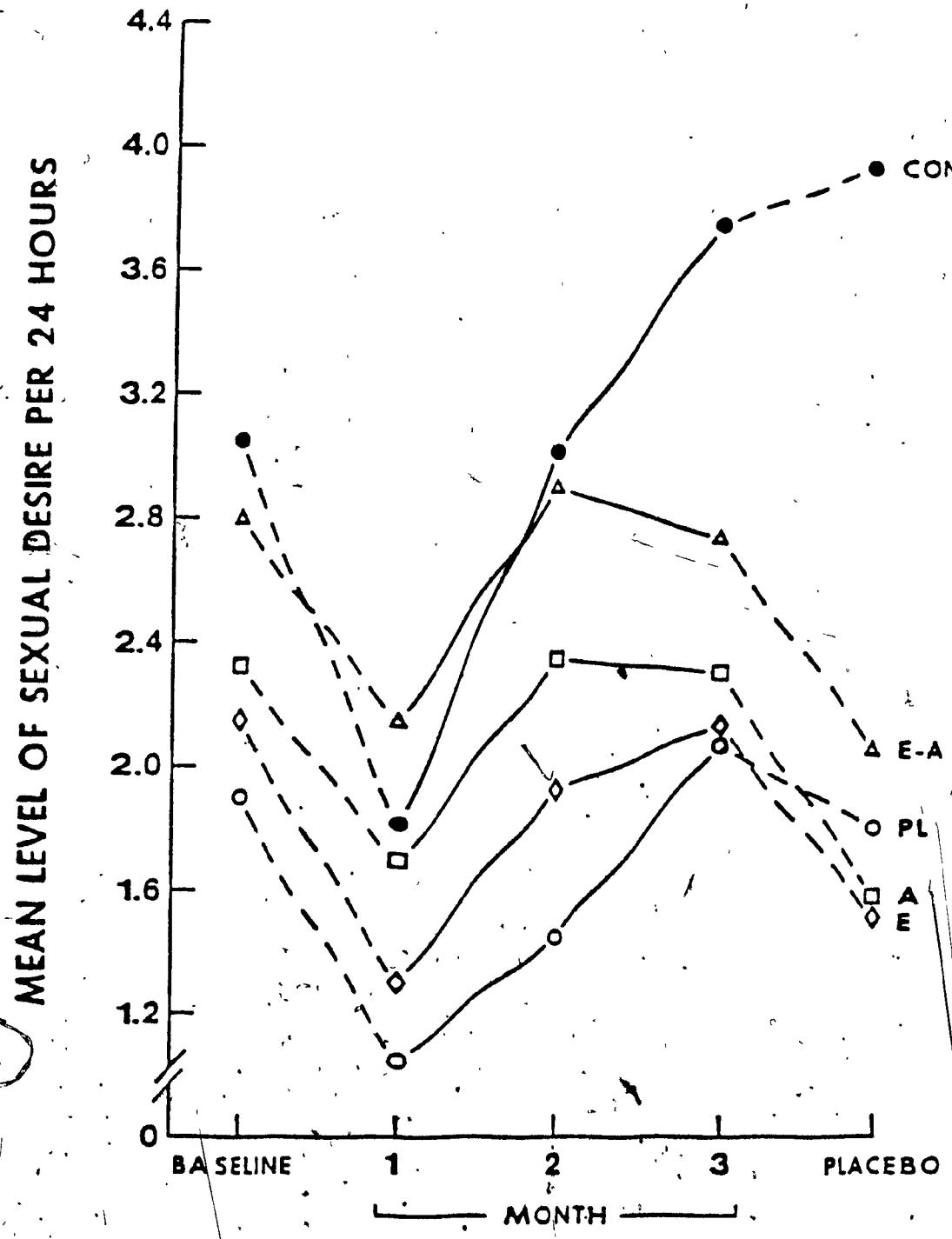

Figure 4, Level of Sexual Desire

Table 6

Mean Level of Sexual Desire Per 24 Hours:
Within and Between Group Tukey Post Hoc Tests

Time Periods	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$2.80^{a,A}$	$2.15^{a,A}$	$2.32^{a,A}$	$1.89^{a,A}$	$3.07^{a,A}$
Month 1	$2.19^{ab,A}$	$1.30^{b,AB}$	$1.69^{a,AB}$	$1.03^{b,B}$	$1.82^{b,AB}$
Month 2	$2.81^{ab,A}$	$1.93^{ab,AB}$	$2.37^{a,AB}$	$1.48^{ab,B}$	$3.02^{a,A}$
Month 3	$2.76^{a,AB}$	$2.15^{a,B}$	$2.31^{a,B}$	$2.15^{a,B}$	$3.76^{a,A}$
Placebo	$2.08^{b,B}$	$1.61^{ab,B}$	$1.66^{a,B}$	$1.82^{ab,B}$	$3.92^{a,A}$

Note: Means with the same superscript do not differ significantly

placebo phase. The between group comparisons showed that although there were no significant differences between the five groups in mean level of sexual desire at baseline, by month three of treatment, the E, the A and the PL groups reported significantly reduced levels of sexual desire compared to the hysterectomy CON group. Thus, only the E A group did not differ from the CON group during the third treatment month. During the placebo phase, following withdrawl of hormones, all four treatment groups reported a significantly reduced level of sexual desire compared to the hysterectomy CON group.

B). Sexual Fantasies

Changes in mean number of sexual fantasies are presented in graphic form in Figure 5. The ANOVA on these data showed significant main effects for Group, $F(4,43)=2.69$, $p < .04$; and for Time, $F(4,172)=9.66$, $p < .0001$; and a significant Group x Time interaction, $F(4,172)=1.82$, $p < .05$. Tukey post hoc tests appear in Table 7. The within group comparisons showed that the E-A group and the hysterectomy CON group both reported a significant increase in the mean number of sexual fantasies from month one to month three of treatment.

There were no significant differences in the mean number of sexual fantasies between the five groups at baseline. However, at month three of treatment, both the E group and the PL group reported significantly fewer fantasies than the hysterectomy CON group whereas the E-A and A groups did not differ significantly from the hysterectomy CON group at that time. At the end of the placebo phase, subjects in all four treatment groups reported a significantly reduced number of sexual fantasies than the women in the CON group.

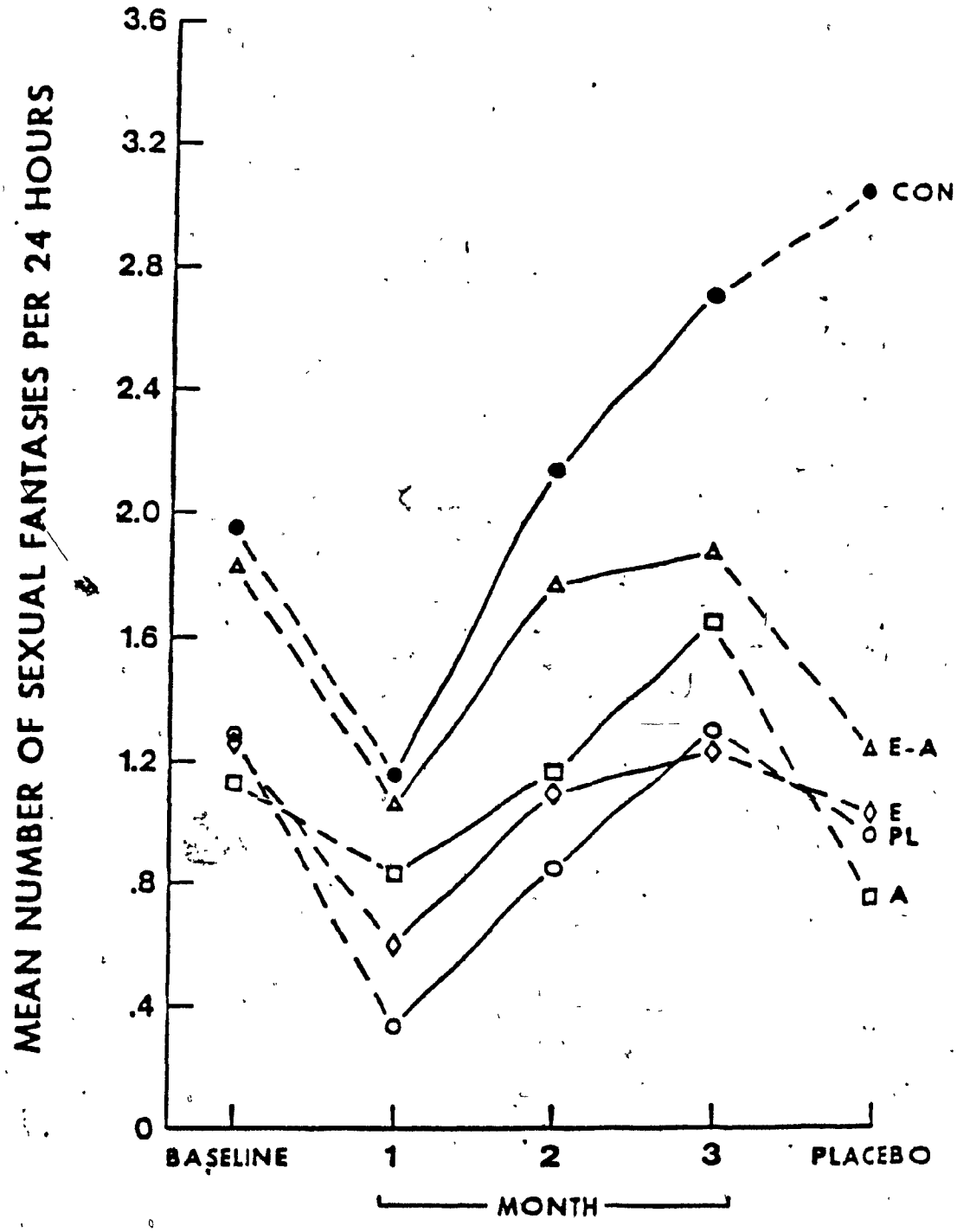

Figure 5. Sexual Fantasies

Table 7

Mean Number of Sexual Fantasies Per 24 Hours
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups E-A	E	A	PL	Hysterectomy CON
Baseline	$1.82^{ab,A}$	$1.27^{a,A}$	$1.17^{a,A}$	$1.28^{a,A}$	1.95^{*A}
Month 1	$1.09^{a,A}$	$.60^{a,A}$	$.81^{a,A}$	$.33^{b,A}$	$1.18^{a,A}$
Month 2	$1.79^{ab,A}$	$1.11^{a,A}$	$1.17^{a,A}$	$.86^{ab,A}$	$2.14^{b,A}$
Month 3	$1.88^{b,AB}$	$1.23^{a,B}$	$1.64^{a,AB}$	$1.30^{ab,B}$	$2.71^{b,A}$
Placebo	$1.23^{ab,B}$	$.94^{a,B}$	$.77^{a,B}$	$.96^{ab,B}$	$3.08^{b,A}$

Note: Means with the same superscript do not differ significantly
a,b Within group Tukey tests
A,B Between group Tukey tests
* Baseline is significantly different from Placebo

C) Mean Level of Sexual Arousal Attained

Changes in the mean level of sexual arousal attained during intercourse are shown in graphic form in Figure 6. Because sexual intercourse was banned for the first six postoperative weeks, only the baseline mean, the mean of the first two weeks of the third treatment month and the mean of the last two weeks of the placebo month were those subjected to a statistical analysis. The ANOVA on these data demonstrated significant effects for Group, $F(4,43)=2.68$, $p < .05$ and Time, $F(2,86)=9.94$, $p < .001$ and a significant Group x Time interaction, $F(2,86)=3.38$, $p < .03$. Within and between group comparisons between cell means appear in Table 8. The E-A and the A groups reported a significant decrease in sexual arousal from both baseline and treatment levels to the end of the placebo month. The between group Tukey tests showed that, at the treatment phase, the E group reported significantly lower levels of sexual arousal as compared to the A group. After hormones were withdrawn however, the A group attained significantly lower levels of sexual arousal compared to both the PL and CON groups. However, Figure 6 indicates that the PL group was stable with respect to sexual arousal throughout the course of the study at levels not significantly different from those of the hysterectomy CON group.

D) Number of Sexual Encounters and Number of Orgasms

The ANOVA on the mean number of sexual encounters per 24 hours showed only a significant main effect for Time, $F(2,86)=3.03$, $p < .05$. Tukey tests between the row means appear in Table 9. Although there was no change overall in the number of sexual encounters per 24 hours between baseline and treatment, there was a significant decrease in sexual intercourse between the treatment and placebo phases and between preoperative baseline compared to the placebo

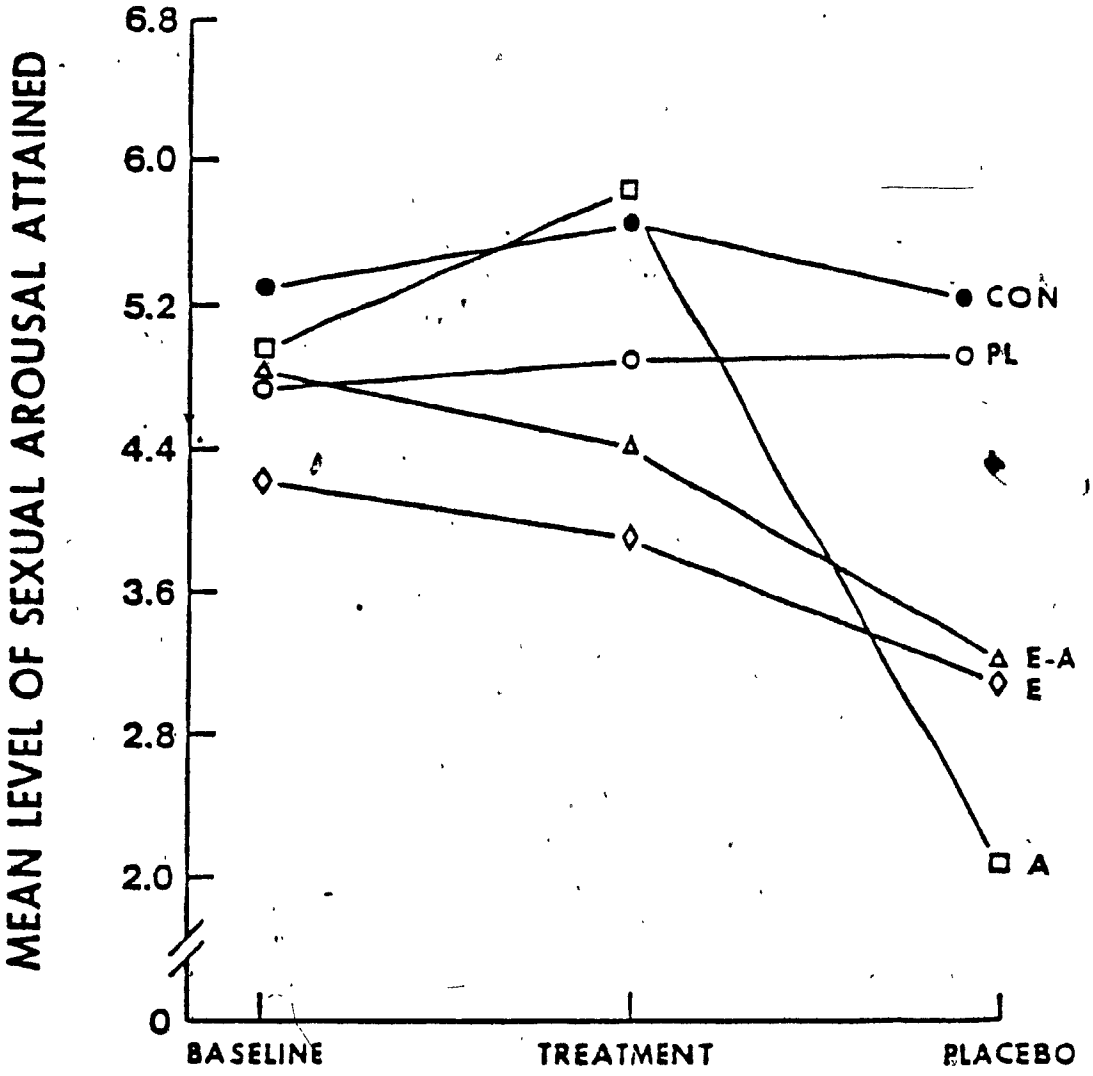

Figure 6. Level of Sexual Arousal

Table 8

Mean Level of Sexual Arousal Attained:
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$4.82^{a,A}$	$4.20^{a,A}$	$4.96^{a,A}$	$4.78^{a,A}$	$5.39^{a,A}$
Treatment	$4.39^{a,AB}$	$3.98^{a,B}$	$5.83^{a,A}$	$4.91^{a,AB}$	$5.53^{a,AB}$
Placebo	$3.26^{b,AB}$	$3.50^{a,AB}$	$2.11^{b,B}$	$4.93^{a,A}$	$5.23^{a,A}$

Note: Means with the same superscript do not differ significantly
a,b Within group Tukey Tests
A,B Between group Tukey Tests

Table 9

Mean Number of Sexual Encounters Per 24 Hours
Tukey Post Hoc Tests Between the Row Means

Time Period	Treatment Groups				Hysterectomy	Row
	E-A	E	A	PL	CON	Means
Baseline	.32	.20	.40	.19	.50	.31[a]
Treatment	.40	.33	.41	.10	.38	.40[a]
Placebo	.26	.14	.21	.13	.23	.19[b]

Note: Means with the same superscript do not differ significantly

phase.

The mean number of orgasms attained showed no statistically significant main effects for Group or Time nor any significant interaction effect when analyzed by means of an ANOVA.

Level of Well-Being, Energy-Level and Mood

The ANOVA on mean daily mood ratings showed only a significant main effect for Time, $F(4,172)=4.72$, $p < .001$. Tukey post-hoc tests on the row means of the time periods (Table 10) showed that there was a significant improvement in mood both from baseline and month one to month three of the treatment phase irrespective of group.

The ANOVA on mean level of well-being showed only a significant main effect for Time, $F(4,172)=18.17$, $p < .0001$. Table 11 contains the results of Tukey tests performed on the row means. Mean scores on level of well-being decreased significantly from baseline to month one and then increased significantly until month three of treatment across groups. Furthermore, an overall significant decrease in well-being was reported from month three to the end of the placebo phase across groups.

Consistent with this finding, the ANOVA on mean energy level showed only a significant main effect for Time, $F(4,172)=17.13$, $p < .0001$. Tukey post-hoc tests on the row means of the time periods (Table 12) showed a significant decrease in energy level between baseline and month one of treatment, a stable increase from month one to month three of treatment and a significant decrease from month three of treatment to the end of the placebo phase across groups. The pattern of energy level scores throughout the study, therefore, is very similar to that of mean level of

Table 10

Mean Daily Ratings of Mood:
Tukey Post Hoc Tests Between the Row Means

Time Period	Treatment Groups				Hysterectomy	Row
	E=A	E	A	PL	CON	Means
Baseline	4.50	3.80	4.09	3.60	4.32	4.08^{b}
Month 1	3.95	3.62	4.55	3.64	3.94	3.90^{b}
Month 2	4.85	4.31	4.37	4.47	4.27	4.47^{ab}
Month 3	4.56	4.29	4.52	4.49	4.78	4.52^{a}
Placebo	4.02	3.76	4.25	4.39	4.53	4.15^{ab}

Note: Means with the same superscript do not differ significantly

Table 11

Mean Level of Well-Being:
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy	Row
	E-A	E	A	PL	CON	Means
Baseline	4.17	3.99	4.24	3.77	4.40	4.12^{a}
Month 1	3.63	3.39	4.57	3.45	3.42	3.64^{b}
Month 2	4.72	4.45	5.33	4.41	4.15	4.58^{ac}
Month 3	4.59	4.51	5.65	4.73	5.11	4.85^{ac}
Placebo	4.16	4.04	4.58	4.29	4.88	4.35^{*}

Note: Means with the same superscript do not differ significantly

* The difference between Month 3 and Placebo is significant at the .01 level.

Table 12

Mean Energy Level:
Tukey Post Hoc Tests Between the Row Means

Time Period	Treatment Groups				Hysterectomy	Row
	E-A	E	A	PL	CON	Means
Baseline	4.24	4.18	4.53	3.88	4.35	4.23^{a}
Month 1	3.42	3.03	4.69	3.15	3.23	3.43^{b}
Month 2	4.83	4.35	5.30	4.19	3.97	4.51^{b}
Month 3	4.56	4.52	5.53	4.63	4.66	4.72^{ac}
Placebo	4.05	3.89	4.38	3.96	4.48	4.12^{*}

Note: Means with the same superscript do not differ significantly

* The difference between Month 3 and Placebo is significant at the .01 level.

well-being.

Level of Activity and the Number of Times a Subject Left the Home for Business or Social Purposes

These two measures were intended to provide an indication of subjects' level of physical activity during the course of the study. The ANOVA on mean level of activity showed a significant main effect for Time, $F(4,172)=32.34$, $p < .0001$ but no significant main effects for Group or Interaction. Significant decreases in level of activity from baseline to month 1 and stable, consistent increases from then until the end of the study occurred across groups (Table 13).

Analysis of the mean number of times a subject left the home for business or social purposes yielded only a significant effect for Time, $F(4,172)=66.33$, $p < .001$. Tukey post-hoc tests on the row means for each time period (Table 14) show a significant overall decrease in the mean number of times subjects left their homes from baseline to the first and second postoperative months followed by consistent increases on this measure of physical activity following the second postoperative month. By the end of the placebo month, subjects had resumed the level of activity they reported at baseline irrespective of group.

Number of Arguments and Involvement in the Argument

In an attempt to measure changes in aggressivity, subjects were asked to record the number of arguments they engaged in each day as well as the degree of their involvement in arguments when they occurred. The ANOVAs on both these measures showed no significant effects throughout the course of the study; none of the hormone

Table 13

Mean Level of Activity Per 24 Hours:
Tukey Post Hoc Tests Between the Row Means

Time Period	Treatment Groups				Hysterectomy	Row
	E-A	E	A	PL	CON	Means
Baseline	3.96	4.20	4.50	4.01	4.03	4.12^{a}
Month 1	3.07	2.60	3.22	2.57	2.78	2.84^{b}
Month 2	4.67	3.97	4.31	3.85	4.17	4.22^{a}
Month 3	4.75	4.50	4.92	4.40	4.59	4.68^{a}
Placebo	4.38	4.19	4.56	4.16	4.58	4.37^{a}

Note: Means with the same superscript do not differ significantly

Table 14

Mean Number of Times Subjects Left Their Homes Per 24 Hours: Tukey Post Hoc Tests Between Row Means

Time Period	Treatment Groups E-A	E	A	PL	Hysterectomy CON	Row Means
Baseline	1.97	2.01	1.84	2.03	1.53	1.89[a]
Month 1	.41	.50	.34	.50	.41	.44[b]
Month 2	1.38	1.67	.94	1.52	1.49	1.43[b]
Month 3	1.58	1.97	1.53	1.78	1.69	1.72[a]
Placebo	1.42	2.16	1.45	2.01	1.90	1.80[a]

Note: Means with the same superscript do not differ significantly

treatments had any systematic effect on these self-report measures of aggression.

The Psychological Test Battery

The individual tests that comprised the Psychology Test Battery were separately analyzed in a 5 (Treatment Group) x 3 (Time Periods) design for repeated measures for unequal n's.

The Multiple Affect Adjective Checklist

a) Anxiety

Mean anxiety scores subjected to an ANOVA revealed a significant main effects for Group, $F(4,43)=2.62$, $p < .05$; and for Time, $F(2,86)=15.3$, $p < .001$. Post-hoc Tukey tests on the row means of the five groups and on the column means of the three time periods appear in Table 15. Mean anxiety scores decreased significantly from baseline to treatment and increased significantly from treatment to the placebo phase; baseline and plaebo scores did not differ. The group comparison showed that the PL group had significantly higher mean anxiety scores than did the A and CON groups across time.

b) Hostility

The ANOVA on mean hostility scores showed no significant changes throughout the course of the study.

c) Depression

Mean depression scores which were subjected to an ANOVA demonstrated a significant main effect for Time, $F(2,86)=10.68$, $p < .0001$ and a significant Group x Time Interaction, $F(2,86)=2.57$, $p < .01$. Within and between

Table 15

Mean Anxiety Scores:
Tukey Tests Between the Row and Column Means

Time Period	Treatment Groups				Hysterectomy	Row
	E-A	E	A	PL	CON	Means
Baseline	10.3	11.0	9.3	13.0	8.7	10.5^{a}
Treatment	8.6	8.7	6.9	11.9	8.1	8.8^{b}
Placebo	11.5	10.9	9.3	12.6	7.9	10.5^{a}
Column Means	10.1^{AB}	10.1^{AB}	8.5^{B}	12.5^{A}	8.2^{B}	9.9

Note: Means with the same superscript do not differ significantly
a,b Tukey Tests between row means
A,B Tukey Tests between column means.

group post-hoc Tukey tests appear in Table 16. The three hormone groups showed a significant decrease in depression scores between baseline and treatment and a significant increase from treatment to the placebo phase. In all three groups, baseline and placebo scores did not differ significantly. At the treatment phase, the A group attained a significantly lower mean depression score than the PL group. A graph of these data (Figure 7) indicates that depression scores of the PL and CON groups remained stable throughout, with the PL group having obtained fairly high scores while the hysterectomy CON group had relatively low scores.

The Menopausal Index

a) Somatic Symptoms

The ANOVA on mean somatic symptom scores showed significant main effects for Group, $F(4,43)=4.20$, $p < .005$, for Time, $F(2,86)=9.98$, $p < .001$, and a significant Group x Time interaction, $F(2,86)=3.77$, $p < .001$. Post hoc Tukey tests appear in Table 17. The E-A, the E, annd the PL group reported significantly increased somatic symptom scores from baseline to the placebo phase. The PL group alone had increased scores from baseline to treatment. Between-group post-hoc tests indicated that, at the treatment phase, the E-A, the A, and the hysterectomy CON groups had significantly lower somatic symptom scores than the PL group. Following withdrawal of hormones, all four treatment groups reported significantly higher somatic symptom scores compared to the hysterectomy CON group. A graph of these findings (Figure 10) points out the steep rise in somatic symptom scores in the PL group from baseline to treatment while scores of all the other groups either decrease or remain stable during this time period.

b) Psychosomatic Symptoms

Table 16

Mean Depression Scores:
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$14.3^{a,A}$	$13.3^{a,A}$	$12.9^{a,A}$	$15.0^{a,A}$	$12.4^{a,A}$
Treatment	$12.3^{b,AB}$	$11.0^{b,AB}$	$8.9^{b,B}$	$15.4^{a,A}$	$10.9^{a,AB}$
Placebo	$15.4^{a,A}$	$13.7^{a,A}$	$11.1^{a,A}$	$15.1^{a,A}$	$10.3^{a,A}$

Note: Means with the same superscript do not differ significantly
a,b Within group Tukey tests
A,B Between group Tukey tests

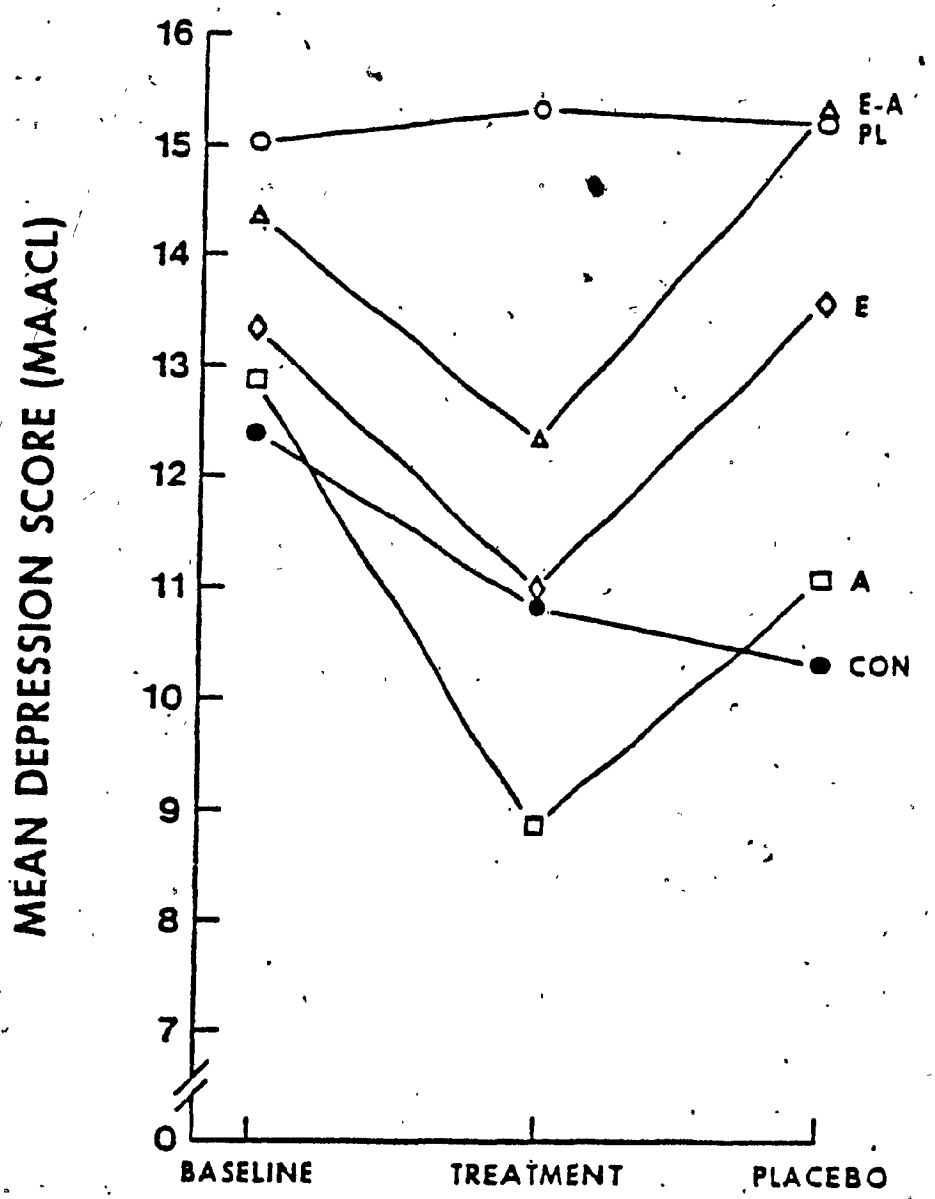

Figure 7. Depression Scores

Table 17

Mean Somatic Symptom Scores:
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$7.08^{a,A}$	$10.42^{a,A}$	$10.28^{ab,A}$	$8.338^{a,A}$	$6.67^{a,A}$
Treatment	$4.17^{a,B}$	$11.08^{a,AB}$	$5.57^{a,B}$	$15.63^{b,A}$	$5.67^{a,B}$

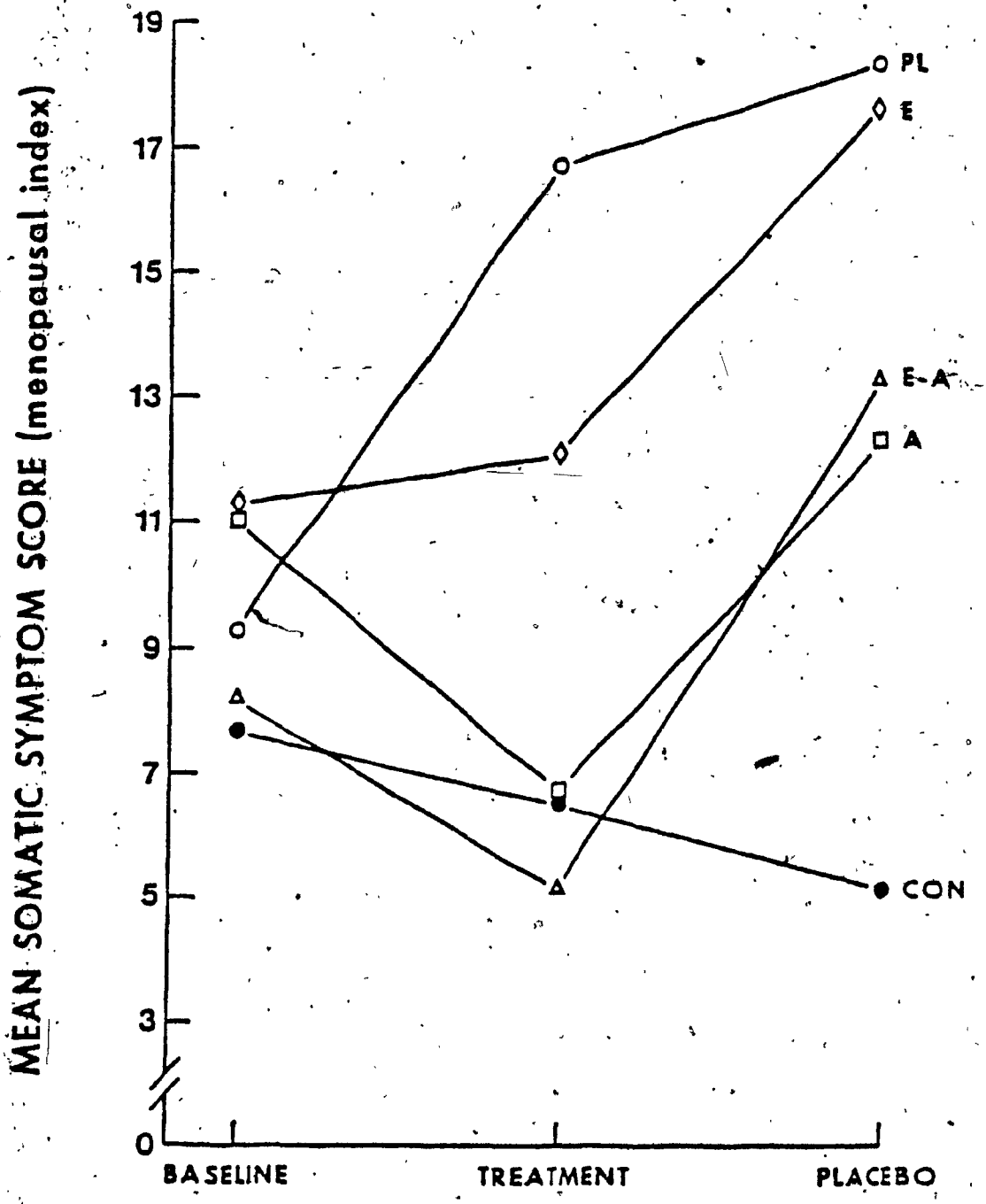

Figure 8. Somatic Symptom Scores

An ANOVA on mean psychosomatic symptom scores found only a significant effect for Time, $F(2,86)=6.06$, $p < .01$. Post-hoc Tukey tests between the row means for the three time periods (Table 18) showed that psychosomatic symptom scores increased significantly from the treatment to the placebo phase and from baseline to the placebo phase across groups.

c) Psychological Symptoms

Mean psychological scores subjected to an ANOVA showed a significant main effect for Time, $F(2,86)=9.51$, $p < .001$ and a significant Group x Time interaction, $F(2,86)=3.25$, $p < .05$. Post-hoc within and between group tests were carried out, the results appearing in Table 19. Scores of the E-A and the A groups decreased significantly from baseline to treatment; the A group scores also showed a significant decrease from baseline to the placebo phase. Between-group Tukey tests demonstrated that the only significant comparison was the higher psychological symptom score in the PL group compared to the A group during the treatment phase. A graph of these data (Figure 9) highlights the stability of the PL group psychological symptom scores and the hysterectomy CON group scores throughout the study, the former at a high level and the latter at relatively low levels.

d) Total Score

The scores of the three symptom constellations -- somatic, psychosomatic and psychological, were summed for each individual subject at each time period and the resulting mean total scores of the menopausal index for each group were subjected to an ANOVA. There was a significant main effect for Group, $F(4,43)=3.08$, $p < .02$, for Time, $F(2,86)=5.30$; $p < .005$ and a significant Group x Time interaction, $F(2,86)=3.07$, $p < .005$. Within and

Table 18

Mean Psychosomatic Symptom Scores:
Post Hoc Tukey Tests Between the Row Means

Time Period	Treatment Groups				Hysterectomy	Row
	E-A	E	A	PL	CON	Means
Baseline	10.0	9.42	4.0	9.25	5.22	8.39^{a}
Treatment	7.92	9.75	3.14	11.0	3.89	7.43^{a}
Placebo	13.92	11.83	8.71	12.13	3.22	10.33^{b}

Note: Means with the same superscript do not differ significantly

Table 19

Mean Psychological Symptoms Scores:
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E→A	E	A	PL	CON
Baseline	$22.5^{a,A}$	$16.8^{a,A}$	$18.1^{a,A}$	$22.9^{a,A}$	$11.7^{a,A}$
Treatment	$13.6^{b,AB}$	$17.3^{a,AB}$	$5.4^{b,B}$	$19.5^{a,A}$	$8.3^{a,AB}$
Placebo	$17.8^{ab,A}$	$17.5^{a,A}$	$7.0^{b,A}$	$20.9^{a,A}$	$6.1^{a,A}$

Note: Means with the same superscript do not differ significantly
a,b Within group Tukey tests
A,B Between group Tukey tests

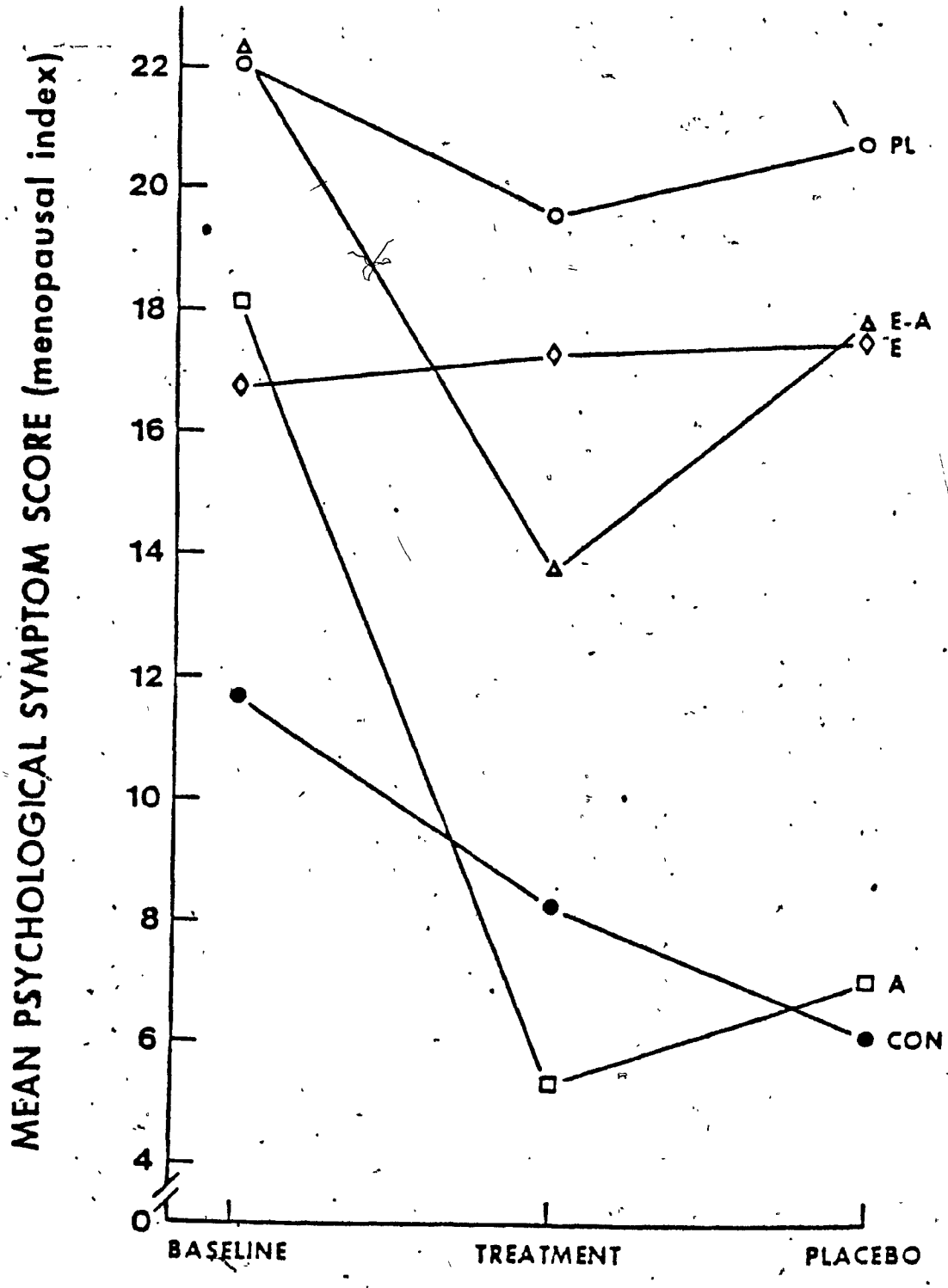

Figure 9. Psychological Score (MI)

between group post-hoc tests (Table 20) showed that mean total scores of groups E-A and A decreased significantly from baseline to the treatment phase and increased significantly from treatment to the end of the placebo month. There were no significant within-group changes in the E, the PL or in the hysterectomy CON groups throughout the study. Between-group post hoc tests showed that, during the treatment phase, the E-A, the A and the CON groups had significantly lower total scores on the Menopausal Index than the PL group whereas the group that received E did not differ from the PL group. At the end of the placebo phase, only the E and the PL groups had significantly higher scores than the hysterectomy CON group. These findings are presented graphically in Figure 10.

Digit Span.

The results of an ANOVA on mean digit span scores showed a significant main effect for Time, $F(2,86)=7.55$, $p < .001$, and a significant Group x Time interaction, $F(2,86)=3.64$, $p < .001$. Within and between group Tukey tests appear in Table 21. The E-A, E, and CON groups demonstrated a significant increase in digit span scores from baseline to treatment. Only the E group had significantly decreased scores from the treatment to the placebo phase. It was also found that the E-A group and the CON group showed significant increases in digit span scores from baseline to the placebo phase.

Although mean digit span scores did not differ between groups at baseline, both the E group and the CON group had significantly higher scores than the PL group during the treatment phase. However, at the end of the placebo month, the CON attained significantly higher scores than the E and

Table 20

Mean Total Score:
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$39.6^{a,A}$	$35.8^{a,A}$	$35.4^{a,A}$	$40.5^{a,A}$	$23.6^{a,A}$
Treatment	$25.7^{b,B}$	$38.1^{a,AB}$	$14.1^{b,B}$	$46.1^{a,B}$	$17.9^{a,B}$
Placebo	$44.0^{a,AB}$	$46.8^{a,A}$	$27.1^{a,AB}$	$48.6^{a,A}$	$13.4^{a,B}$

Note: Means with the same superscript do not differ significantly

a,b Within group Tukey tests

A,B Between group Tukey tests

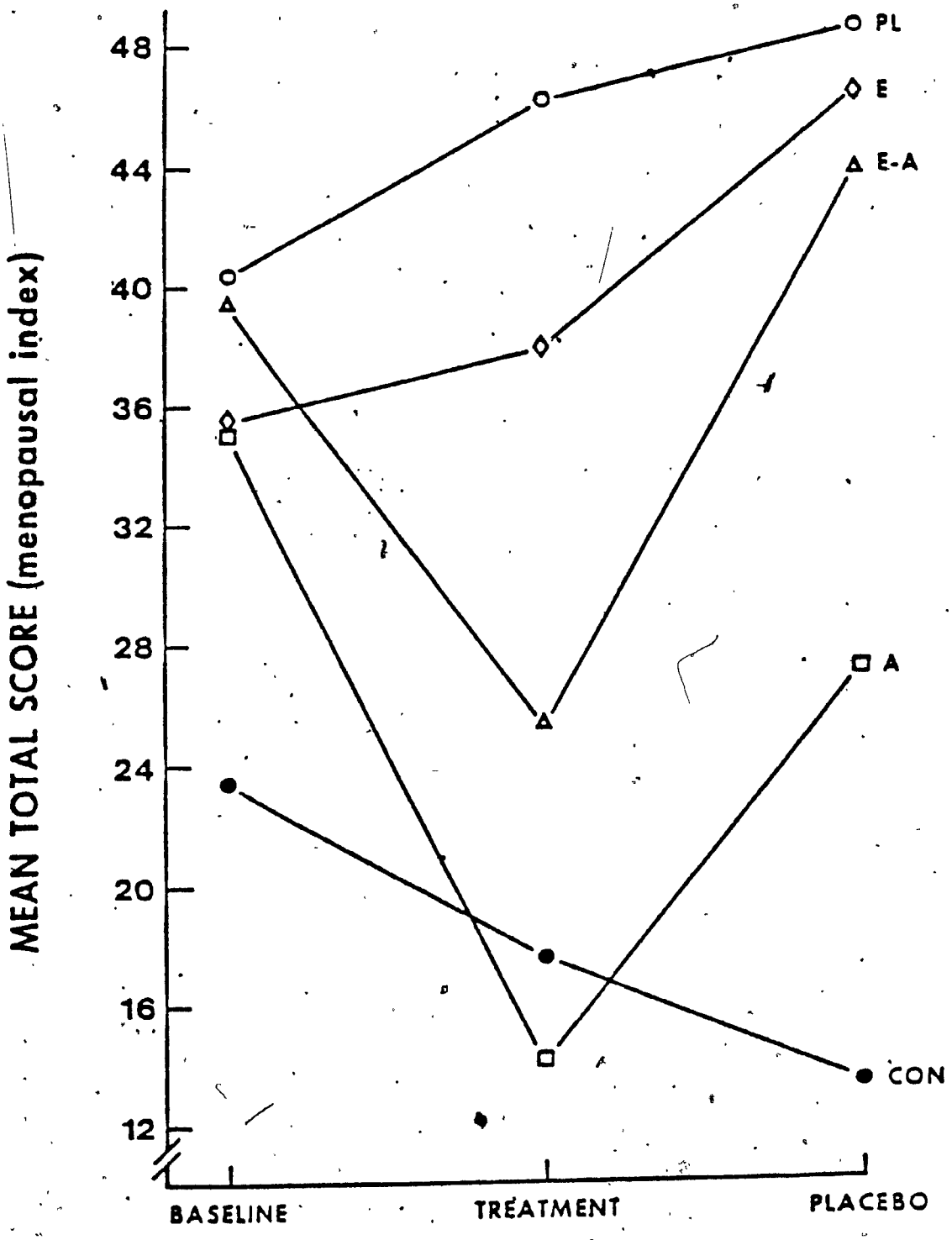

Figure 10. Total Score (Menopausal Index)

Table 21

Mean Digit Span Scores:
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$6.00^{a,A}$	$6.50^{a,A}$	$6.43^{a,A}$	$6.25^{a,A}$	$6.56^{a,A}$
Treatment	$6.58^{b,AB}$	$6.92^{b,A}$	$6.71^{a,AB}$	$6.00^{a,B}$	$7.00^{b,A}$
Placebo	$6.33^{b,AB}$	$6.25^{a,B}$	$6.43^{a,AB}$	$6.00^{a,B}$	$7.11^{b,A}$

Note: Means with the same superscript do not differ significantly
a,b Within group Tukey tests
A,B Between group Tukey tests

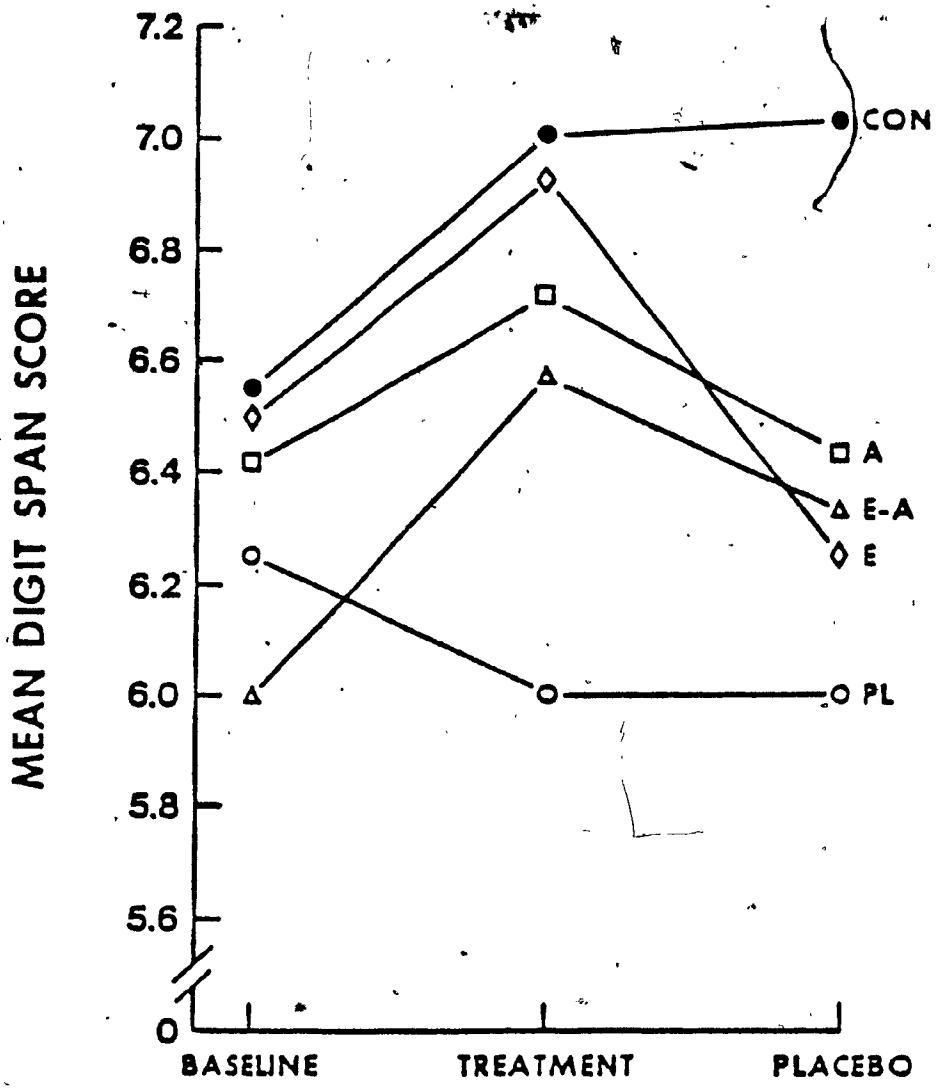

Figure 11. Digit Span

the PL groups. A graph of these findings (Figure 11) shows that the hysterectomy CON group achieved the highest digit span scores at each test period whereas the PL group scores were the lowest of all the groups postoperatively.

Abstract Reasoning.

Mean scores on this subtest of the DAT subjected to an ANOVA demonstrated a significant main effect for Time, $F(2,86)=89.85$, $p < .0001$, and a significant Group x Time interacttion, $F(2,86)=3.28$, $p < .01$. Within and between group Tukey tests (Table 22) showed that all five groups achieved a significant increase in abstract reasoning scores from baseline to treatment phase, but only the three groups that received hormones had scores that were significantly higher at placebo as compared to baseline.

Between group post-hoc tests showed no significant differences in abstract reasoning scores between any of the groups at any of the time periods. The graph of these means (Figure 12) shows that the hysterectomy CON group attained scores that were considerably higher than those of the other four groups at each time period although this difference did not achieve statistical significance.

Clerical Speed and Accuracy (CSA).

Mean CSA scores subjected to an ANOVA demonstrated a significant main effect for Time, $F(2,86)=63.8$, $p < .0001$ and a significant Group x Time interaction, $F(2,86)=2.91$, $p < .005$. Table 23 contains the results of the within and between group post-hoc tests. CSA scores increased significantly from baseline to the treatment phase in all five groups. However, scores of only the three hormone groups (E-A, E, and A) decreased significantly from the

Table 22

Mean Abstract Reasoning Scores:
Within and Between Group Post Hoc Tukey Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$27.4^{a,A}$	$29.0^{a,A}$	$26.3^{a,A}$	$27.0^{a,A}$	$34.9^{a,A}$
Treatment	$31.2^{b,A}$	$31.5^{b,A}$	$30.0^{b,A}$	$29.5^{b,A}$	$36.9^{b,A}$
Placebo	$29.3^{ac,A}$	$30.0^{ac,A}$	$28.3^{ac,A}$	$29.8^{b,A}$	$36.7^{b,A}$

Note: Means with the same superscript do not differ significantly
a,b,c Within group Tukey tests
A Between group Tukey tests

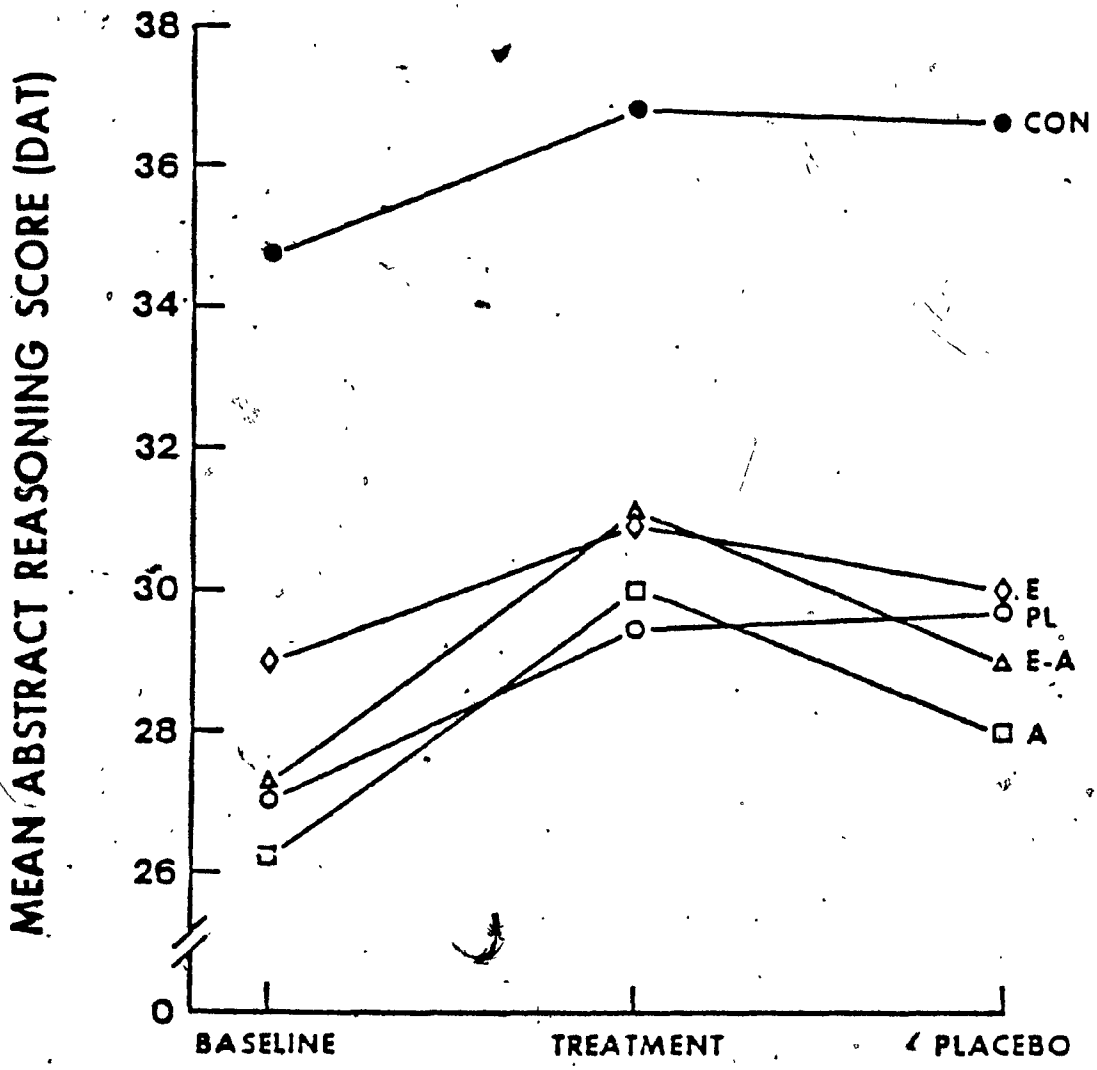

Figure 12. Abstract Reasoning

Table 23

Mean Clerical Speed and Accuracy Scores:
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$50.2^{a,A}$	$56.0^{a,A}$	$50.3^{a,A}$	$51.8^{a,A}$	$57.8^{a,A}$
Treatment	$55.2^{b,A}$	$58.5^{b,A}$	$55.4^{b,A}$	$54.2^{b,A}$	$60.2^{b,A}$
Placebo	$52.7^{a,A}$	$56.8^{a,A}$	$53.4^{c,A}$	$54.0^{b,A}$	$60.4^{b,A}$

Note: Means with the same superscript do not differ significantly
a,b,c Within group Tukey tests
A Between group Tukey tests

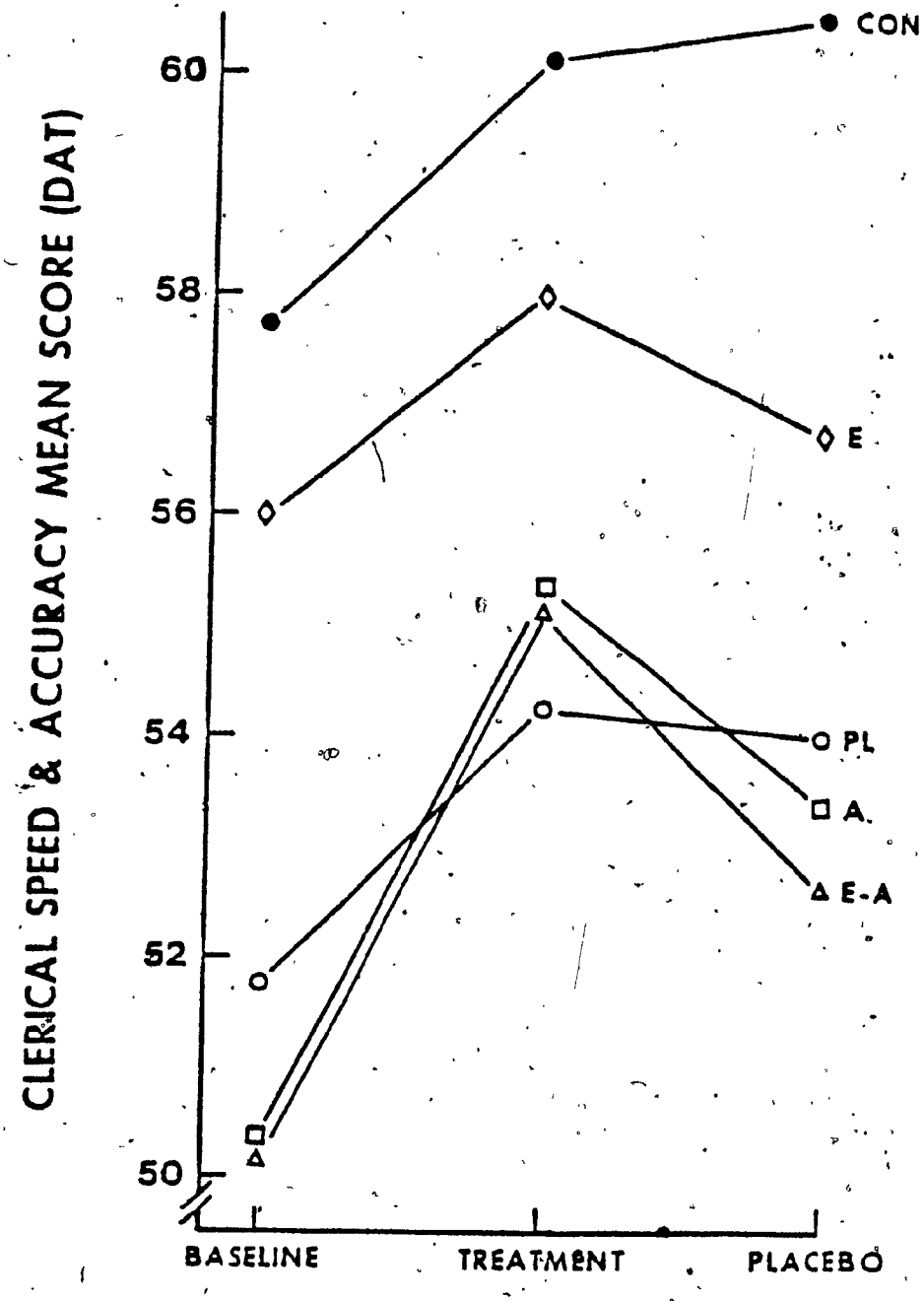

Figure 13. Clerical Speed and Accuracy

treatment to the end of the placebo phase. Furthermore, the A, PL and CON groups showed a significant increase in CSA scores from preoperative baseline levels to the end of the placebo phase. Between-group post-hoc tests on CSA scores showed no significant differences between any of the groups at any of the three time periods. Figure 13 shows that the hysterectomy CON group achieved consistently higher scores on this measure than the four treatment groups although the differences never attained statistical significance.

Plasma Hormone and Gonadotrophin Levels.

Venous blood samples, obtained at three times during the study (baseline, three days following the third injection and the last day of the placebo month), were assayed for plasma levels of total estrogens, testosterone, LH and FSH. Data on each of these measures were subjected to an ANOVA in order to determine whether there had been any changes in plasma levels of the sex steriods or gonadotrophins as a result of surgery or hormone therapy.

a) Total Estrogens.

The ANOVA on total plasma estrogens demonstrated significant main effects for Group, $F(4,43)=11.39$, $p < .0001$; for Time, $F(2,86)=82.8$, $p < .0001$, and a significat Group x Time interaction, $F(2,86)=25.0$, $p < .0001$. Within and between group Tukey tests (Table 24) indicated that the three hormone groups (E-A, E, and A) had significantly higher total plasma estrogen levels during the treatment phase than they did at baseline and significantly lower levels at the end of the placebo phase compared to treatment levels. The hysterectomy CON group alone maintained stable total plasma estrogen levels throughout the course of the study. Between group post hocs showed a significant difference in plasma estrogen levels at

Table 24

Mean Total Plasma Estrogens (pg/ml):
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$88.8^{a,B}$	$48.8^{a,B}$	$41.4^{a,B}$	$69.9^{a,B}$	$121.7^{a,A}$
Treatment	$234.1^{b,A}$	$302.5^{b,A*}$	$108.4^{b,A}$	$10.8^{ab,B}$	$90.8^{a,A}$
Placebo	$7.3^{a,B}$	$14.6^{a,B}$	$9.3^{a,B}$	$5.1^{b,B}$	$68.9^{a,A}$

Note: Means with the same superscript do not differ significantly
a,b Within group Tukey tests
A,B Between group Tukey tests
* E > E-A, A, PL, and CON

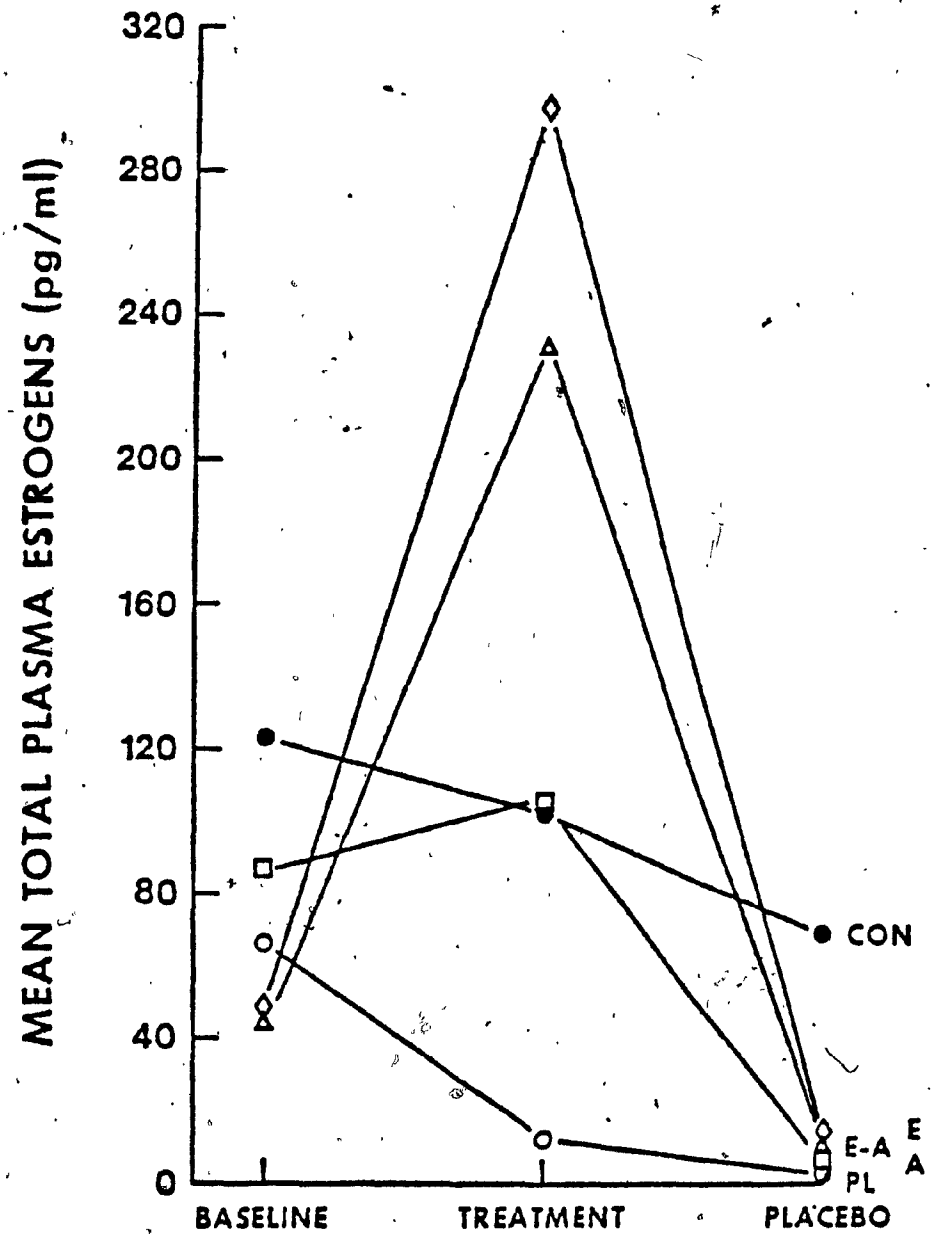

Figure 14. Total Plasma Estrogens

baseline between the hysterectomy CON group and the four treatment groups whose levels did not differ from each other. During the treatment phase, the PL group had significantly lower plasma estrogen levels than the other four groups and the E group had significantly higher levels than the other four groups. At the end of the placebo phase, the four treatment groups had significantly lower plasma estrogen levels than the hysterectomy CON group. The precipitious decline in estrogen levels from the treatment to the placebo phase in the three hormone groups is shown in Figure 14.

b) Plasma Testosterone Levels.

The ANOVA on mean plasma testosterone levels demonstrated a significant main effect for Time, $F(2,86)=12.39$, $p < .001$; and a significant Group x Time interaction, $F(2,86)=4.68$, $P < .001$. The within and between group Tukey tests appear in Table 25. Both treatment groups that received testosterone (E-A and A) had significantly increased levels of this hormone from baseline to the treatment phase and significantly lower levels at placebo compared to treatment. The PL and CON group maintained stable plasma testosterone levels throughout the course of the study. The between group Tukey tests showed that, during the treatment phase, the E-A group had significantly higher plasma testosterone levels than the E, the PL and the CON groups. Figure 15 is a graph of the mean changes in plasma testosterone levels across time.

c) Plasma FSH Levels.

The ANOVA Summary Table for mean plasma FSH levels demonstrated a significant main effect for Group, $F(4,41)=7.46$, $p < .0001$; for Time, $F(2,82)=102.6$, $p <$

Table 25

Mean Plasma Testesterone Levels (ng/100 ml): Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$80.6^{a,AB}$	$99.1^{A,AB}$	$71.2^{a,A}$	$114.6^{a,B}$	$90.8^{a,AB}$
Treatment	$132.8^{b,A}$	$91.2^{ab,B}$	$111.5^{b,AB}$	$88.7^{a,B}$	$89.8^{a,B}$
Placebo	$83.7^{a,A}$	$65.5^{b,A}$	$68.2^{a,A}$	$86.6^{a,A}$	$79.4^{a,A}$

Note: Means with the same superscript do not differ significantly
a,b Within group Tukey tests
A,B Between group Tukey tests

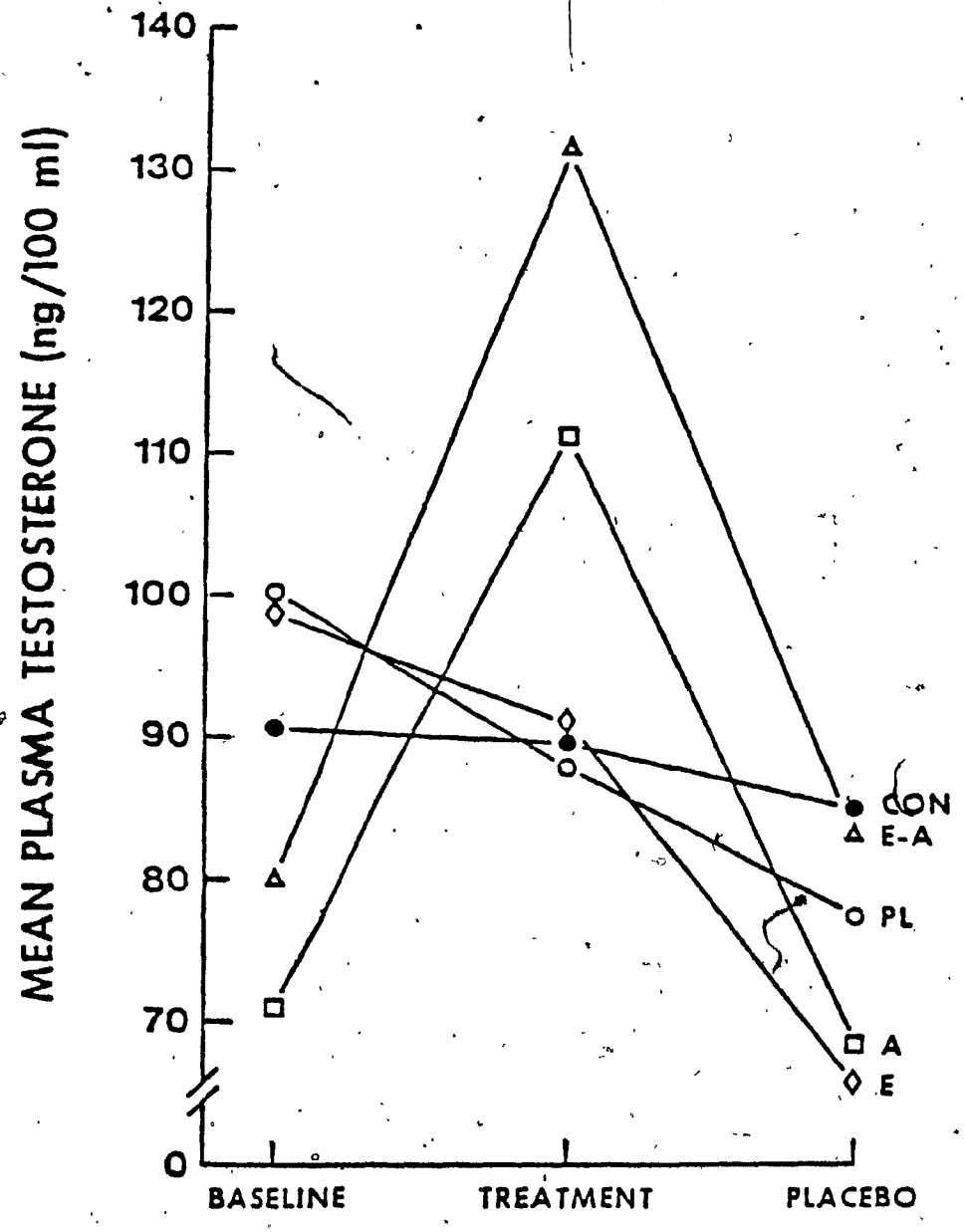

Figure 15. Plasma Testosterone Levels

.0001, and a significant Group x Time interacction, $F(2,82)=5.90$, $p < .0001$. Within and between group Tukey tests (Table 26) showed that the three hormone groups had higher FSH levels during the treatment and placebo phases compared to baseline. PL group FSH levels increased from baseline to the treatment phase only while levels of this gonadotrophin remained stable in the hysterectomy CON group throughout the study. Between group comparisons showed that there were no differences in FSH levels at preoperative baseline. However, during the treatment phase, the PL group had significantly higher FSH levels than the three hormone groups and the hysterectomy CON group. By the end of the placebo phase, the hysterectomy CON group had significantly lower FSH levels compared to all four of the oophorectomized groups. A graph of these data is presented in Figure 16.

D) Plasma LH Levels.

Results of mean plasma LH levels subjected to an ANOVA demonstrated significant main effects for Group, $F(4,39)=4.89$, $p < .01$, and for Time, $F(2,78)=46.5$, $p < .0001$ and a significant Group x Time interaction, $F(2,78)=2.47$, $p < .01$. Tukey post-hoc tests are presented in Table 27. The E-A, the E and the PL groups all had higher plasma LH levels at treatment compared to preoperative baseline and higher levels at placebo compared to the treatment phase. The A group experienced a significant increase in LH levels only from baseline to placebo whereas plasma LH values of the hysterectomy CON group remained stable at a low level throughout the study. Between group comparisons showed no significant differences in LH levels at baseline. However, at the treatment and placebo phases, the E-A group, the E group and the PL group had significantly higher plasma LH levels than the intact hysterectomy CON group. Mean differences in plasma LH levels appear in graphic form in Figure 17.

Table 26

Mean Plasma FSH Levels (μg/100 ml):
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$20.1^{a,A}$	$16.9^{a,A}$	$14.3^{a,A}$	$15.4^{a,A}$	$12.8^{a,A}$
Treatment	$82.2^{b,B}$	$82.0^{b,B}$	$65.2^{b,B}$	$170.6^{b,A}$	$29.6^{a,B}$
Placebo	$129.5^{c,}$	$129.7^{c,A}$	$125.9^{c,A}$	$181.4^{b,A}$	$44.7^{a,B}$

Note: Means with the same superscript do not differ significantly
a,b,c Within group Tukey tests
A,B Between group Tukey tests

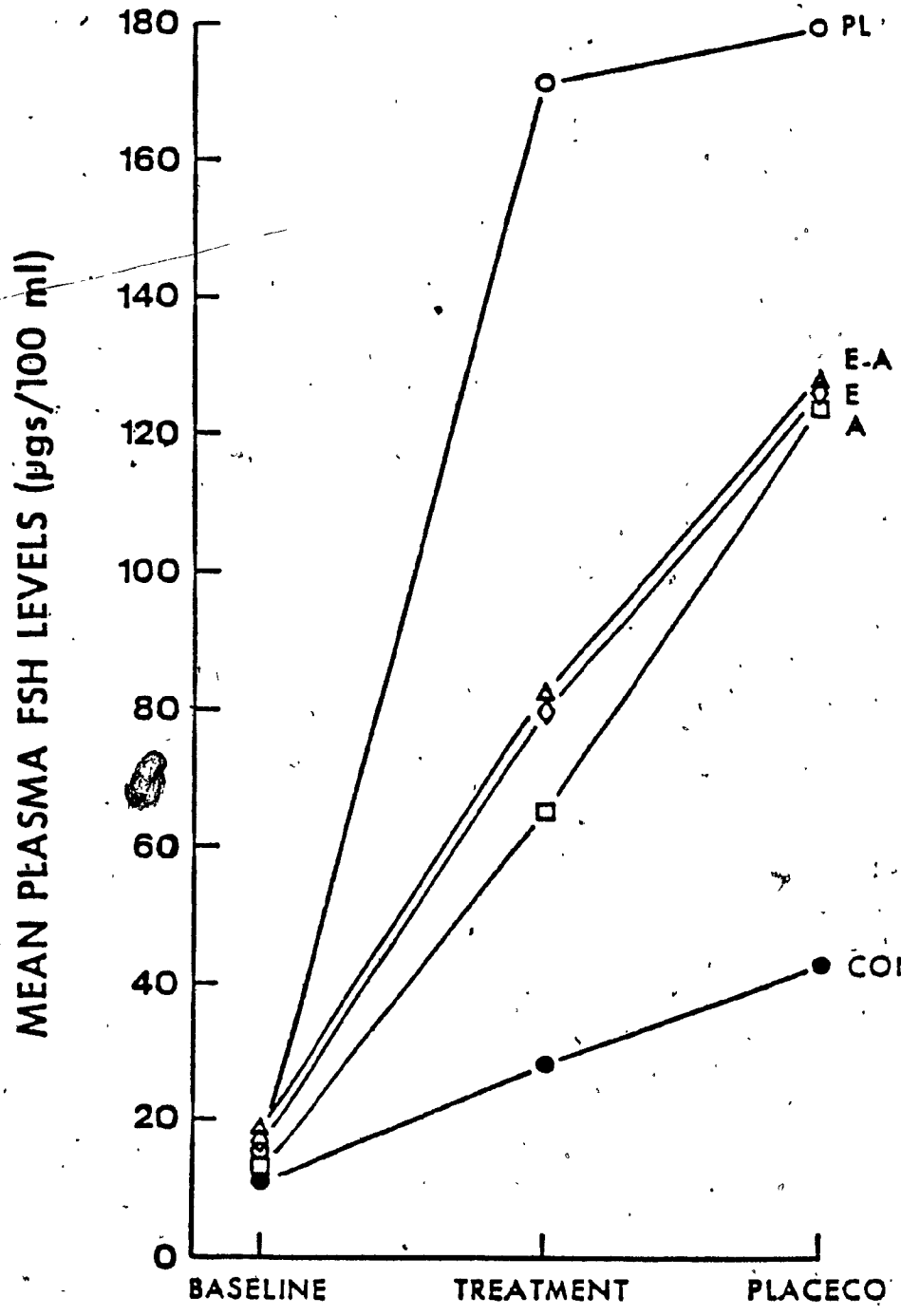

Figure 16. Plasma FSH Levels

Table 27

Mean Plasma LH Level (μg/100 ml):
Within and Between Group Tukey Post Hoc Tests

Time Period	Treatment Groups				Hysterectomy
	E-A	E	A	PL	CON
Baseline	$4.4^{a,A}$	$3.5^{a,A}$	$1.8^{a,A}$	$4.0^{a,A}$	$3.4^{a,A}$
Treatment	$23.9^{b,A}$	$26.1^{b,A}$	$11.6^{ab,B}$	$22.4^{b,A}$	$5.6^{a,B}$
Placebo	$25.9^{bc,A}$	$26.3^{bc,A}$	$14.9^{b,AB}$	$27.4^{bc,A}$	$7.7^{a,B}$

Note: Means with the same superscript do not differ significantly
a,b,c Within group Tukey tests
A,B Between group Tukey tests

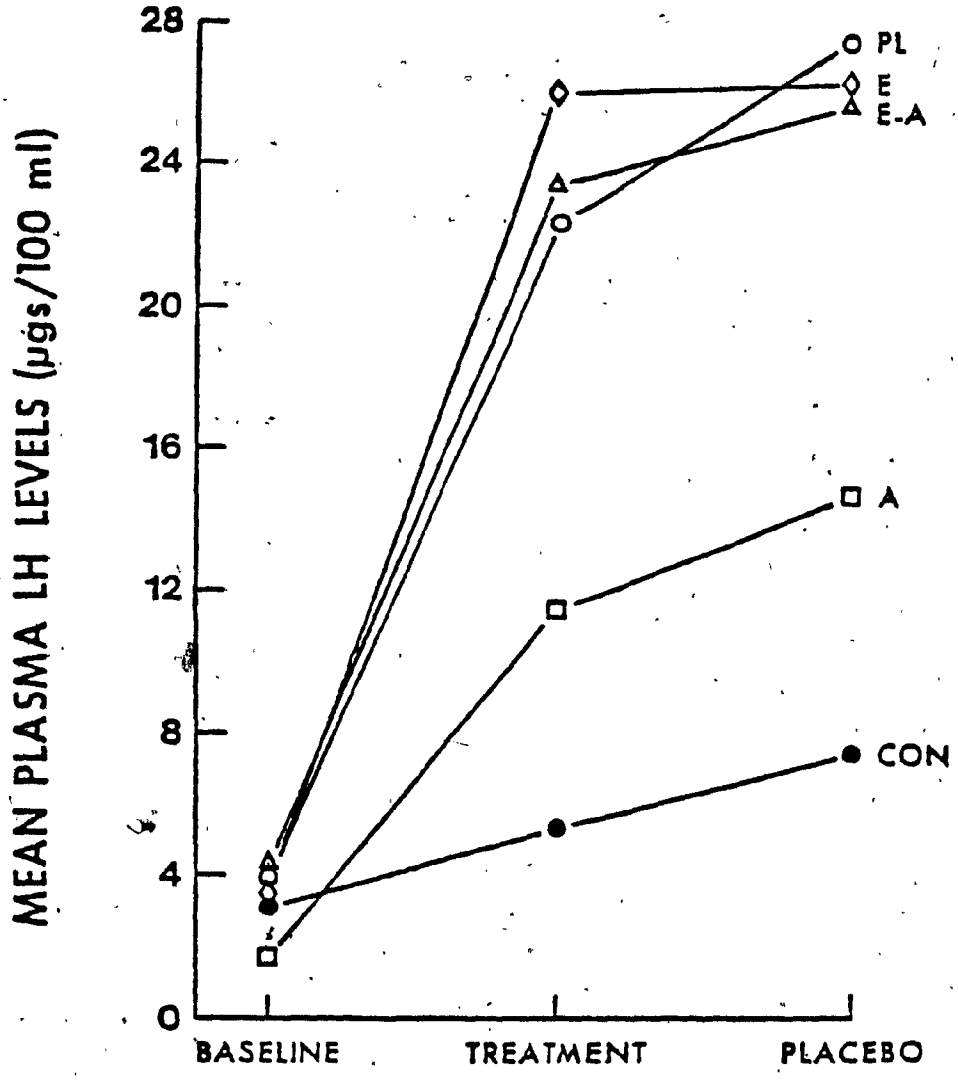

Figure 17. Plasma LH Levels

DISCUSSION

Baseline assessment of this sample of 48 subjects showed that there were no significant differences among groups in years of scolarity, occupational status, in neuroticism and extraversion scores of the EPI or in Marital Adjustment Scale scores. It can therefore be concluded that the groups were homogeneous with respect to these characteristics. The hysterectomy CON group, however, was significantly younger than the women in the four treatment groups. This was an expected finding since age is the major criterion that guides the decision to remove or to retain normal-looking ovaries at the time of an abdominal hysterectomy. It is also important to note that the neuroticism and extraversion EPI scores all fell within the range of scores for the normal population. Furthermore, all subjects obtained Marital Adjustment Scale scores of over 100 which is the cut-off score used to discriminate satisfactory from distressed marital relationships (Burgess et al., 1971). Thus, apart from age, not only were the groups educationally and occupationally equivalent, but they had normal personality profiles as measured by the EPI and satisfactory marital relationships.

One of the major goals of this study was to assess the differential effects of estrogen and androgen on somatic, affective, sexual and cognitive functioning in women who had undergone hysterectomy and bilateral oophorectomy. A general finding was that on every measure but one where there was a statistically significant interaction effect as determined by an ANOVA, there were no differences in scores between the five groups at baseline, demonstrating the success of the randomization procedure. The single exception was the higher total plasma estrogen levels of

the younger hysterectomy CON group. Thus, the likelihood that group differences found at other times during the study were attributable to the effects of the treatments was strengthened. Hormone effects with respect to the four areas of functioning previously mentioned will be discussed separately.

Somatic Symptoms

The consistent finding in the literature that hot flushes are alleviated by estrogen administration was confirmed in this study. Further evidence of the efficacy of exogenous estrogen in the amelioration of this symptom is related to the finding that when hormones were withdrawn during the placebo month, the E-A and E groups reported a significantly higher incidence of hot flushes than the intact hysterectomy CON group and did not differ from the incidence reported by the other oophorectomized treatment groups at that time.

Variations in the relation between hot flush frequency and total plasma estrogen levels provide a basis for speculation on the manifestation of this symptom in menopausal women. Recall that at preoperative baseline, the hysterectomy CON group had significantly higher plasma estrogen levels than those of the four treatment groups although there were no differences among the five groups in hot flush frequency at that time. At the end of the placebo phase, however, the hysterectomy CON group still had significantly higher plasma estrogen levels than the four treatment groups but the oophorectomized women all reported a significantly increased incidence of hot flushes. It is interesting to note that the magnitude of the difference in plasma estrogen levels between the hysterectomy CON group and the four treatment groups was much greater at the placebo phase than at baseline. when

the oophorectomized subjects had negligible levels of circulating estrogens. These data suggest that hot flushes may be precipitated only when plasma estrogen levels fall below some minimal threshold.

Data from the DMRS on other somatic symptoms showed that they did not respond to estrogen administration in a manner similar to hot flushes. There were no significant effects of any of the treatments on headaches, on nausea, on quality of sleep or on appetite. Means scores on quality of sleep and on appetite showed significant changes across time irrespective of group consistent with a post-operative recovery period. Since one of the objectives of this study was to discriminate hormone-responsive symptoms from those that are seemingly independent of hormone administration, these nonsignificant findings are equally interesting as the positive effects of sex steriods on other symptoms. These results challenge the assumption that the above symptoms are causally related to circulating levels of sex hormones.

The second instrument used to measure somatic symptoms, the Menopausal Index, yielded somewhat different results; the two groups that received androgen (E-A and A) reported fewer somatic symptoms during the treatment phase that did the PL group, whereas the E group scores did not differ significantly from the PL group. It is worth noting from a methodological perspective that the estrogen effect on hot flushes was obscured by the fact that, in the Menopausal Index, a number of disparate symptoms were grouped together with it. The discrepancy between the two measures suggests that somatic symptoms be studied individually until empirical evidence concerning a rationale for clustering these symptoms becomes available.

Two questionnaire items which likely reflect aspects

of both physical and psychological functioning are energy level and well-being. Significant decreases in sense of well-being and energy level occurred from baseline to month one of treatment across groups. By the second treatment month, subjects were reporting mean scores on these measures which were significantly above baseline levels. Mean scores on these variables appear in Tables 11 and 12. They point out the interesting observation that the A group alone reported a stability or an increase in energy level and well-being from baseline to month one of treatment in contradistinction to the decline experienced by the other four groups. Although the between group differences did not achieve statistical significance, the observation that androgen-treated women maintained levels of well-being and energy-level in the immediate postoperative period is of potential clinical importance; general anabolic effects of androgen may serve to enhance postoperative recovery in hysterectomized and oophorectomized women. This observation, therefore, merits further research with larger sample sizes.

Affective Functioning

The DMRS item which measured mood changes showed only a significant effect for time. Mean scores increased (indicating reduced depressive feelings) from both baseline and month one compared to the third treatment month across groups. The absence of a significant interaction effect suggested that none of the hormone preparations had any effect on mood. However, when depression was measured by means of the MAACL, the A group alone achieved significantly lower scores than the PL group during the treatment phase reflecting their more positive affective status. This finding is in accord with those of Itil (1976) and Klaiber et al. (1976) who demonstrated that androgen administration caused a decrease in depressive

mood in males. This effect was not maintained after hormones were withdrawn. At the end of the placebo month, there were no differences in depression scores between any of the groups. Within group changes, however, which demonstrated significant decreases in depression in all three hormone groups at treatment compared to baseline and significant increases following hormone withdrawal, strongly suggest that depression is ameliorated by hormone administration but does not permit discrimination between effects of the two sex steriods.

The estrogen replacement therapy literature contains an almost equal number of studies which have found a beneficial effect of estrogen on depression (Dennerstein et al., 1979; Durst and Maoz, 1980; Fedor-Freyburgh, 1977; Furuhjelm & Fedor-Freybergh, 1976; Rauramo et al., 1975; Rhoades, 1975) and those which found no difference between estrogen and placebo on measures of depression (Campbell, 1976; Coope, 1976; George et al., 1973; Schneider et al., 1977; Strickler et al., 1977; Thompson & Oswald, 1977). Adding to this confusion are the methodological problems in almost all of these studies which render their interpretation difficult. It is, therefore, not possible to conclude whether the present findings on hormones and depression are consistent with the literature on estrogen replacement therapy studies.

Of important clinical relevence are the mean depression scores reported by the PL group (mean = 15.5) throughout the course of the study. The normative values for non-symptomatic females is 11.1 and that for female psychiatric patients, 16.1 (Manual for the Multiple Affect Adjective Checklist, 1965). In this study, mean depression scores of the PL group at all of the three time periods sampled, approached those of a psychiatric population. These data suggest that high depression scores following

bilateral oophorectomy in premenopausal women are related to changes in hormonal status. While the severity of depression in these patients may be experienced as distressful, it does not qualitatively constitute clinical depression in the sense that significant disturbances in daily functioning and neurovegetative changes (e.g. insomnia, anorexia, digestive disturbances) are concomitants. These findings do imply, however, that untreated oophorectomized women are at a high risk for the development of feelings of sadness and that hormone replacement therapy contributes to the alleviation of dysphoric mood states arising from an altered endocrine status. However, hormone administration is ineffective as the sole therapeutic strategy for the treatment of depression when it is of a clinical magnitude. It should be recalled that Schneider et al. (1977) found that exogenous estrogen was effective in reducing depression scores from a high normal to a normal range in menopausal women. However, estrogen administration did not reduce the scores of subjects, who at baseline, had obtained very high scores indicative of clinical depression. The importance of careful psychological assessment of depression in these cases is crucial.

The only direct evidence for a beneficial effect of estrogen on depression was provided by Klaiber et al. (1979) who demonstrated that severely depressed women given oral conjugated estrogen in dosages ranging from 15 to 25 mg per day three times a week (450 to 750 mg per month) showed significant decreases in depression scores. In the present study, subjects received 10 mg of estradiol intramuscularly per month. It would seem that the results of the Klaiber et al. (1979) study, therefore, were likely due to a pharmacological effect of estrogen rather than to a physiological effect. Supportive evidence stems from the finding that when estrogen was administered to menopausal

women in doses sufficient to achieve vaginal cornification (indicative of a physiological effect), there were no significant changes in depression (Riply, Shorr and Papanicolaou, 1940). It is likely, therefore, that the beneficial effect of estrogen on depression is dose-related. The demonstration in the present study of a decrease in depression scores from baseline to treatment and an increase from treatment to placebo in both groups that received relatively modest doses of estrogen (E-A and E) supports this hypothesis.

Hostility, the third affect measured by the MAACL, showed no significant changes over time in any of the groups despite the reports of a significant positive correlation between plasma testosterone levels and measures of aggression and hostility in males (Doering et al., 1974; Persky et al., 1971).

Sexual Functioning

The adminstration of estrogen and androgen, singly and in combination, yielded differences in the effects of the sex steroids on several parameters of female sexuality. Mean level of subjective sexual desire was monitored daily by each woman for five months. It was explained to the subjects that this questionnaire item was intended to measure personal awareness of sexual desire irrespective of sexual activity. Only the groups that received androgen (E-A and A) did not report significant decreases in sexual desire from baseline to the first postoperative month. Concomitantly, only these two groups showed significantly increased plasma testosterone levels from baseline to the treatment phase. These findings suggest that exogenous androgen was the critical factor in the maintenance of sexual desire levels at that time. Furthermore, by the third treatment month, all groups except the one which had

received E-A reported significantly lower levels of sexual desire than the hysterectomy CON group. The E-A combined drug, therefore, induced levels of sexual desire which most closely resembled those of the endocrinologically - intact CON group. Figure 15 shows that the E-A group had significantly higher levels of plasma testosterone than the other four groups during the treatment phase thus supporting the notion that androgen does play a critical role in levels of sexual desire in females. Following hormone withdrawal, all subjects who had undergone bilateral oophorectomy reported a significantly decreased level of sexual desire compared to the hysterectomy CON but the four groups did not differ from each other. This finding supports the notion that sexual desire is an androgen-related phenomenon.

The other subjective component of sexuality studied, namely, the mean number of sexual fantasies, showed a similar relationship to testosterone levels. During the treatment phase, the E-A group which had the highest plasma testosterone levels and the A group whose testosterone levels did not differ from those of the E-A group, both reported numbers of sexual fantasies which did not differ significantly from the mean of the CON group. Once again, when hormones were withdrawn, the four groups of oophorectomized women reported significantly fewer sexual fantasies than the hysterectomy CON group.

Androgen also demonstrated a beneficial effect over estrogen during the third treatment month with regard to the mean level of sexual arousal attained during intercourse. By the end of the placebo phase, however, the A group reported a significantly decreased level of sexual arousal as compared to the PL and CON groups.

Changes in these three parameteres of sexual

functioning demonstrate consistency between the behavioral data and plasma testosterone levels during the treatment phase. However, at the end of the placebo phase, when the four treatment groups showed significant decreases on the behavioral measures compared to the hysterectomy CON, there were no differences in plasma testosterone levels between any of the groups. One possible explanation for this apparent discrepancy may relate to the fact that the assay method for plasma testosterone used in this study did not distinguish free testosterone from protein-bound testosterone. Thus, absolute testosterone levels are not necessarily indicative of the quantity of biologically-active, unbound, circulating steroid. Furthermore, there is reason to believe that the amount of unbound steroid changes as a function of hormonal status (Burke & Anderson, 1979). For example, it has been shown that testosterone administration not only results in higher absolute levels of testosterone but also decreases the amount of SHBG resulting in less testosterone binding. Therefore, plasma testosterone levels of those subjects who received exogenous testosterone during the treatment phase of the present study likely contained a high fraction of unbound, biologically-active hormone, effects of which were reflected in the behavioral data. The amount of SHBG available may also be relevant to our understanding of what was occurring during the placebo phase. Recall that during this phase, the hysterectomy CON group who had retained ovaries, had higher levels of total plasma estrogens than the four groups of oophorectomized women. These significant levels of plasma estrogens would compete with any available testosterone for SHBG. However, testosterone binds preferentially to SHBG (Mercier-Bodard, 1970). Therefore, although there were no absolute differences in testosterone levels between groups at the placebo phase, it is probable that the oophorectomized subjects in the four treatment groups had less free testosterone than the

hysterectomy CON group at that time because of their significantly lower levels of plasma estrogens. A decrease in testosterone-related behaviors would be an expected consequence of the increase in this steroid's binding capacity. Such differences in free and bound fractions of the steroid between groups would explain why changes in behavioral measures do not seem to correspond with the reported plasma testosterone levels at the placebo phase in this study.

That estrogen administration alone was not responsible for changes in the parameters of sexual functioning discussed is supported by the finding that although total plasma estrogens were highest in the E group at treatment, subjects in this group reported mean scores of sexual desire and sexual fantasies that were similar to those of the untreated PL group and a lower level of sexual arousal than the four other groups. The absence of an effect of estrogen on sexual desire, fantasies, sexual arousal and frequency of orgasm is consistent with the results of many estrogen replacement therapy studies (Campbell, 1976; Coope, 1976; Dennerstein et al., 1977; Maoz and Durst, 1980; Stickler et al., 1977; Townsend et al., 1980; Utian, 1972). These investigators have reported that although estrogen administration significantly improved vaginal dryness and dyspareunia, there were no changes in sexual desire, sexual arousal, frequency of intercourse and orgasm.

To summarize, the findings in this study with regard to sexual functioning demonstrate that the administration of androgen to oophorectomized subjects, either alone or in combination with estrogen, induced effects on sexuality which closely resembled those of women who had retained ovaries whereas exogenous estrogen was no more effective than placebo. To our knowledge, this is the first

controlled, empirical evidence of the enhancing effect of androgen on specific aspects of human female sexual functioning. Furthermore, these data are consistent with the early, uncontrolled reports of increases in libido as a function of androgen administration in menopausal women (Carter et al., 1947; Groome, 1939; Greenblatt et al., 1942; Kupperan & Studdiford, 1953; Silberman, 1940; Shorr et al., 1938).

That hormone administration had no effect on the frequency of sexual intercourse may have been due to partner variables which were not investigated in this study. Therefore, although the findings demonstrate that exogenous androgen had a beneficial effect on several subjective parameters of female sexual functioning, we were unable to show any changes in interpersonal sexual behavior, most likely because this activity is multidetermined; the partner's sexual desire, attitudes toward the surgery etc. would all affect the frequency of sexual intercourse. Two methodological issues with regard to future research on androgen and female sexuality are suggested by these data. Firstly, differential response of various parameters of sexual functioning to hormone administration implies that sexuality is not a unitary phenomenon. It would seem important, therefore, to carefully operationally define and investigate the various aspects of sexual behaviour rather than study changes in "libido", an ill-defined, global term subject to individual interpretation. Secondly, the investigation of changes in interpersonal sexual behavior as a function of hormonal status must as well include data gathered from the partner in order to control for possible effect of his behavior on the frequency of sexual encounters.

Cognitive Functioning

Significant effects of hormones on several measures of cognitive functioning emerged in this study. Results of the short-term memory test administered suggest an important role for estrogen. The E-A and the E groups showed significant increases in digit span scores from baseline to the treatment phase. At treatment, the E group and the hysterectomy CON group had significantly higher mean digit span scores than the PL group whose scores were the lowest of all the groups postoperatively. At the placebo phase, the mean score of the E group fell such that it was lower than the hysterectomy CON concomitant with a significantly lower level of total plasma estrogens. These data clearly indicated that the administration of estrogen to oophorecomized women had a beneficial effect on short-term memory. The significance of this finding is underlined by the high incidence of memory disturbances at the time of menopause reported in both epidemiological and hormonal studies. Furthermore, the decrease in PL group scores from baseline to treatment attests to the fact that sudden and drastic hormonal changes subsequent to bilateral oophorectomy have a detrimental effect on short-term memory which is distinct from the changes that are known to occur over time with aging (Rabinowitz, Craik & Ackerman, 1982).

Two well-controlled experiments found no changes in memory as a function of exogenous estrogen (Rauramo et al., 197; Van Hulle & Demol, 1976). However, in both studies, different oral estrogens in varying dosages were administered (estradiol valerate, 2 mg per day and estriol, 4 mg per day respectively). In the present study, 10 mg of estradiol valerate was administered intramuscularly once a month. It is known that injections differ from oral estrogens in that the injected hormone acts directly on target tissues without prior absorption through the gut and detoxification in the liver. Also, the injectable route is likely to provide higher and more sustained blood levels

than oral administration (Hulka, Chambless, Deubner & Wilkinson, 1982). The discrepancy between the finding of a beneficial effect of estrogen on short-term memory in this study and those of Rauramo et al.(1975) and Van Hulle and Demol (1976) may, therefore, be due to the dosages and/or to the differing mechanisms of action of oral and injectable estrogens. The wide-ranging implications of this issue strongly suggest that it merits further, rigorous research efforts.

Results of the two subtests of the Differential Aptitude Test, namely Abstract Reasoning (AR) and Clerical Speed and Accuracy (CSA) were equivocal. On both measures, all five groups achieved significant increases in scores from baseline to the treatment phase. In AR, the three hormone groups also had decreased scores from the treatment to placebo phases but significantly increased scores from baseline to placebo. Moreover, there were no significant differences in scores between the groups at any of the time periods. Therefore, although all of the hormone preparations seemed to improve performance on these tasks, the effect is attenuated by the finding that performance increased from baseline to the placebo phase whereas plasma estrogen levels decreased during those two points in time. Thus, firm evidence for an effect of hormone on these measures is lacking.

Plasma Hormone and Gonadotrophin Levels

Concordance between the results of hormone and gonadotrophin assays in this study and those of other investigations served to increase confidence in the hormone-behavior relation observed.

The hysterectomy CON group's mean baseline levels of plasma estrogens (mean=122 pg/ml) were consistant with values found in the follicular phase of the menstrual cycle by

Aksel et al. (1976) and by Stone, Dickey and Mickal (1975). Furthermore, CON group estrogen levels at baseline were significantly higher than those of the older, treatment group subjects whose baseline levels were similar to those found by Aksel et al. (1976) in perimenopausal women.

The finding that there was no change in plasma estrogen levels from baseline to the end of the fourth postoperative month in the CON group is consistent with the report by Stone et al. (1975). They observed a significant drop in plasma estrogen levels within the first four postoperative days in reproductive-aged women who had undergone hysterectomy with ovarian conservation. However, by the end of the first postoperative month, estrogen values had returned to preoperative levels.

The absence of significant differences in plasma testosterone levels between baseline and placebo within each group, is in accord with the observations of Jacobs et al. (1977). They reported that groups of postmenopausal and oophorectomized women had levels of plasma testosterone that were within the range of those in premenopausal women. The Jacobs et al. (1977) assays, as in this study, measured both free and bound testosterone. However, Judd, Lucas and Yen (1974) found that free testosterone decreased substantially in both premenopausal and postmenopausal women following bilateral oophorectomy.

Changes in gonadotrophin levels following a surgical menopause have been well documented. It has been shown that by the third postoperative day following bilateral oophorectomy, LH levels increased by six to eight-fold whereas plasma FSH increased by eight to 12-fold (Yen and Tsai, 1971). In the present study, plasma LH increased seven-fold and plasma FSH, 11-fold in the PL group four

months postoperatively compared to baseline levels. These proportional changes are, therefore, consistent with those previously reported. During treatment, the E-A, the E and the PL groups had higher LH levels than the hysterectomy CON. In no group did LH levels show a further significant increase from treatment to placebo, suggesting that exogenous hormone was not effective in controlling levels of this gonadotrophin. With regard to FSH, the PL group had higher levels at treatment than the four other groups. Furthermore treatment levels were higher than preoperative baseline in all of the oophorectomized subjects. At the placebo phase, the three hormone groups had significantly higher FSH levels compared to their levels during treatment indicating that hormone administration had supressed FSH to some degree. Overall, changes in gonadotrophin levels in this study were in agreement with the findings of Utian et al. (1978) who reported that incremental doses of estrogen administered to premenopausally oophorectomized women never succeeded in reducing LH or FSH levels to preoperative values.

Several findings that occurred with surprising frequency and consistency in this study merit attention. On a number of measures in which the ANOVA demonstrated only a significant effect for Time, the post-hoc tests showed increases in symptoms or deterioration in functioning from the treatment to the placebo phase across groups; headaches and anxiety increased from treatment to placebo while well-being, energy level and the number of sexual encounters decreased during the same time period. This observation is counterintuitive if it is assumed that hormone-independent symptoms would improve postoperatively simply as a function of increasing time since surgery. One possible explanation for these findings is that headaches, anxiety, energy level, well-being and number of sexual encounters are indeed related to endocrine status but that

the effect was not sufficiently robust to attain statistical significance in the present study. The potential clinical importance of these effects suggests the need for clarification of possible hormone relationships by replication with larger sample sizes.

Another pattern in the data that was manifested on numerous measures (hot flushes, sexual desire, sexual arousal, the somatic, psychological and total scores of the Menopausal Index, and digit span) was an increase in symptoms or a deterioration in functioning in the PL group from preoperative baseline to the treatment phase followed by a stability in their scores for the remainder of the study. These changes occurred coincident with decreases in plasma estrogens and increases in gonadotrophin levels. Moreover the hysterectomy CON group maintained stability on these same measures throughout the study corresponding with stability in hormone and gonadotrophin levels. The three hormone groups, however, acted differently. Subjects who received E-A, E and A generally reported increases in functioning from baseline to treatment and drastic decreases from treatment to placebo. These changes, once again, resembled those in levels of circulating hormones. Several authors have proposed that the abruptness of hormonal changes rather than their absolute levels is responsible for changes in hormone-related behaviors. For example, the premenstrual tension syndrome, whose symptoms include anxiety, depression and irritability, occurs coincident with a precipitous fall in estrogen and progesterone levels during the last two to three days of the menstrual cycle (Golub, 1976; Ivey & Bardwick, 1968). Furthermore, women who used sequential oral contraceptive pills which induce hormonal fluctuations resembling those of a normal menstrual cycle, reported negative mood states premenstrually whereas those who used combination pills which maintained stable levels of hormones throughout the

cycle, showed no cyclic affective changes (Paige, 1971). Additional evidence was provided by studies of postpartum depression. Progesterone levels drop from 150 ng/ml at the end of pregnancy to under 7 ng/ml on the third day after birth and disappears completely by the seventh postpartum day. Similarly, estrogen drops from an average of 2,000 ng/ml in late pregnancy to 20 ng/ml on the third day after birth and then levels off at about 10 ng/ml until the changes of menstruation occur (Nott, Franklin, Armitage & Gelder, 1976). It has been shown that women who have the highest levels of progesterone in late pregnancy and consequently experience the greatest decrease in progesterone levels after delivery are at a greater risk for the development of postpartum depression (Dalton, 1980). Finally, several investigators have found that premenopausal women who undergo a surgical menopause resulting in abrupt and drastic hormonal changes report a higher frequency and severity of hot flushes (Chakravarti, Collins, Newton, Oram & Studd, 1977; Hunter, 1976) and headaches (Dennerstein, 1978) than women who experience a natural menopause during which hormone levels decrease gradually over time. These findings, taken as a whole, strongly suggest that the drastic changes in behavior observed in the PL group following surgery in this study are due to the sudden drop in their hormone levels as a consequence of bilateral oophorectomy. Similarly, the significant deterioration in behavior reported by the three hormone groups from the treatment to the placebo phase likely resulted from the abruptness and the magnitude of the decline in their circulating estrogen levels. These observations imply that administration of sex steroids to premenopausally oophorectomized women during the immediate postoperative period is particularly important in order to obviate the consequences of abrupt, drastic changes in circulating levels of gonadal hormones. Furthermore, a gradual decrease in dosages of exogenous hormones over time

will minimize symptom frequency and severity in menopausal women who desire or are required to halt treatment with exogenous hormones.

The consistent pattern in the PL group just described, that is, an increase in symptoms from preoperative baseline to treatment and subsequent stability in scores for the duration of the study, permitted the conclusion that there was no placebo effect on the symptoms and behaviors measured in this investigation. This observation is discrepant with those of numerous estrogen replacement studies (Campbell, 1976; Coope, 1976; George et al., 1973, Rauramo et al., 1975; Strickler et al., 1977; Thompson & Oswald, 1977; Utian, 1972; Van Hulle & Demol, 1976) which found either no beneficial effects of estrogen over placebo or an amelioration in functioning with both estrogen and placebo. In the majority of cases, various oral estrogen preparations in different dosages were administered to heterogenous populations of both naturally and surgically menopausal women. The lack of a placebo effect in this study may have been due both to the more rigorous experimental control and to the parenteral route of hormone administration used. In accordance with the present findings, it may be concluded that premenopausal women who undergo bilateral oophorectomy are likely to experience significant increases in several somatic symptoms and a deterioration in aspects of affective, sexual and cognitive functioning as a result of abrupt changes in hormonal status due to the surgery.

Visual inspection of the figures for the various measures indicate that the hysterectomy CON group had the fewest and least severe symptoms and that they maintained the highest level of functioning in several areas. It is tempting, therefore, to make a plea for ovarian conservation in premenopausal women at the time of

hysterectomy in the absence of ovarian pathology. However, the finding that these women were younger and had higher levels of total plasma estrogens preoperatively than women in the four treatment groups does not allow the conclusion that, had ovaries been conserved in the other subjects, their symptom incidence and level of functioning would have paralleled those of the hysterectomy CON group.

Several methodological, theoretical, and clinical issues were raised by the findings of the present study. Some investigators have expressed skepticism concerning the reliability of daily self-reporting particularly over the course of such a long investigation (150 days of monitoring per subject over the five months). The fear has been that subjects would habituate to the questionnaire items over time and lose interest in the task. The data on hot flush frequency however, strongly supports the reliability of daily questionnaire measurement, particularly when one considers the double -blind nature of this study. Recall that women who received estrogen following surgery had low frequencies of hot flushes that were not greater than those reported by the hysterectomy CON group whereas those who received A or PL, known to be ineffective in the alleviation of hot flushes, had very high frequencies of His symptom. When hormones were withdrawn, all four groups of oophorectomized women reported increased frequencies of hot flushes compared to the intact CON group. These findings are consistent with the known effects of estrogen on this symptom and they were reported systematically though subjects were unaware of the drug being administered. Furthermore, the stability of PL and CON group scores during the four postoperative months, on this measure as well as on the majority of other measures, provides further support for the reliability of these data. It would seem, therefore, that daily monitoring should provide a reliable and accurate method of measuring

individual menopausal symptoms in future prospective studies.

A second issue relates to the differential response of a myriad of so-called, menopausal symptoms, to hormone replacement therapy. Although hot flushes were effectively alleviated by both estrogen-containing preparations, the administration of androgen alone had no beneficial effects over placebo on this symptom. However, exogenous androgen induced reports of lower psychological symptom scores, lower total symptom scores, higher levels of sexual desire, number of sexual fantasies, sexual arousal and lower depression. These findings strongly suggest that menopausal symptoms may not have a common hormonal etiology. Thus, the usual clinical practice of administering estrogen alone is unlikely to alleviate all, or even most, of the symptoms commonly reported. The critical clinical implication, therefore, is that exogenous estrogen will be highly effective in reducing hot flush frequency but will not itself provide relief in postmenopausal women who are troubled by fatigue; lack of sexual desire and sexual arousal and by a host of psychological symptoms.

These observations may also serve as the basis for a critical evaluation of the proposed "domino effect" with respect to menopausal symptoms. Campbell and Whitehead's (1976) hypothesis that the alleviation of hot flushes in menopausal women will cause them to sleep better, be less irritable, less depressed, suffer fewer headaches etc., was not confirmed by these data; findings of the present study do not support the contention that other symptoms which occur coincident with hot flushes are caused by them nor are they alleviated by the same therapeutic intervention, that is, by estrogen administration alone. The need to reassess a relevant theoretical issue, namely, the concept

of a menopausal syndrome follows from this argument. By definition, a syndrome is a group of signs and symptoms that occur together and characterize a particular abnormality. Epidemiological studies (Greene, 1976; McKinlay & Jefferys, 1967; Thompson et al., 1973), psychiatric studies (Weissman, 1979; Winokur, 1973) and results of the present study fail to support the view that symptoms commonly reported at the time of menopuase constitute a syndrome. Despite such contradictory evidence, tenacious adherence to this concept has inhibited the development of more refined and specific research measures and clinical techniques. It would seem that the most appropriate strategy for future research, therefore, would be to consider and investigate symptoms commonly reported at the time of menopause independently in order to empirically test their possible differential response to various pharmacological and psychological interventions.

In summary, the results of this study demonstrated that the administration of estrogen and androgen, singly and in combination had differential effects on somatic, affective, sexual and cognitive functioning in oophorectomized women. Overall, the estrogen-androgen combined drug was the most effective in alleviating the largest number of symptoms. This hormonal preparation also induced the highest levels of plasma testosterone and levels of total plasma estrogens that were intermediate between those of the estrogen-alone drug and endogenous levels of the hysterectomy CON group. Moreover, the somatic, psychological and cognitive performance of oophorectomized subjects who received the combined drug most closely paralleled that of the younger, endocrinologically-intact hysterctomy CON group. These results provide strong support for the superior efficacy of the combined hormonal preparation in the postmenopause. Administration of both sex steroids constitutes true

hormone replacement therapy with all the demonstrated benefits that accrue to it as opposed to the more limited clinical range of effectiveness of the most common treatment, namely, estrogen replacement therapy.

To our knowledge, the demonstration of a beneficial effect of androgen on several parameters of sexuality in the human female, is the first empirical evidence, within the context of a well-controlled design, that was based on subjects who were neither suffering from malignant disease nor sexual dysfunctions. The high incidence of disturbances of libido following hysterectomy and bilateral oophorectomy reported in the literature may be related to the loss of ovarian androgens which continue to be secreted, often in increased quantities, by the postmenopausal ovary (Vermulen & Verdonck, 1978). These observations further supported the conclusion with regard to the superior efficacy of the estrogen-androgen combined preparation in menopausal hormone replacement therapy. Future research is needed to both corroborate and to extend these findings with the goal of improving the quality of life in an ever increasing segment of the population.

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Appendix A

Consent Form

Initial Interview Form

Computation of Drug Dosage Equivalence

CONSENT FORM

Your doctor has advised you that you need to have a hysterectomy (removal of the uterus) and ovariectomy (removal of the ovaries). The surgical procedure itself is very safe. Occasionally, and this varies from woman to woman, symptoms may arise after the operation due to the fact that there are reduced levels of hormone normally secreted by the ovaries. We know that the drugs used to treat these symptoms can be helpful but we want to get more information on their general effects and to try and learn more about which particular drug will be suitable for you. Therefore we are conducting a study to obtain certain kinds of information which will be useful to both physicians and patients. The areas which concern us are changes in mood, in memory and in sexual functioning. I would like you to meet with Barbara Sherwin, a psychologist who is also a nurse who works with me. She will explain the procedure of the study before you are asked to sign this form. After your operation you will be started on one of three hormone preparations or on a preparation with no active hormone. All of the hormones are in common use. Your hormone treatment may be changed during the course of the study in order to enable us to compare the different therapies. You may be assured that you will receive careful and appropriate medical treatment whether or not you continue to participate in this study. All the information gathered will be confidential -

only the psychologist will have access to it. In order to partially compensate you for your effort in providing the information we need, 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 placed on the treatment which is best for you.

I understand that I will be taking part in a study with Dr. concerning hysterectomy and that I will be receiving one of three possible hormone preparations or a preparation with no active hormone. I will be receiving the drugs free of charge.

DATE_____

_____

_____

WITNESS

INITIAL INTERVIEW FORM

NAME _____

ADDRESS _____

TELEPHONE _____

AGE _____

DATE OF MARRIAGE _____

NUMBER OF CHILDREN _____

LEVEL OF EDUCATION _____

CURRENT OCCUPATION _____

SMOKING _____

ALCOHOL _____

MEDICATIONS (CURRENT) _____

HOBBIES _____

ONSET & DESCRIPTION OF SYMPTOMS _____

_____

_____

HISTORY OF PAST ILLNESS _____

_____

_____

PAST PSYCHIATRIC ILLNESS _____

_____

SEXUAL HISTORY PRIOR TO SYMPTOM ONSET _____

_____

HUSBAND (WORKING' RETIRED' STATE OF HEALTH) _____

_____

_____

Computation of Drug Dose Equivalence

A) Estrogen-Androgen Combined Drug (Climacteron)

Each ml contains:

Testosterone enanthate benzilic acid hydrozone	150.0 mg
equivalent to testosterone	69.0 mg
Estradiol dienanthate	7.5 mg
equivalent to estradiol	4.1 mg
Estradiol benzoate	1.0 mg
equivalent to estradiol	.7 mg

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

B) Estrogen Drug (Delestrogen)

Each ml contains:

Estradiol valerate	10 mg
equivalent to estradiol	7.6 mg

Therefore 1 ml of Climacteron and .63 mg of Delestrogen contain equivalent amounts of estradiol.

C) Androgen Drug (Delatestryl)

Each ml contains:

Testosterone enanthate 200	mg
equivalent to testosterone 144	mg

Therefore 1 ml of Climacteron and .48 ml of Delatestryl contain equivalent amounts of testosterone.

D) Placebo

Sesame Oil	1 mg

Appendix B

Daily Menopausal Rating Scale

Menopausal Index

Digit Span Instructions and Stimuli

Daily Menopausal Rating Scale

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.

NAME _____ DATE _____

TIME FILLED OUT _____

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

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

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

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

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

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

4. 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

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

1 2 3 4 5 6 7

a) 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

6. In the past 24 hours I went out (e.g. with friends, family, on business),

Circle the number of times

1 2 3 4 5

7. 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

SEXUALITY

The following 6 items relate to sexual functioning. 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.

8. 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

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

10. 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

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

Menopausal Index

Below are a list of symptoms sometimes reported by menopausal women. Please indicate the degree to which you are now experiencing each of these symptoms by circling the most appropriate number on the scale. Remember, we are interested in how you are experiencing these symptoms NOW.

1. HOT FLUSHES

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

2. COLD SWEATS

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

3. FEELINGS OF SUFFOCATION

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

4. WEIGHT GAIN

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

5. RHEUMATIC PAINS

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

6. COLD HANDS AND FEET

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

7. NUMBNESS AND TINGLING

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

8. BREAST PAINS

ALMOST NEVER	1	2	3.	4	5	6	7	VERY OFTEN

9. UNUSUALLY HEAVY MENSTRUAL FLOW

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

10. SKIN CRAWLS

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

11. TIRED FEELINGS

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

12. HEADACHES

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

13. POUNDING OF THE HEART

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

14. DIZZY SPELLS

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

15. IRRITABLE AND NERVOUS

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

16. FEEL BLUE AND DEPRESSED

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

17. FORGETFULNESS

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

18. TROUBLE SLEEPING

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

19. CAN'T CONCENTRATE

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

20. CRYING SPELLS

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

21. BLIND SPOTS BEFORE EYES

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

22. EXCITABLE

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

23. ATTACKS OF PANIC

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

24. LOSS OF INTEREST IN MOST THINGS

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

25. FEELING TENSE OR WOUND UP

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

26. WORRY NEEDLESSLY

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

27. PRESSURE OR TIGHTNESS IN HEAD OR BODY

ALMOST NEVER	1	2	3	4	5	6	7	VERY OFTEN

DIGIT SPAN

Instructions

I want to see how well you can pay attention. I am going to say some numbers and when I am through I want you to say them right after me. Listen

Set 1	Set 2	Set 3
6439	3279	9346
7286	4968	6827
42731	15286	13724
75836	61843	63857
619473	539418	374916
392487	724856	784293
5917423	8129365	3247195
4179386	4739128	6839714
58192647	27469318	74629185
38295174	49382761	47159283

Appendix C

ANOVA Summary Tables

Table C.1

Mean Age: ANOVA Summary Table

Source	MS	df	F
Group	165.2	4	5.05*
Error	32.7	43	

* $p < .002$

Table C.2

Years of Scolarity:
ANOVA Summary Table

Source	MS	df	F
Group	5.79	4	.63
Error	9.22	43	

Table C.3

Occupational Status:
ANOVA Summary Table

Source	MS	df	F
Group	184.1	4	.56
Error	327.1	43	

Table C.4

Mean Neuroticism Scores:

ANOVA Summary Table

Source	MS	df	F
Group	18.7	4	1.23
Error	15.3	43	

Table C.5

Mean Extraversion Scores:
ANOVA Summary Table

Source	MS	df	F
Group	14.5	4	1.77
Error	8.2	43	

Table C.6

Marital Adjustment Scale Scores:

ANOVA Summary Table

Source	MS	df	F
Group	228.4	4	1.77
Error	129.2	43	

Table C.7

Hot Flushes: ANOVA Summary Table

Source	MS	df	F
Group	3.86	4	5.71*
Error	.66	43	
Time	2.65	4	12.98*
Time x Group	.81	16	3.97*
Error	.20	172	

* $p < .0001$

Table C.8

Headaches: ANOVA Summary Table

Source	MS	df	F
Group	3.34	4	1.26
Error	2.64	43	
Time	1.25	4	2.36*
Time x Group	.83	16	1.57
Error	.53	172	

* $p < .05$

Table C.9

Nausea: ANOVA Summary Table

Source	MS	df	F
Group	1.10	4	.46
Error	2.37	43	
Time	.07	4	.22
Time x Group	.28	16	.80
Error	.36	172	

Table C.10

Sleep Quality:
ANOVA Summary Table

Source	MS	df	F
Group	9.29	4	2.35
Error	3.96	43	
Time	2.69	4	3.27*
Time x Group	.59	16	.72
Error	.82	172	

* $p < .01$

Table C.11
Appetite: ANOVA Summary Table

Source	MS	df	F
Group	3.72	4	1.03
Error	3.60	43	
Time	4.34	4	11.14*
Time x Group	.30	16	.78
Error	.39	172	

* $p < .0001$

Table C.12
Level of Sexual Desire:
ANOVA Summary Table

Source	MS	df	F
Group	15.76	4	4.92*
Error	3.20	43	
Time	6.74	4	11.96*
Time x Group	1.20	16	2.30*
Error	.52	172	

* $p < .001$

Table C.13
Sexual Fantasies:
ANOVA Summary Table

Source	MS	df	F
Group	12.61	4	2.69*
Error	4.68	43	
Time	5.60	4	9.66**
Time x Group	.95	16	1.82*
Error	.52	172	

* $p < .05$
** $p < .0001$

Table C.14
Sexual Arousal:
ANOVA Summary Table

Source	MS	df	F
Group	10.31	4	2.68*
Error	3.85	43	
Time	7.06	2	9.94**
Time x Group	2.40	8	3.38*
Error	.71	86	

* $p < .03$
** $p < .001$

Table C.15

Number of Sexual Encounters:
ANOVA Summary Table

Source	MS	df	F
Group	.14	4	.75
Error	.19	43	
Time	.45	2	8.03*
Time x Group	.10	8	.67
Error	.14	86	

* $p \leq .05$

Table C.16

Number of Orgasms:
ANOVA Summary Table

Source	MS	df	F
Group	.58	4	.99
Error	.58	43	
Time	.15	2	.44
Time x Group	.38	8	.98
Error	.39	86	

Table C.17

Well-Being: ANOVA Summary Table

Source	MS	df	F
Group	4.02	4	1.20
Error	3.36	43	
Time	10.11	4	18.17*
Time x Group	.71	16	1.29
Error	.55	172	

* $p < .0001$

Table C.18

Energy Level: ANOVA Summary Table

Source	MS	df	F
Group	5.35	4	1.81
Error	2.96	43	
Time	10.59	4	17.13*
Time x Group	.72	16	1.17
Error	.61	172	

* $p < .0001$

Table C.19
Mood: ANOVA Summary Table

Source	MS	df	F
Group	1.90	4	.52
Error	3.66	43	
Time	2.89	4	4.72*
Time x Group	.62	16	1.01
Error	.61	172	

* $p < .001$

Table C.20
Level of Activity:
ANOVA Summary Table

Source	MS	df	F
Group	1.76	4	.53
Error	2.21	43	
Time	21.74		32.34*
Time x Group	.29	16	.44
Error	.67	172	

* $p < .0001$

Table C.21
Times Left the Home:
ANOVA Summary Table

Source	MS	df	F
Group	1.46	4	1.29
Error	1.13	43	
Time	16.03	4	66.33*
Time x Group	.26	16	1.13
Error	.24	172	

* $p < .0001$

Table C.22
Number of Arguments:
ANOVA Summary Table

Source	MS	df	F
Group	1.58	4	1.14
Error	1.39	43	
Time	.38	4	1.41
Time x Group	.30	16	1.10
Error	.27	172	

Table C.23
Involvement in Arguments:
ANOVA Summary Table

Source	MS	df	F
Group	4.70	4	.75
Error	6.29	43	.75
Time	.01	4	.00
Time x Group	.52	16	.47
Error	1.09	172	

Table C.24
Anxiety: ANOVA Summary Table

Source	MS	df	F
Group	71.42	4	2.62*
Error	27.29	43	
Time	40.66	2	15.30**
Time x Group	4.63	8	1.74
Error	2.65	86	

* $p < .05$
** $p < .0001$

Table C.25
Hostility: ANOVA Summary Table

Source	MS	df	F
Group	27.09	4	1.15
Error	23.59	43	
Time	.38	2	.14
Time x Group	5.11	8	1.88
Error	2.71	86	

Table C.26

Depression: ANOVA Summary Table

Source	MS	df	F
Group	81.67	4	1.24
Error	65.76	43	
Time	45.21	2	10.68**
Time x Group	10.87	8	2.57*
Error	4.23	86	

* $p < .01$
** $p < .0001$

Table C.27

Somatic Symptoms: ANOVA Summary Table

Source	MS	df	F
Group	326.42	4	4.20*
Error	77.80	43	
Time	215.64	2	9.98**
Time x Group	81.52	8	3.77*
Error	21.61	86	

* $p < .005$
** $p < .0001$

Table C.28
Psychosomatic Symptoms:
ANOVA Summary Table

Source	MS	df	F
Group	255.86	4	2.25
Error	113.88	43	
Time	93.39	2	6.06*
Time x Group	27.65	8	1.80
Error	15.40	86	

* $p < .01$

Table C.29
Psychological Symptoms:
ANOVA Summary Table

Source	MS	df	F
Group	727.46	4	1.69
Error	430.72	43	
Time	399.61	2	9.51**
Time x Group	136.42	8	3.25*
Error	42.03	86	

* $p < .05$
** $p < .001$

Table C.30

Total Symptom Scores:

ANOVA Summary Table

Source	MS	df	F
Group	3174.61	4	3.08*
Error	1029.58	43	
Time	777.69	2	5.30**
Time x Group	450.65	8	3.07**
Error	146.61	86	

* $p < .05$

** $p < .05$

Table C.31

Digit Span: ANOVA Summary Table

Source	MS	df	F
Group	2.41	4	2.03
Error	1.18	43	
Time	1.08	2	7.55*
Time x Group	.52	8	3.64*
Error	.14	86	

* $p < .001$

Table C.32
Abstract Reasoning:
ANOVA Summary Table

Source	MS	df	F
Group	275.47	4	1.84
Error	149.90	43	
Time	98.85	2	89.85**
Time x Group	2.98	8	2.71*
Error	1.10	86	

* $p < .05$
** $p < .0001$

Table C.33
Clerical Speed and Accuracy:
ANOVA Summary Table

Source	MS	df	F
Group	259.57	4	1.21
Error	215.01	43	
Time	145.85	2	63.80**
Time x Group	6.64	8	2.91*
Error	2.28	86	

* $p < .005$
** $p < .0001$

Table C.34
Total Plasma Estrogens:
ANOVA Summary Table

Source	MS	df	F
Group	34918.71	4	11.39*
Error	3065.06	43	
Time	190426.81	2	82.85*
Time x Group	57451.48	8	25.00*
Error	2298.47	86	

* $p < .0001$

Table C.35
Plasma Testosterone:
ANOVA Summary Table

Source	MS	df	F
Group	1284.68	4	.74
Error	1735.72	43	
Time	6242.38	2	12.39*
Time x Group	2361.84	8	4.68*
Error	503.60	86	

* $p < .001$

Table C.36
Plasma FSH: ANOVA Summary Table

Source	MS	df	F
Group	26442.20	4	4.46*
Error	3545.05	41	
Time	125286.17	2	102.62*
Time x Group	7202.44	8	5.90*
Error	1220.88	82	

* $p < .0001$

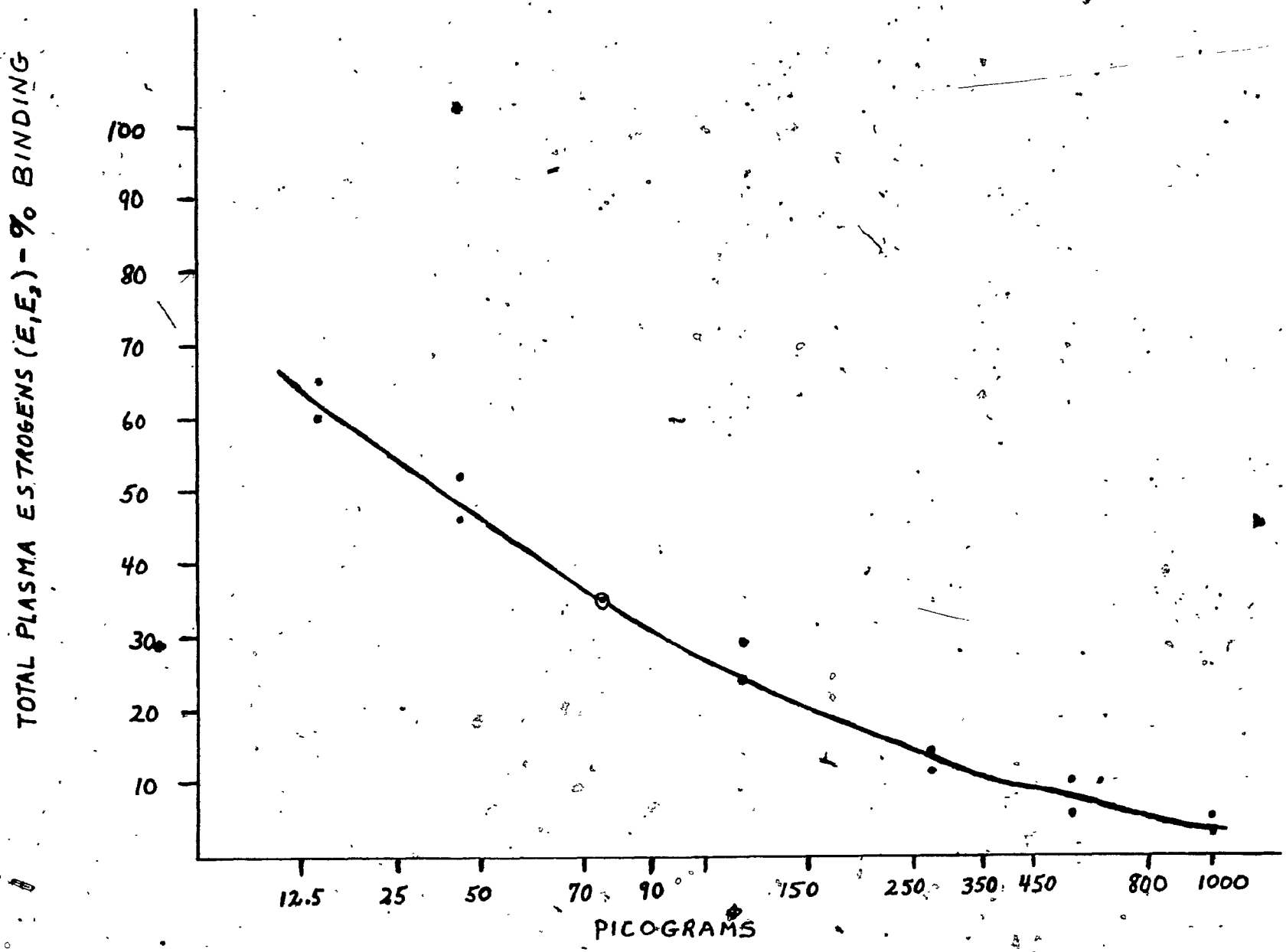
Table C.37
Plasma LH: ANOVA Summary Table

Source	MS	df	F
Group	855.59	4	4.89*
Error	174.91	39	
Time	3472.62	2	46.47**
Time x Group	184.48	8	2.47*
Error	74.73	78	

* $p < .01$
** $p < .0001$

Appendix D

Standard Curve for Total Plasma Estrogen Levels



Standard Curve for Total Plasma Estrogen Levels