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Variation in Mood and 3-methoxy-4-hydroxyphenylglycol (MHPG) During the Menstrual Cycle of Normal Women

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VARIATION IN MOOD AND 3-METHOXY-4-HYDROXYPHENYLGLYCOL (MHPG) DURING THE MENSTRUAL CYCLE OF NORMAL WOMEN

by

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VITA

The author, Merrily O'Connor-Miller, was born on October 17, 1941. She is the daughter of Robert L. Smith and Patricia Petrone Smith.

Her elementary education was obtained in parochial schools in Skokie, Illinois, and her secondary education at Marywood School, Evanston, Illinois, from which she graduated in 1959.

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CHAPTER I

INTRODUCTION

In 1931 Frank used the term "premenstrual tension" to describe the fatigability, irritability, lack of concentration, and pain associated with the premenstrual phase of the female reproductive cycle. Generally, before and since this time variation in mood, especially negative affect, was attributed to women because of the feminine cycle. The classic study of Benedek and Rubenstein (1939) first postulated the sexual cycle as a psychosomatic unit, a physiological cycle with a psychodynamic response pattern. They, too, found increased depression and anxiety at the premenstruum, depression at the menses, and increased pleasant affect and sexuality at ovulation. Since then, research on the psychological aspects of menstruation has attempted to corroborate this psychophysiological formulation in relation to all women or specific personality types.

Research into the physiological changes in women as a function of the menstrual cycle has also progressed. Recent studies indicate the important role of the catecholamines, especially norepinephrine (NE), in the activation of the sexual cycle within the hypothalamic-pituitary-ovarian system.

Also during the past two decades considerable data have accumulated in support of a catecholamine hypotheses of affective disorders. Simply stated, this hypothesis proposes that depressions are related to an absolute or relative decrease in catecholamines, especially NE, primarily in the central nervous system (CNS). Conversely, elation is related to an elevation of these catecholamines (Schildkraut, 1965). Three-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of brain NE is excreted in the urine, and correlations have been reported between urinary MHPG excretion and affect. In this disseration, the changes in anxiety and depression over the menstrual cycle as measured by self-report inventories will be studied in relation to MHPG levels as found in 24-hour urine collections of 11 women over an entire menstrual cycle.

CHAPTER II

REVIEW OF THE LITERATURE

Physiology of the Menstrual Cycle

To study fluctuations of mood as a function of the menstrual cycle, the hormonal changes which comprise the menstrual cycle must be documented. Recent research has divided the cycle into five phases: follicular, ovulatory, luteal, premenstrual, and menstrual (Moghissi, Syner, & Evans, 1972).

The follicular phase lasts from the end of menses to a sharp rise in luteinizing hormone (LH). During this phase there is a gradual rise in estrogens, the major ones being estrone, estradiol, and estriol. The estrogen peak has been found to occur approximately one day before the LH peak (Abplanalp, Livingston, Rose, & Sandwisch, 1977; Ribeiro, Mishell, & Thorneycroft, 1974). This estrogen peak stimulates LH from the pituitary gland. LH then induces ovulation. Simultaneously during the follicular phase, follicular stimulating hormone (FSH) stimulates the growth of follicles in the ovaries in preparation for ovulation. Levels of FSH begin with an early rise, a decline, and then a surge corresponding to the LH peak.

The ovulatory phase of the cycle is defined by the event of ovulation. Yen, Vela, Rankin, and Littell (1970) found LH peaks with an ascent of one to three days, followed by ovulation, and then an LH decline of one day. The lowest basal body temperature coincides with the first significant rise in LH levels.

The luteal phase follows ovulation. With 48 hours after the LH peak, there is an elevated level of progesterone. This rise in progesterone is concomitant with a rise in basal body temperature (Yen et al., 1970). The LH, FSH, and the estrogens go to their lowest levels during the cycle other than the premenses. With the development of the corpus luteum, progesterone rises, peaking from five to eight days after the LH peak. Also there is a secondary rise in estrogens (Mishell, Nakamurra, Crosignani, Stone, Kharma, Nagata, & Thorneycroft, 1971). Basal body temperature is usually maintained above 98°F. Both estrogen and progesterone reach their nadir approximately two days before menstruation. This period is the premenstrual phase of the cycle.

The menses occurs as a result of the withdrawal of stimulation by estrogen and progesterone to the edometrium. Bleeding usually occurs about 14-16 days after ovulation and lasts on an average of five days. The statistically average cycle is 28 days; yet few women have

regular 28 day cycles. It is normal to have cycles as short as 20 days and as long as 45 (Weidiger, 1976). Figure 1 illustrates the hormonal changes throughout the cycle.

This is a description of the phasic changes in the pituitary gonadotropins, LH and FSH, and the ovarian steroids, the estrogens and the progesterones. Recent studies suggest the neuroendocrine control of these cyclic hormone secretions in women. Figure 2 presents a simple schematic representation based on the portal vessel chemotransmitter hypothesis of the relationship between the brain neurotransmitter systems, hypothalamic peptidergic neurons, the anterior pituitary, and the ovary. The hypothalamic peptidergic neurons, in this case those that release lutenizing hormone releasing factor (LHRF) are complexly influenced. The biogenic amines, dopamine (DA), serotonin (5HT), acetylcholine (ACH), and NE act on LHRF in various combinations with either stimulatory or inhibitory effects. Also the peripheral hormones can bear on both the amines and the hypothalamic LHRF which further complicates the process. LHRF then enters the hypothalamohypophsialy portal system, is carried to the anterior pituitary, and influences the release of the pituitary gonadotropins, LH and FSH. LH then causes the synthesis of estrogen in the theca cells in the ovary. The ovary's secretion of steroids--the estrogens and

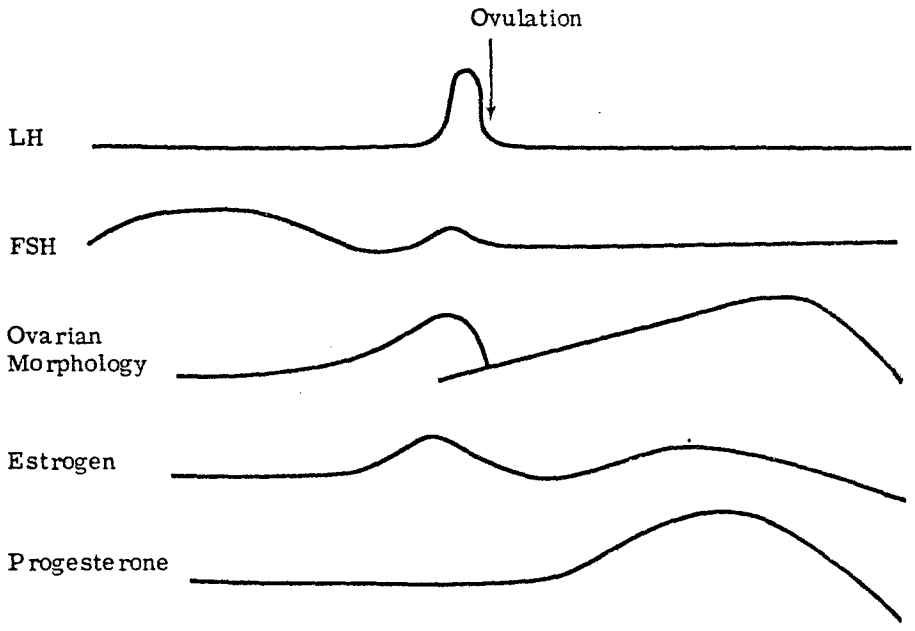

Figure 1. Scheme relating plasma LH, FSH, estrogen, and progesterone with follicular maturation, ovulation, and development of the corpus luteum.

Note: Reproduced from (Strott, Yoshimi, Ross, & Lipsett, 1969, p. 1166)

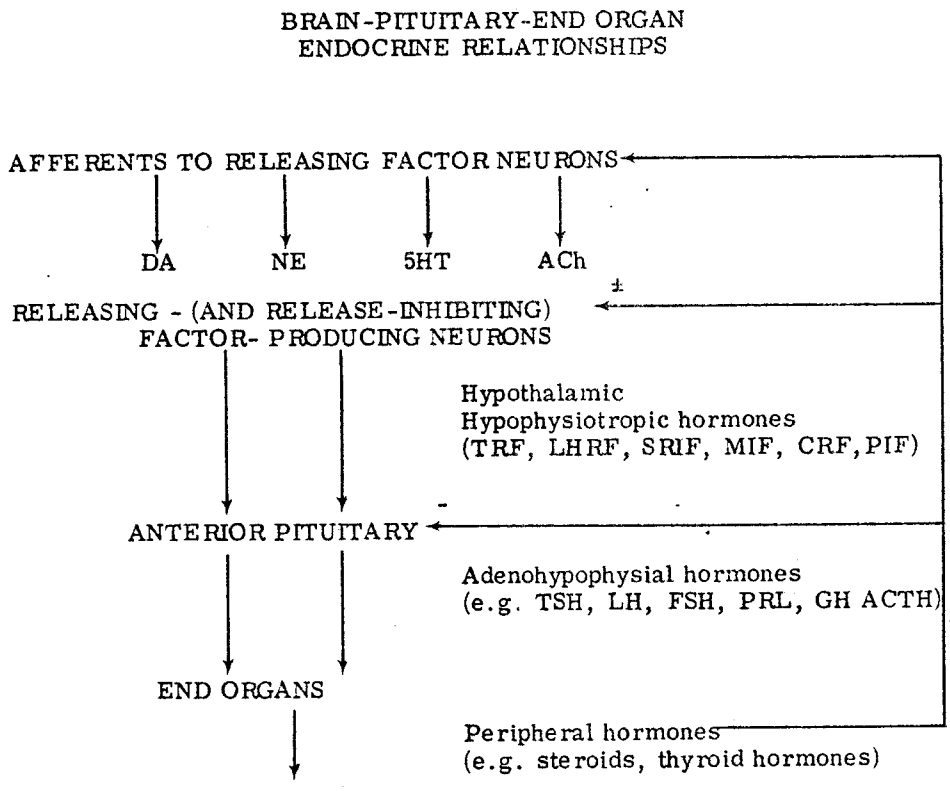

Figure 2. Schematic representation of relationships between brain neurotransmitter systems, hypothalamic peptidergic (releasing factor) neurons, anterior pituitary, and peripheral endocrine organs illustrating established feedback loops. Dopamine, DA; norepinephrine, NE: serotonin, 5HT; acetylcholine, ACh; thyrotropin-releasing factor, TRF; luteinizing hormone releasing-factor, LHRF; somatostatin, SRIF; melanocyte-stimulating hormone release-inhibiting factor, MIF; corticotropin-releasing hormone, CRF; prolactin-inhibiting factor, PIF; thyroid-stimulating hormone, TSH; luteinizing hormone, LH; follicle-stimulating hormone, FSH; prolactin, PRL; growth hormone, GH; and adrenocorticotrophic hormone, ACTH.

Note: Reproduced from (Nemeroff & Prange, 1978, p. 1004)

possibly progesterone and androgen--may feedback at three levels and the pituitary hormone, LH and FSH, at two levels. For example, estrogen may modulate LH and FSH in the pituitary. Estrogens may also penetrate the brain and influence the monamines. Another feedback loop may involve LH traveling back to the hypothalamus (Nemeroff & Prange, 1978).

Yen (1977) discussed the hypotheses explaining the LH surge which then triggers ovulation. Among them, he mentioned the role of progesterone in stimulating LH at midcycle when estrogen levels are high. The increase in estrogen at midcycle may increase the relative neuronal release of NE and DA which in turn increases the release of LHRF. Progesterone may enhance this effect.

Experiments with animals have tested the role of brain catecholamines in influencing ovulation. Rubinstein and Sawyer (1970) tested whether depletion of hypothalamic catecholamines affected the stimulation of ovulation in proestrus rats. Partial and total depletions of catecholamines were created from timed injections of reserpine and monamine oxidase (MAO) inhibitors. Short term treatment with reserpine blocked spontaneous ovulation and elevated the threshold for electrically stimulated ovulation. After longer reserpine action which depleted catecholamine pools, MAO inhibitors restored enough catecholamine to allow stimulated but not spontaneous

ovulation. Injection of epinephrine (E) into the third ventricle was found the most effective catecholamine in triggering ovulation.

Sawyer, Hilliard, Kanematsu, Scaramuzzi, and Blake (1974) report that a 50 microgram (µg) intraventricular dosage of NE was completely effective in inducing a surge of LH which resulted in ovulation in estrogen-primed rats. A 50 µg dosage of DA did not trigger the surge in fact acted as an inhibitor when NE was injected one to two weeks after DA. This contradicts other research which found that DA was effective in stimulating ovulation (Kamberi, Mical, & Porter, 1970; Schneider & McCann, 1970).

Kalra, Kalra, Krulich, Fawcett, and McCann (1972) found that injections of progesterone into estrogen-primed rats resulted in an LH and FSH surge. They wished to test whether adrenergic blockers would affect these LH and FSH surges. Drugs used to modify brain catecholamines were injected prior to the progesterone administration. Both the DA and NE blockade prevented the release of gonadotropins; however, when DA was normalized and NE levels remained low, the blockade of progesterone induced LH release remained effective. The authors concluded that NE mediates progesterone-induced release of the gonadotropins necessary for ovulation.

Kalra and McCann (1973) found that the stimulation of the preoptic region or the median eminence-arcuate region of the brain in proestrus rats led to elevation of plasma LH. Blockade of catecholamines or NE alone made stimulation of the preoptic region ineffectual in increasing LH levels. Taken with their other research, the authors conclude that NE acts as a synaptic transmitter in the preoptic-tuberal pathway leading to the release of LH necessary for ovulation.

The hypothesis advocating the necessary activity of the monoamines in the female sexual cycle was tested in the above studies with the administration of various drugs which manipulate levels of brain monoamines. Other studies with animals have measured monoamines and related enzymes and metabolites to discover fluctuating levels of amine activity during the menstrual cycle.

Measurement of monoamine activity is often indirect. A frequent method of measurement is the estimation of MAO, a major enzyme in the catabolism of brain catecholamines. Based on the relief of depression by MAO inhibitors, it is assumed that increased MAO activity is related to depression and low NE levels.

Zolovick, Pearse, Boehlke, and Eleftheriou (1966) estimated the activity of MAO in the hypothalamus, amygdala, and frontal cortex of the brain during the estrus cycle of female rats. The MAO activity was lowest at

diestrus in all three areas and highest at proestrus when follicular action is heightened. The hypothalamus evidenced the greatest amount of activity throughout the cycle. Actual brain tissue was analyzed for these results.

Platelet MAO, which is similar to MAO in the brain, has been studied in relation to the menstrual cycle. Redmond, Murphy, Baulu, Ziegler, and Lake (1975) found a significant difference between a mid-cycle peak in platelet MAO and a premenstrual low point during three cycles of six female rhesus monkeys. Also ovariectemized monkeys showed higher MAO levels than controls. The authors conjecture that peak platelet MAO activity might be time-lagged and actually correlated with low estrogen levels which occur within ten days before the estrogen peak prior to ovulation.

Using human subjects, Belmaker, Murphy, Wyatt, and Loriaux (1974) also found peak platelet MAO activity during the ovulatory phase and lowest values occurring five to eleven days later. These studies suggest that increased MAO activity is related to an increase in estrogen.

In contrast, other studies associate low MAO activity with high estrogen levels. Klaiber, Kobayashi, Broverman, and Hall (1971) found that plasma MAO activity was significantly lower during the ovulatory phase when estrogen was high than postovulatory when progesterone

was highest. Also amenorrheic and postmenopausal women had higher levels of MAO than menstruating women at pre-ovulation. Their MAO levels went down when given estrogen therapy while addition of progesterone increased the MAO activity over that observed during estrogen therapy alone. Also Briggs and Briggs (1972) found plasma MAO activity in women at midcycle to be significantly lower than that of male controls. During the luteal phase, the men and women were not different. Southgate, Grant, Pollard, Pryse-Davies, and Sandler (1968) found an increase in endometrial MAO during the late luteal to premenstrual phases. Histochemical and biochemical assays of biopsy tissue were examined in their study. Furthermore, Grant and Pryse-Davis (1968) studied the effect of oral contraceptives on endometrial MAO and depressive mood. The highest incidence of depression was associated with progesterone compounds which produced high MAO activity throughout the cycle. The lowest occurrence of depression was found in women treated with highly estrogenic sequential contraceptives which showed weak MAO activity during the cycle. Finally, Robinson, Davis, Nies, Ravaris, Sylwester, and Burlington (1971) found MAO activity from biopsies of the hindbrain of 26 autopsies and plasma and platelet MAO assayed in 113 normal subjects to be highly correlated with increasing age. Depressive illness is also correlated with increasing age and loss of estrogen

in women. These studies seem to indicate that the estrogen increase at midcycle is associated with lower MAO activity which in turn may reflect elevated catecholamine levels and therefore elevation in mood.

Direct measurement of NE during the female menstrual cycle has been undertaken. Zuspan and Zuspan (1973) investigated the theory that NE was involved in the control of gonadotropin secretion during the human menstrual cycle. They studied two normally cycling women for a complete menstrual cycle with blood determinations of LH, FSH, E, and NE and urinary determinations of creatinine, NE, and E. Both subjects showed a significant increase in plasma amines coincidental with or preceding the LH surge before ovulation. They also showed a gradual rise in urinary NE after ovulation which was greater than preovulatory levels. Rosner, Nagle, deLaBorde, Pedroza, Badano, Figuero, Casas, and Carril (1976) found that plasma NE peaked one day prior to concomitant with the LH peak. Plasma estradiol also reached a peak on the day of the LH peak.

In another phase of their work, a single intravenous 100 µg dose of LHRF was administered to four subjects on day ten of the cycle. A significant rise in plasma NE was found occurring before an LH surge. Zacur, Tyson, Ziegler, and Lake (1978) failed to corroborate this relationship between NE and the pituitary gonadoptopin LH.

Also, Patkai, Johannson, and Post (1974) found no cyclic changes in urinary NE. However, they had divided the cycle into equal segments.

Badano, Nagle, Casas, Miechi, Murkin, Turner, Aparicio, and Rosner (1978) investigated the plasma levels of NE in 11 free-cycling women. Blood samples were taken daily from day -8 to -4 and every eight hours from day -3 to +2. Ovulation, determined during surgery for benign gynecologic problems, was designated as day 0. In nine ovulatory patients, estradiol levels peaked 48 hours before the LH peak. The NE was at low levels until eight hours after the estradiol peak when NE increased significantly. The NE fell again in the next eight hours and rose again reaching maximal levels 24 hours after the estradiol peak. Sixteen hours before the LH peak, NE gradually declined. Two anovulatory women showed atypical patterns of estradiol, progesterone, NE, and LH. The NE showed much variation without correlation with the estradiol or LH. This study supports previous research with women and animals that NE and possibly other catecholamines may act as a triggering mechanism to ovulation. It also indicates that contradictory results in MAO and NE measurement during the menstrual cycle may depend on the time of measurement. Catecholamine levels appear to change rapidly at the time of ovulation.

The studies cited above report fluctations over the cycle from both brain and peripheral catecholamine pools. Animal research cited indicates the activation of NE and MAO in the brain. Research on humans has analyzed urinary, plasma, and platelet levels. Whether these levels of MAO and NE in humans are from CNS or peripheral sources is unclear.

Psychological Variation During the Menstrual Cycle

The earliest studies on the variations of mood during the menstrual cycle include that by Frank (1931) who used the term "premenstrual tension" to label the weight gain, irritability, fatigability, and lack of concentration associated with the premenstrual and menstrual phases of the female reproductive cycle. He described women who suffered such severe pain that they required bedrest. Another group were those who show exacerbation of general disorders such as asthma prior to menstruating. He was at the time reporting methods of treatment for severe symptoms. His research is one of the first publications to designate a premenstrual syndrome.

By 1939, the use of vaginal smears and basal body temperature to determine the hormonal cycle had been established. Therefore, Benedek and Rubenstein (1939, Part I and II) studied the correlations between the physiological factors and the psychological factors. They used

vaginal smears, temperature charts, and the associative material from nine analytic patients. Seventy-five cycles of which 23 were ovulatory were studied. The authors investigated primarily the associations, the dreams, and the transference. They noted that at the follucular phase where estrogen is the predominating hormone, the psychological material of the women dealt with heterosexual tendencies; the dominant feelings were of well-being and alertness. If there was no opportunity for gratification for libidinal urges, the mood of the women was irritable and restless. The psychological content within a Freudian model was then characterized by aggression and anxiety, i.e., fear of attack, penis envy, and intense wishes to castrate. Of course, since the majority of the subjects were characterized as neurotic in this study, most of them did not attain sexual gratification. Tension or depression increased as ovulation approached. At ovulation, relaxation and an attitude of passivity along with psychic energy directed toward the self generally occurred in the women. During the early luteal phase, under the influence of progesterone, the dream content reflected mother-daughter conflicts and then concerns about impregnation and motherhood.

When there was another estrogen peak during the luteal phase, heterosexual fantasies were again present as during the follicular phase. This was a relatively quiet

phase of affect. During the premenstrual phase, when there was a drop in the level of progesterone and estrogen, dream content and the associations of the women reflected elimination tendencies illustrated on a genital level by childbirth, abortion, castration and on a pregenital level as anal or uretheral discharge. The emotions were characterized by fear of pain and mutilation and by feelings of regret and inadequacy. At menses, with low hormone production, there was emotional relaxation; fear, apprehension, and rebellion decreased. Conclusions made by Benedek and Rubenstein (1939, Part II) were as follows: (1) correlations were seen between the physiological and psychological cycle; (2) instinctual drives of adult women are related to hormone production; (3) instinctual tendencies are genital when hormone production is high and pregenital when they are low; and (4) psychic tension often increases with an increase in hormone production.

In contrast to the work of Benedek and Rubenstein (1939) who studied the repressed sexual drive of neurotic women as correlated with the phases of the cycle, Altman, Knowles, and Bull (1939) studied the conscious mental states of ten normal women. They took daily psychological measures and interviewed each subject daily as to pain, sleep, mood, tension, worry, physical and mental activity. They reported the following findings: (a) ovulation

occurred with elation in 67.8% of cases, with activity in 85.3% and with tension in 31.4%; and (b) the premenstrual phase occurred with depression in 61.5%, with activity in 71.8%, and with tension in 80% of cases.

Many correlational studies have drawn attention to the increase of negative affect at the premenstruum and menstruum. They have attempted to correlate extraordinary events such as crime or suicide with the premenstrual or menstrual phases. Dalton summarized much of this work and has been a leading contributer of this type of research. Dalton (1961) reported that in a sample of 156 newly convicted female prisoners, 49% committed their crimes during the menstruum or premenstruum. Among 51 prisoners who were reported for disorderly conduct, 54% were menstruating. In this study Dalton divided the cycle with days one to four in menstruation, 13-16 in ovulation, and 25-28 in premenstruum. Dalton (1961) corroborated Dalton's work with school girls (Dalton, 1960). She found 27% of the girls' weekly grades went down during premenstruum and 17% went up; 25% went down during the menstrual week and 30% went up after menstruation. In this study she divided the cycle into four weeks. She then concentrated on the menstrual and premenstrual weeks (Dalton, 1960).

Exacerbation of psychiatric symptoms in relation to the menstrual cycle has been studied frequently. One

study (Glass, Heninger, Lansky, & Tolan, 1971) evaluated 166 female psychiatric emergencies. These patients were seen in the emergency room during the premenstruum twice the expected frequency. A certain type of woman presented herself during the premenstrual weeks. She was a non-psychotic woman who had a severe history of medical illness, past marital and sexual problems and a record of suicidal attempts. Jacobs and Charles (1970) similarly studied 200 randomly selected patients coming into an emergency room. They used Dalton's method defining midcycle as the 13-16 days and 25-28 days as premenstruum. The women sought psychiatric help most frequently during menstruation (24.5%), then during the premenstrual phase (22.5%), and finally during midcycle (18%). There was no clear difference between the menstrual and premenstrual phases. Diamond, Rubenstein, Dunner, and Fieree (1976) also found that psychiatric hospitalization occurred significantly more frequently during the menstrual and the premenstrual phase.

Tonks, Rack, and Rose (1967) obtained information on 95 women who attempted suicide. A statistically significant increase in attempts was found at the premenstruum. The trend was found primarily in women living with a male. Fewest premenstrual attempts were made by parous women who complained of premenstrual tension.

Dalton's (1959) findings that more hospital admissions for suicide attempts occurred during the menses than other phases have been criticized since the psychiatric admissions were actually premenstrual rather than menstrual because of the lag in hospital admissions. Mandell and Mandell (1967) wanted to corroborate the findings of Dalton. They described 87 menstruating women who called a suicide prevention center. Highest number of calls were found the first day of menstruation, second highest were found during the premenstruum, and third highest at midcycle. Ribeiro (1960) reported 22 cases of suicide by Hindu women, 19 of whom were menstruating.

Other recent studies can be divided according to the methodology employed: (1) those studies using retrospective reports; (2) those studies using single measures from various phases of the cycle; and (3) those studies using daily self-reports. In the first category of retrospective reports, Coppen and Kessel (1963) sent out a menstrual questionnaire to 500 women, ranging in age from 18 to 25. Twenty-two percent were menstruating at the time of completing the form. This group did not differ from the nonmenstruating group in severity of symptoms. The form asked the women whether they became depressed, anxious or nervous around the time of their period. Irritability, depression, tension, headache, and swelling occurred most frequently one or more days before

menses. One woman in nine reported severe pain, irritability or headaches associated with her period. One woman in 16 reported that she gets depressed or tense. Statistical analyses, however, were not employed to clarify these findings.

Lamb, Ulett, Masters, and Robinson (1953) also conducted a survey of 127 nurses with a mean age of 20.3. Of these, 28% reported some dysmenorrhea sometimes; 50% had it always. Depression, irritability, temper outbursts occurred at premenses singly or together in 85% of the subjects. This type of retrospective survey is suspect, however, because of possible faulty memory, the mood when taking the test, and the popular belief that poor mood results from "getting your period."

The second category of studies, those taking a single measure of affect at a different phase of the cycle further corroborate the existence of heightened negative affect during the premenses and menses. Lamb et al., (1953) compared five women who complained of the premenstrual syndrome and five who did not. The authors conducted interviews at the time of ovulation, premenses, and onset of menstruation. Then each subject was rated on mood, activity level, and assertiveness. They found that at the premenstruum those who complained of premenstrual tension became depressed and were either hypo- or hyperactive, whereas controls were not. Premenstrual

complainers also tended to be more hostile and aggressive than the controls whereas at other times of the cycle they were more submissive.

Ivey and Bardwick (1968) tested anxiety levels of college women ages 19 to 22. The women were told they were cooperating in a study on the menstrual cycle and that they would be tested at ovulation and premenses. They were asked to talk for five minutes about any event in their lives. This verbal sample was then scored according to Gottschalk's (1961) Verbal Anxiety scale for death, mutilation, separation, guilt, shame, and diffuse anxiety. Anxiety levels were significantly higher premenstrually than at ovulation for all subjects for two complete cycles. Also they found consistent themes of hostility and depression and inability to cope at the premenses. Attention must be paid to the fact that the subjects knew the times of the cycle at which they were being tested. To evaluate the impact of this confound, the authors asked the women what they guessed was the purpose of the study. The authors claim none of the women suspected their moods were being assessed.

Luschen and Pierce (1972) studied 48 women from ages 18 to 22, having 24 subjects in a premenstrual group and 34 in an ovulatory group. Ovulation was defined as 15 days prior to the next expected menses. Despite the fact that the 15th day prior to menses is not always the

day of ovulation, differences were found. The ovulatory group was significantly more other-directed than the premenstrual group. Also women at ovulation had higher sexual arousability scores than those at premenses. One possible confound in this study was that birth control pill takers were in the groups. The authors claimed that their scores did not differ from those of the free-cycling women.

To investigate the changes in symptoms and affect overtwo consecutive cycles, Moos, Kopell, Melges, Yalom, Lunde, Clayton, and Hamburg (1969) tested a group of 15 women on the 2nd, 7th, 14th, 19th, 24th, 25th, 26th, 27th, and 28th days. Mood was measured by the Nowlis Mood Adjective Checklist (1965). Results show pain and water retention highest at menses, dropping to the lowest point during the follicular phase, and rising again after the 16th day. Anxiety was highest during the menstrual phase and dropped at midcycle, then began to rise during the luteal phase. Pleasant affect and activation peaked at midcycle and were lowest at menstruation. Sexual arousal also peaked at midcycle. Surprisingly, depression showed no noticeable changes over the cycle. Correlations between the two cycles were generally high at the menstrual, intermenstrual and premenstrual phases. Although phase changes were not analyzed statistically,

this study does show fluctuations in mood over a cycle which seems to be fairly consistent from cycle to cycle.

The work of Paige (1971) showed increase in negative affect at the time of premenses and menses. In this study, free-cycling women were compared to women on combination contraceptives and women on sequential contraceptives. They were measured on the 4th, 10th, 16th, and 26th days with the Gottschalk Verbal Anxiety Scale (1961). Total negative affect for all the groups across the cycle was not different. Cycle day for the normal group had a significant effect on the magnitude of negative affect, anxiety and hostility. Free-cycling women showed the usual U-shaped curve of high negative affect at menses, low at midcycle and high at premenses.

Golub (1976) assessed the magnitude of depression and anxiety in women between the ages of 30 and 45 who were described as "active women leading productive lives" (p. 10). She used the Lubin (1967) Depression Adjective Checklist (DACL) and the Spielberger, Gorsuch, and Lushene (1970) State-Trait Anxiety Inventory (STAI). About 75% had higher premenstrual depression and about 65% had higher premenstrual anxiety than intermenstrual depression and anxiety. The mean scores were significantly higher at premenses than intermenses. In comparing premenstrual to intermenstrual, however, the information

culled was unspecific since "intermenstrual" could refer to follicular, periovulatory or luteal phases, all having different hormone balances.

Abplanalp et al. (1977) administered the state-anxiety form of the STAI before and after a mildly stressful interview. Half the subjects were interviewed during their menses and the other half during the peri-ovulatory phase. The time of ovulation, however, was correctly estimated only in about 59% of the cases when compared with the results of the biochemical analyses. State-anxiety differences between pre and post interview were not significant despite phase of the cycle at which the subject was interviewed. Where Golub (1976) found significant changes in anxiety between the premenstruum and intermenstruum, Abplanalp et al. (1977) found no variation in state-anxiety between the menstrual and intermenstrual phases. In general, the research cited above, using a single measurement per phase, is conflicting yet does indicate that there is a fluctuation of mood with negative affect high at menses, low at ovulation, and high again at premenses. Only in Ivey and Bardwick (1968) was there an attempt to establish ovulation by basal body temperature. Therefore although changes in mood are found, the precise nature of the changes as they relate to hormonal changes is not clear.

Other studies collected daily self-reports. Silbergeld, Brast, and Noble (1971) had eight subjects, four who were first on Enovid for two cycles, then were freecycling for two cycles, and four subjects who were reversed. Each night subjects rated their feelings on the Nowlis Adjective Checklist (1965) and the Moos (1977) Menstrual Distress Questionnaire (MDQ). On nine days throughout the cycle, they were scored on the Gottschalk Verbal Anxiety Scale (1961) based on talking freely for five minutes. The data were divided into six phases: menstrual, midfollicular, early ovulatory, late ovulatory, midluteal and premenstrual. Only for anxiety rated by an unaware experimenter was there a significant treatment by phase interaction. Analysis for phase effects showed an increase in physical symptoms at the menstrual and premenstrual phases. The women reported more crying, irritability, and tension and were rated more tense and aggressive during the premenstrual phase than during the other phases.

Wilcoxon, Schrader, and Sherif (1976) took daily self-reports. Their subjects, from an introductory psychology course, were 11 males, 11 females/no pill, and 11 females/pill. They divided the cycle into three phases: intermenstrual, premenstrual, and menstrual. Sample by phase interactions were significant. Females/no pill peaked on negative affect at menses while females/pill

peaked premenstrually. Impairment of concentration and report of stressful events increased premenstrually for both groups and decreased menstrually for females/pill. Stressful events, however, accounted for more of the variance for negative affect than cycle phase. The authors also noted that caution be used in interpreting the data because on all 13 factors they measured, subjects' variance, amount of individual difference, contributed more to the variance than sample, cycle phase, or interaction of sample and cycle although all these were significant.

The psychological literature on the menstrual cycle shows many methodological problems such as (1) the absence of exact determination of ovulation, (2) the possible confound by cultural stereotypy concerning menstruation, and (3) the large amount of individual variation of women during their menstrual cycles. Yet the trend seems to indicate the existence of an increase in irritability, tension, and depression at the onset of menstruation. Also midcycle, or the ovulatory phase, is a time of fewer symptoms.

MHPG and the Catecholamine Hypothesis of Affective Disorder

These fluctuations in affect are often attributed to biochemical changes occurring during the menstrual cycle. Also changes in affect have been related to changes in

brain catecholamines. According to Schildkraut (1965, p. 509), the "catecholamine hypothesis of affective disorders proposes that some if not all depressions are associated with an absolute or relative decrease in catecholamines, particularly NE, available at central adrenergic receptor sites. Elation, conversely, may be associated with an excess of such amines." He reviewed pharmacological studies of antidepressant drugs which indicated the effects of these drugs on catecholamines. The MAO inhibitors increase brain NE by direct inhibition of the enzyme MAO which deaminates NE. Imiprimine-like drugs increase free NE by inhibiting neuronal reuptake. Reserpine, a drug which causes depression, depletes catecholamines by interfering with storage in the neuron. The catecholamine hypothesis has been inferred from drug studies but these are indirect ways of measuring catecholamines. Direct measurement of NE and other catecholamines is complicated by two factors: (1) the majority of urinary and plasma NE is secreted from peripheral sources rather than the brain, and (2) an accurate method of measuring brain NE is yet to be confirmed (Bunney & Davis, 1965; Schildraut & Kety, 1967).

One of the most important contributions in support of this hypothesis of affective disorders is studies in the urinary excretion of 3-methoxy-4-hydroxyphenolglycol (MHPG). Research has found that MHPG is the major metabolite of brain NE. Mannarino,

Kirshner, and Nashold (1963) recovered NE, normetanephrine (NM), and MHPG in the cerebrum, cerebellum and urine of cats following intraventricular injections of NE. The principle metabolite in the urine was a conjugate of MHPG formed in the liver. Schanberg, Schildkraut, Breese, and Kopin (1968) found that after injection of NM in the cisterna magna of rats a sulfur conjugate of MHPG was the major metabolite found in the brain over time. Also after intracisternal injection of NE, the sulfur conjugate of MHPG was also found to be the metabolite present in the brain, accounting for 30% of the radioactive injection of NE. In the dog, a significant fraction of NE, about 25% was excreted as MHPG (Maas & Landis, 1968).

In reviewing the literature, Maas, Fawcett, and Dekirmenjian (1972) conclude that the majority of urinary NE, NM, and 3-methoxy-4-hydroxymandelic acid (VMA) have had their origins in the body pools of NE rather than the brain pools. However, MHPG seems to originate primarily in the brain. This theory is substantiated by Maas, Hattox, Greene and Landis (1979) who compared plasma MHPG taken from the internal jugular vein with the plasma MHPG taken from the radial artery. The venous-arterial difference was significant, implying that MHPG comes from the brain. By measuring the arterial-venous difference and total blood flow, they were able to estimate that 63% of MHPG excreted in the urine is derived from the brain.

Because of these findings, measurement of MHPG in urines of depressed patients has been employed to investigate the catecholamine hypothesis of affective disorder. Maas, Fawcett, and Dekirmenjian (1968) compared a group of severely depressed patients with normal controls. Urinary levels of MHPG were significantly lower for the patient group than the controls. Levels of metanephrine (M) and NM which are thought to originate from peripheral sources did not differ between groups. Maas, Dekirmenjian, and Fawcett (1971) replicated these findings. Also DeLeon-Jones, Maas, Dekirmenjian, and Sanchez (1975) reported that patients diagnosed as having primary affective disorder whether bipolar, single episode unipolar or recurrent unipolar have significantly lower MHPG levels than normal controls. Another classification of depression, the psychotically depressed, were significantly lower than normals whereas nonpsychotic and undiagnosed were not different. Agitated in comparison to retarded depressions showed no difference in MHPG. There is apparent agreement among researchers that some depressed patients excrete less than normal levels of MHPG.

Shifts in MHPG levels are also seen in manic-depressive patients. DeLeon-Jones, Dekirmenjian, and Fawcett (1973) studied a manic-depressive patient over a cycle of two depressive phases alternating with two manic

phases. They reported that mean MHPG level for depressive period was 805, standard deviation (SD)=45 µg per 24 hours; the mean for the manic phases was 1182, SD=49 µg per 24 hours. Urinary MHPG increased prior to the switch to mania. Similarly, Post, Stoddard, Gillin, Buchsbaum, Runkle, Black, and Bunney (1977) found lower MHPG levels during depressive episodes than during manic episodes in a single manic-depressive patient. The MHPG levels did not change prior to the switch, however, as in DeLeon-Jones et al. (1973).

The MHPG levels in depressed patients have also been found to fluctuate with drug therapy. Greenspan, Schildkraut, Gordon, Baer, Aronoff, and Durell (1970) studied MHPG in manic-depressive patients treated with lithium. Pretreatment, agitated depressed patients had significantly lower MHPG levels than either hypomanic or normothymic patients; also VMA levels were lower in the agitated depression group. During treatment, the hypomanic group showed decreases in MHPG whereas the agitated depression group showed a significant increase in MHPG. Both hypomanic and depressed patients had significantly decreased NE, NM, E, M, and VMA levels. The authors suggest that MHPG is associated with brain NE and depression whereas the heightened agitation, anxiety, motor activity found in this type of patient

would be associated with the increase in NE, NM, E, and M arising from an increase in peripheral activity.

Also Fawcett, Maas and Dekirmenjian (1972) found a significant negative correlation between behavioral improvement after administration of dextroamphetamine and tricyclic antidepressant drug treatment and low pre-treatment MHPG excretion. Five of six patients who were rated as improved by physicians and staff showed a slight increase in MHPG after dextroamphetamine treatment while five of six nonresponders showed a decrease in MHPG. Low pretreatment MHPG excretion and improvement in depression ratings were correlated significantly, reaching .58 after three weeks and .84 after four weeks of tricyclic drug therapy. Maas, et al. (1972) reported that depressed patients who responded to imipramine with improved depression ratings had lower pretreatment MHPG excretion than nonresponders who were in the normal range.

Furthermore, Beckmann and Goodman (1975) measured MHPG in 24 unipolar depressed patients, 16 of whom were treated with imipramine and eight of whom were treated with amitriptyline. The nine imipramine responders were significantly lower in MHPG than the seven nonresponders. For the amitryptyline patients, responders had significantly higher predrug MHPG levels. The group as a whole showed a significant decrease in MHPG after treatment which contradicts the findings of the Maas group.

These studies suggest that depression is a heterogenous disease since some but not all depressives differ from normals and since there are various responses to drug therapy among depressed patients. Maas (1975) concludes that there might be two types of depressed individuals: a type A patient who has (a) lower pre-treatment MHPG levels, (b) a positive response to imipramine, (c) an elevation of mood from dextro-amphetamine, and (d) little or no increment in MHPG after treatment; and a type B patient who has (a) normal or high MHPG, (b) favorable response to amitriptyline, (c) a lack of mood change from dextroamphetamine, and (d) decrements in urinary MHPG following treatment with imipramine or dextroamphetamine.

A number of studies of MHPG in cerebrolspinal fluid (CSF) do not support the catecholamine hypothesis of affective disorder. They report that depressed subjects had CSF MHPG levels within the normal range (Shopsin, Wilk, Sathananthan, Gershon, & Davis, 1974; Wilk, Shopsin, Gershon, & Shul, 1972). Wilk et al. (1972) found that manic-depressives (N=6) had significantly higher MHPG levels; three subjects, however, were in the normal range. These studies added to those reporting various responses of depressive to drug treatment suggest that the relationship between MHPG levels and affect is not a straight line relationship.

There are three recent studies of MHPG which are directly relevant to this present study of normal women during the menstrual cycle. Since the present study will be concerned with normal subjects rather than depressed, data collected by Hollister, Davis, Overall, and Anderson (1978) on MHPG excretion in normal subjects are most relevant. The range of mean values for 17 subjects was 1,316 to 4,252 µg per 24 hours. Coefficients of variation calculated from each subject's three consecutive 24 hour collections ranged from 3.1% to 23%. Less than five percent of the time was an individual's second value taken after a lapse of several weeks different from the first by more than $\pm$ 1,760 µg. It was estimated that approximately 95% of all 24 hour collections for the normal population would fall between 900 and 3,525 µg. No statistically significant effects were found for sex of subject. Earlier, DeLeon-Jones et al. (1975) reported approximately 1,300 µg normal for women; and Maas et al. (1968) reported 1,700 normal for men.

Another recent publication (Sweeney, Maas, & Heninger, 1978) which is highly relevant to this present study measured urinary MHPG and state-anxiety in 24 depressed patients. The measure for state-anxiety was the STAI (Spielberger et al., 1970) which was also used in this present study. Patients were placed in an increased activity or a restricted activity group. There

were no differences in MHPG or in state-anxiety on account of activity group across the control, experimental, and post experimental periods. Change scores from the control to experimental periods were computed for urinary MHPG and for state-anxiety and yielded a correlation of .85 for the active group and .68 for the restricted group. Increases in state-anxiety were associated with increases in MHPG. Those who showed increases in anxiety and in MHPG had a lower baseline MHPG than those with higher levels who showed decreases in anxiety and MHPG. The authors point out that it cannot be predicted that those with low baseline MHPG will have low state-anxiety. They also point out the anxiety-MHPG levels relationship emerged when there was a treatment intervention rather than within the natural course of events.

When studying MHPG in normal women during the menstrual cycle, DeLeon-Jones, Steinberg, Dekirmenjian, and Garver (1978) found a significant increase in MHPG at days -5,-4,-3 prior to menses and a decline in MHPG at days -2 and -1 prior to menses. This work was viewed as preliminary to this present study since there were only four subjects and no attempt was made to determine ovulation.

In review, five issues can be emphasized which led to the hypotheses of this study: (1) MHPG is a likely

measure of CNS NE since 63% of MHPG comes from the brain, (2) an increase in NE is associated with the LH surge requisite for ovulation, (3) an increase in MHPG has been noted on days -5,-4,-3 prior to menses, (4) psychological studies suggest that there is an increase in positive affect at ovulation and an increase in anxiety and depression at the premenstruum; and (5) lower levels of NE as measured by MHPG are associated with depression while increases in MHPG are associated with elation and anxiety.

Hypotheses

1. Urinary MHPG peaks during the ovulatory phase.
2. The MHPG level peaks during days -5,-4, and -3 prior to menses.
3. State-anxiety peaks at ovulation in relation to a peak in MHPG.
4. State-Anxiety peaks at days -5,-4, and -3 prior to menses in relation to a peak in MHPG.
5. Menstrual Distress (MDQ Total Score) peaks at the premenstruum as suggested by psychological research on the menstrual cycle.
6. Depression (MDQ Negative Affect) increases at the premenstruum in relation to a low point in MHPG levels.
7. Pleasant Affect (MDQ Arousal) peaks at ovulation in relation to a peak in MHPG.

8. The MHPG level correlates positively with state-anxiety as suggested by previous research with MHPG and state anxiety.
9. The MHPG level correlates negatively with MDQ Negative Affect as suggested by previous research with MHPG and depression.
10. MHPG correlates positively with positive affect as suggested by the expectation that MHPG elevations are related to elation.

CHAPTER III

METHODS

Subjects

The 11 women who served as subjects in this study were selected from volunteers from the student body and staff of the University of Illinois Medical Center. Advertisements were posted throughout the Medical Center. They were paid $30 for one month's participation, $60 for two months, and $100 for three months. The prerequisites for inclusion in the study were that the women were free-cycling, that they had not been taking any form of oral contraceptives within the last six months nor were they less than 12 months post-lactation. By questionnaire of medical history, the women were screened to exclude any known endocrine, renal, cardiovascular, gasteroentric dysfunction or urogenital infections. Also women with any gynecological disturbances such as amenorrhea, hypomenorrhea, or hypermenorrhea were excluded. Women on any form of continuing medication were excluded. Each volunteer had a brief psychiatric interview to determine whether she had a prior or current psychiatric disturbance. Women with a current or previous diagnosis of depression, schizophrenia, or severe anxiety disturbance were excluded since the purpose of the study was to investigate

the menstrual cycles of normal women. Three women were originally excluded because of this criterion.

Of the 15 women who participated in the study, four were eliminated from the statistical analysis. Two women were considered anovulatory because their temperature charts were uninterpretable. One woman had incomplete urine collections. Another woman was excluded because in a post experimental interview, she revealed that she had a history of manic-depressive illness.

The following demographic information was obtained for the remaining subjects. The mean age was 25, SD = 4.09; the age range was 19 to 35. Seven women were single; four were married. Ten women were nulliparous and one woman multiparous. All women reported regular cycles with nine having 27-29 day cycles, one with 30-32 day cycles and one with 33+ day cycles.

Measures

State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970). The Anxiety-State (x-1) scale consists of 20 statements about emotional states with instructions to subjects to describe how they feel at that particular moment. They are to evaluate their feelings from one to four, from "Not at All" to "Very Much So." The concept of anxiety measured is "the transitory emotional condition . . . of consciously perceived

feelings of tension and apprehension and heightened autonomic nervous system activity" (Spielberger, et al., 1970, p. 3). The Anxiety-Trait (x-2) scale consists of 20 items by which people report how they generally feel. Trait-anxiety refers to individual differences in disposition to respond to stressful events with varying amounts of state-anxiety. For state-anxiety, test-retest correlations range from .16 to .54, reflecting the sensitivity of the test to the situational factors at the time of the testing. For trait-anxiety, test-retest correlations are .73 to .86. Using the alpha coefficient as a measure of internal consistency, results for state-anxiety range from .83 to .92 and for trait-anxiety from .36 to .96.

Menstrual Distress Questionnaire (Moos, 1968) Form T. This is a list of 47 symptoms related to the menstrual cycle. Women are asked to rate the symptoms as they are experiencing them that day. Subjects rank each symptom from one to six from "no experience of the symptom" to "acute or partially disabling." The 47 items were factor analyzed and intercorrelated with a sample of 839 women who were asked to describe their menstrual cycle at three phases and their worst menstrual cycle. Eight factors were differentiated: pain, concentration, behavior change, autonomic reactions, water retention, negative affect, arousal, and control. Intercorrelations between the eight scales are all positive ranging from

.59 between pain and negative affect to .18 between arousal and autonomic reactions. Split-half reliabilities, which varied from .74 to .98 were all statistically significant (Markum, 1976). The manual gives normative data for Form A which is based on a report of how a woman feels in retrospect about three different phases of her cycle. The manual then states that the means and standard deviations for Form T, which has instructions to report symptoms for that day, are similar to Form A.

Procedure

When each woman volunteered, an interview appointment was arranged for her. During this interview, it was determined whether or not she would participate on the basis of her medical and psychological history. The few necessary questions about contraceptives and the length and regularity of the menstrual cycle were also interwoven into this interview. At this time the subjects were notified that they would collect 24-hour urines and record their feelings daily. They were asked not to take any medication unless directed by a physician and then to notify the experimenters so that they could be dropped from the experiment. To agree to this, all subjects signed a consent form to participate for approximately 35 days in the study.

If accepted according to the criteria mentioned above, the subject began the procedures the following day. By starting at a random point in each woman's cycle, there was some attempt to control for stereotypic responses on the daily self-reports. Each woman collected urines for a 24-hour period for each day of her cycle. The first specimen of the day was taken upon rising and added to the previous days collection. Completeness of collections were checked through volume measurement and creatinine determinations. Urines were assayed for MHPG by the method of Dekirmenjian and Maas (1970) and creatinine by the method of Bonsnes and Taussky (1945).

Also each subject was instructed to take her basal body temperature before rising from bed each morning. She was instructed to fill out a state-anxiety form and an MDQ form each evening before retiring. These were labelled x-1 and Form T respectively. She also recorded the most significant event of each day and noted the days on which she menstruated. This notation about menstruation, she was told, was to assist the laboratory in analyzing the urine. Since she had to bring in her urines every other day, she also brought in her daily self-reports at this time. Each week the experimenter called each subject to discuss and work out any difficulties. One subject had a broken thermometer at one time.

At the end of a period the approximate length of her cycle, each subject came in for another interview. At this time she was told she could continue in the study if she wished. If she did continue, she followed the same instructions. If she did not, she filled out a detailed questionnaire on her menstrual history and attitudes and on her family medical and psychiatric history. Then the subject was paid. Three subjects participated for three cycles.

Subjects were also asked what they thought the study was about and what their reactions were to the procedures. Of the 11 subjects, five said that the study had something to do with moods during the menstrual cycle. No major life events occurred for any of the subjects during the course of the study.

Partitioning of the Cycle. For statistical analysis the cycle was divided into six phases. To make the cycles uniform for each subject, the days of the cycle were used in the following order: (1) the first five follicular days; (2) three ovulatory days with the middle day viewed as ovulation; (3) the first five luteal days; (4) days -5,-4, and -3 prior to menses as late luteal days; (5) days -2 and -1 prior to menses as premenstrual days; and (6) the first five menstrual days. Ovulation was determined by basal body temperature. Urinary pregnanediol determinations also verified ovulation (Chatterton, unpublished).

CHAPTER IV

RESULTS

Variations in MHPG

The mean urinary MHPG level for the 11 subjects was 1486.35, SD = 297.87, µg per 24 hours. The range of subjects' means was 876.11, SD = 240.90 µg per 24 hours for the lowest individual level to 1925.73, SD = 370.90 for the highest individual level. Only one subject fell slightly below the estimated normal range of 900 to 3,525 µg per 24 hours (Hollister et al., 1978). It compares with the 1300 µg per 24 hours for women reported by DeLeon-Jones et al. (1975). Table 1 gives mean MHPG levels for all subjects.

Hypothesis 1, that urinary MHPG peaks during the ovulatory phase, was supported at the .0002 level of significance. Hypothesis 2, that urinary MHPG peaks during days -5,-4,-3 prior to menses was also supported at the .0002 level of significance. Means are found in Figure 3a.

An analysis of variance for repeated measures indicated a significant phase effect, F (5, 48) = 6.12, p<.0002. Trend analysis indicated a significant quartic trend, F (1,48) = 5.27, p<.05. (Table 2) Deviation from

TABLE 1

Mean Excretion of MHPG in µg per 24 Hours

Subject	Mean MHPG	SD
1	1792.50	325.40
2	1925.73	379.90
3	1304.48	284.50
4	1108.20	209.83
5	1834.82	408.70
6	1865.27	295.64
7	1039.71	279.73
8	876.11	240.82
9	1544.19	428.78
10	1375.81	365.47
11	1675.30	411.83

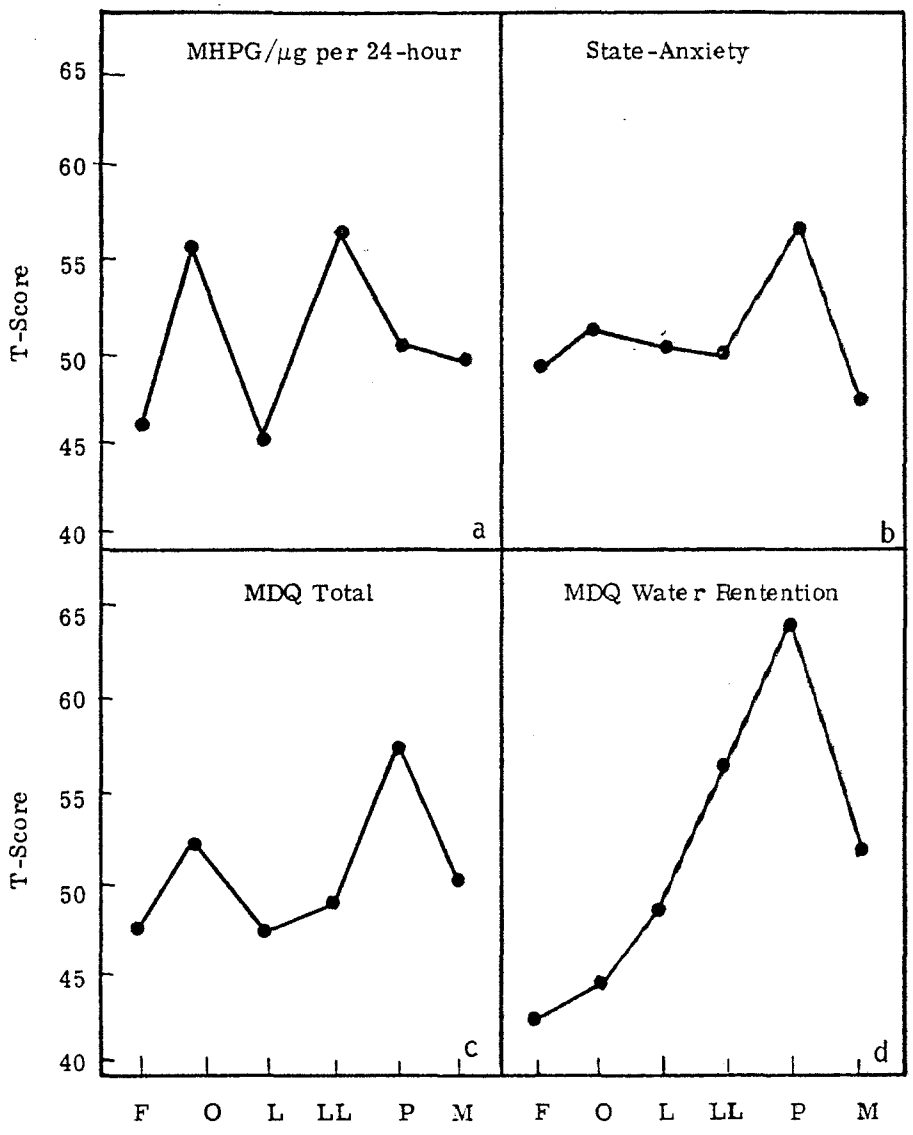

Figure 3. Mean scores of MHPG, state-anxiety, MDQ total, and MDQ water retention for six phases: follicular, F; ovulatory, O; luteal, L; late luteal,LL; premenstrual, P; menstrual, M.

TABLE 2

Trend Analysis for MHPG, State-Anxiety, MDQ Total, and MDQ Water Retention

Source	df	MS	F	P
		MHPG		
Phase	5	776034.87	6.12	.0002
Quartic Trend	1	668321.00	5.28	.05
Dev from Quartic	1	2509937.56	19.27	.05
Phase x Subject	48	126896.02		
		State-Anxiety		
Phase	5	162.80	2.05	NS
Quartic Trend	1	399.71	5.04	.05
Dev from Quartic	1	74.20	.94	NS
Phase x Subject	48	79.29		

TABLE 2 (continued)

Source	df	MS	F	P
		MDQ Total		
Phase	5	261.75	1.83	NS
Quartic Trend	1	939.64	6.55	.05
Dev from Quartic	1	4.84	.03	NS
Phase x Subject	47	143.36		
		MDQ Water Retention		
Phase	5	41.91	10.58	.0001
Linear Trend	1	113.51	28.66	.05
Dev from Linear	4	24.02	6.06	.05
Quadratic Trend	1	31.99	8.08	.05
Dev from Quad	3	21.35	5.39	.05
Cubic Trend	1	54.79	13.83	.05
Dev from Cubic	2	4.64	1.17	NS
Phase x Subject	48	3.96		

quartic was also significant, F (1, 48) = 19.79, $p<.05$. Newman-Keuls test for ordered differences (Table 3) indicated that the late luteal phase was significantly higher ($p<.05$) than the luteal, follicular, and menstrual phases. Also the ovulatory phase was significantly higher ($p<.05$) than the follicular and the luteal phases.

Of the 11 subjects, 91% showed peaks at the ovulatory phase, 55% at the late luteal phase. Fifty-five percent of the women showed both peaks that had been hypothesized. Figure 4 shows the variation in patterns for the 11 subjects for MHPG and the psychological measures.

Variations in the Psychological Variables

State-Anxiety

For state-anxiety, the grand mean was 35.50, SD = 7.21. This is comparable ($t(450) = .48$, $p>.05$) to the mean of unstressed female college students, 35.12, as reported by Spielberger et al. (1972). The premenstrual mean was 40.41, SD = 9.90. Premenstrual state-anxiety was equivalent ($t(668)= 1.36$, $p>.05$) to the anxiety of female freshmen (M = 39.39) during an orientation week, as presented in the normative data (Spielberger et al., 1972).

Hypothesis 3 that state-anxiety peaks at ovulation in relation to a peak in MHPG was supported at the .05 level of significance. Hypothesis 4 that state-anxiety

TABLE 3

Tests on MHPG Means Using the Newman-Keuls Procedure

	L	F	M	P	O	LL	r	(r,48)
L		36.42	139.98	169.21	333.03	347.09	6	4.23
F			103.57	132.78	296.61	310.67	5	4.04
M				29.23	193.04	207.10	4	3.79
P					163.81	177.87	3	3.44
O						14.06	2	2.86

$S_{\bar{p}} = 60.77$

r	=	2	3	4	5	6
$S_{\bar{p}} q$ (r,48)	=	173.81	209.06	230.34	245.53	257.07

	L	F	M	P	O	LL
L					*	*
F					*	*
M						*
P						
O						

*$p<.05$

Note: - Abbreviated F=follicular; O=ovulatory; L=luteal; LL=late luteal; P=premenstrual; M-menses.

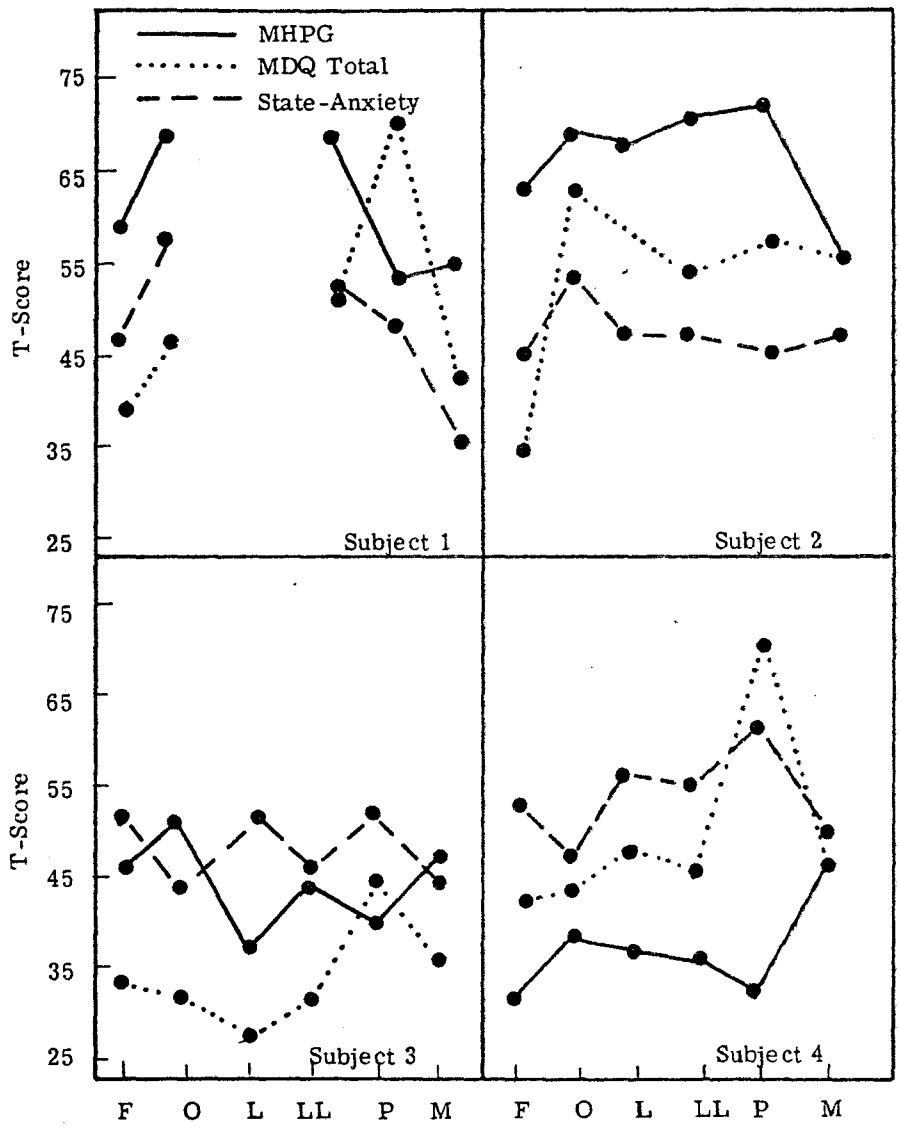

Figure 4. Subject means for MHPG, state-anxiety, and MDQ total during the six phases: follicular, F; ovulatory, O; luteal, L; late luteal, LL; premenstrual, P; menstrual, M.

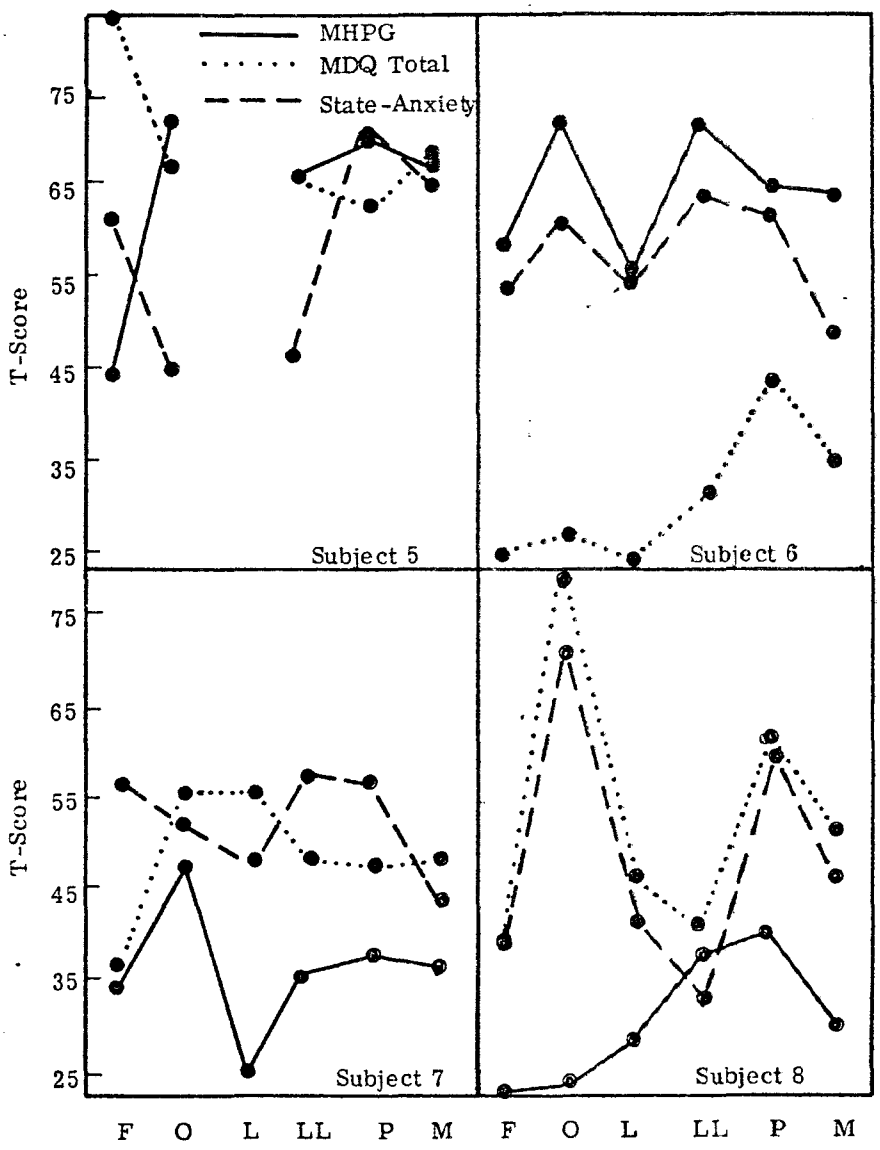

Figure 4. (Continued)

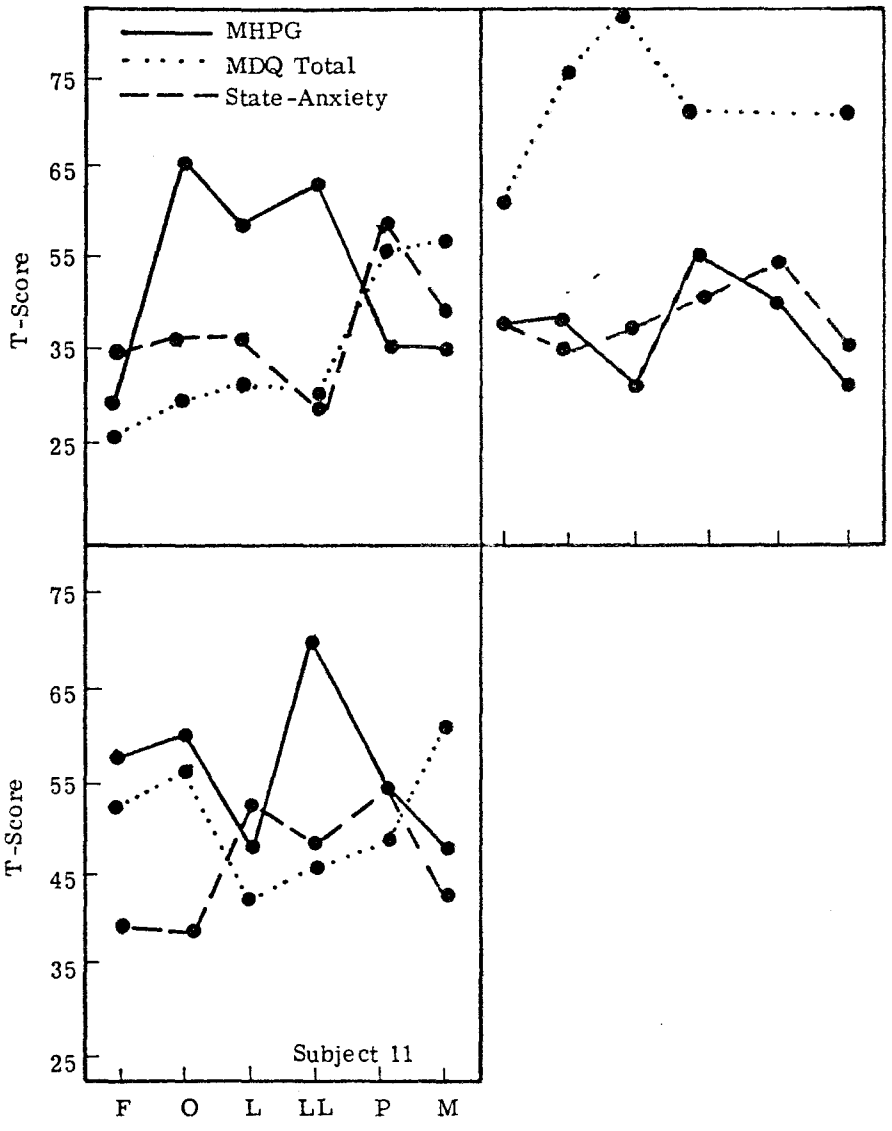

Figure 4. (Continued)

peaks at days -5,-4,-3 prior to menses in relation to a peak in MHPG was not supported. Another peak in state-anxiety was found at premenses (Figure 3b). A quartic trend was significantly predictive of these two peaks at ovulation and premenses, $F(1, 48) = 5.04$, $p<.05$. Analysis of variance for repeated measures across the six phases was computed; the phase effect was not significant.

Fifty-five percent of the women peaked at ovulation. Sixty-four percent peaked at the premenses. Only 18% peaked at both. Only one person showed the identical peaks in MHPG and state-anxiety. (Figure 4)

Menstrual Distress Questionnaire

Hypothesis 5 that MDQ total peaks of the premenstruum was supported at the .05 level of significance. MDQ total also peaked during the ovulatory phase (Figure 3c). Trend Analysis indicated a significant quartic trend, F (1, 47) = 6.55, $p<.05$ (Table 2). Analysis of variance for repeated measures across the six phases did not show a significant phase difference. The premenstrual mean, 76.41, was equivalent to the premenstrual mean, 73.80, presented in the MDQ manual (Moos, 1977), t (21) = .24, $p>.05$.

Of the 11 subjects, 45% peaked at ovulation. At premenses, 65% showed elevated MDQ scores (Figure 2). The same 45% had an elevation in MHPG at ovulation. At premenses, only 27% had an elevation in MHPG and MDQ total.

Hypothesis 6, that depression increases at the premenses was not supported. Also, Hypothesis 7 that pleasant affect increases at ovulation was not supported.

Of the other MDQ factors--pain, concentration, behavior change, autonomic response, and water retention--only water retention showed significant phase changes. Analysis of variance for repeated measures yielded a significant phase effect, F (5, 48) = 10.58, $p<.0001$. Tests for trend indicated a significant linear trend, F (1, 48) = 28.66, $p<.05$; a significant quadratic trend, F (1, 48) = 8.08, $p<.05$; and a significant cubic trend, F (1, 48) = 13.83, $p<.05$. Deviation from cubic was not significant. As can be seen in Figure 3d, water retention shows a continuous rise from the follicular phase to premenses.

Correlations of MHPG with the Psychological Variables

Pearson product-moment correlations between MHPG and the psychological variables--state-anxiety, MDQ total, MDQ negative affect, and MDQ arousal--were computed for each subject. The average r was then obtained by means of Fischer's r to z conversion. The following hypotheses were not supported: (1) hypothesis 8 that MHPG correlates positively with state-anxiety (r = .03 $p>.05$); (2) hypothesis 9 that MHPG correlates negatively with MDQ negative affect (r = .07, $p>.05$); and (3) hypothesis 10

that MHPG correlates positively with MDQ arousal, a measure of pleasant affect (r = .04 p>.05).

Another correlation computed between MDQ total and MHPG was not significant either. The three correlations between state-anxiety and the MDQ variables showed significant intercorrelations: (1) state-anxiety with MDQ total, r = .41, p<.001; (2) state-anxiety with negative affect, r = .81, p<.001; state-anxiety with arousal, r = 0.31, p<.001.

Since it was not expected at this point that the relationship between urinary MHPG and the psychological variables would be a simple linear relationship within individuals, various ways of correlating the biochemical variables with psychological variables were undertaken as preliminary investigation for future research. By inspection of Figure 1 it was noted that the relationships at the first half of the cycle between MHPG and the psychological variables looked positive. At the second half, they appeared to be negative relationships. Hence it was suspected that any significant linear correlations within an individual would be cancelled out across the cycle.

Daily group means from days 6-11 and days 14-21 were correlated between MHPG and the four psychological variables. (Table 4) These days were chosen because they corresponded to ovulation and to the onset of menses.

TABLE 4

Pearson Product-Moment Correlations for MHPG with the Psychological Variables, Days 6-11 and Days 14-21

	MHPG/Neg Aff	MHPG/St-Anx	MHPG/MDQ Tot	MHPG/Ar
	MHPG, 1 day behind the psychological variable			
6-11	.61	.72	.87*	.41
14-21	-.84*	-.27	-.69	-.70
	Same-day			
6-11	.93*	.35	.49	.06
14-21	-.08	-.31	-.46	.18
	Psychological variable, 1 day behind MHPG			
6-11	.02	-.31	.50	.72
14-21	.81*	.43	.75*	.51

*$p<.05$

They were also sequential whereas other days had been dropped out of the follicular and luteal phases to create uniformity of cycle. Three sets of correlations were done: (1) same-day, (2) MHPG time-lagged one day behind each psychological variable, (3) each psychological variable time-lagged one day behind MHPG.

Only one of the eight same day correlations was significant. For days 6-11, MHPG correlated with negative affect, $r = .93$, $p<.05$. These correlations did not indicate a trend.

With MHPG time-lagged behind each pshcyological variable, correlations were positive days 6-11 and negative days 14-21. For MHPG/MDQ Total, $r = .87$, $p<.05$ at days 6-11. For MHPG/MDQ negative affect at days 14-21, $r = -.84$, $p<.05$.

For the psychological variables time-lagged behind MHPG, the correlation coefficients are predominantly positive. At days 14-21, for MHPG/MDQ negative affect, $r = .81$, $p<.05$. Also, for MHPG/MDQ Total, $r = .75$, $p<.05$. Since so many correlations were done, these results were interpreted with caution.

In order to decrease individual variability and to investigate the phase effect on the relationship between MHPG and the psychological variables, Pearson product-moment correlations were computed with the phase means from each subject at each phase. No significant

correlations were found. When these means were plotted for state-anxiety and MHPG, it was noticed that those subject who had a mean MHPG excretion of less than 1700 µg per 24 hours during a given phase, exhibited a different relationship between the psychological and the biochemical variables than those who had a mean excretion level above 1700. (Table 5) Correlation coefficients increased for high and low excreters when the two groups were analyzed separately. At ovulation for low excreters, a significant negative correlation, $r = -.96$, (N=5) $p<.05$. was found. For high excreters, $r = .66$, $p>.05$ (N=6). At premenses, a significant positive correlation was found for low excreters, $r = .66$, $p<.05$ (N=8). At premenses there were only three high excreters; therefore the correlation coefficient was not computed. The cycle means for low excreters (N=7) were correlated for state-anxiety and MHPG resulting in $r = .70$ $p<.05$. For high excreters (N=4), $r = -.07$, $p>.05$. For the group as a whole, $r = .024$, $p>.05$. Differences between high and low excreters were not as apparent when the MDQ variables were correlated with high or low MHPG excretion level.

TABLE 5

Phase Correlations for High and Low Excreters

Phase	High	Low	All
	State-Anxiety/MHPG		
Follicular	-.21 (4)	.57 (7)	-.11
Ovulatory	.66 (6)	-.96*(5)	-.13
Luteal	-	.59 (7)	.06
Late Luteal	.71 (6)	-.14 (5)	-.01
Premenstrual	-	.66*(8)	.01
Menstrual	-	-.20 (9)	.51
	MDQ Total/MHPG		
Follicular	.80 (4)	.39 (7)	.05
Ovulatory	-.04 (6)	-.86 (5)	.38
Luteal	-	-.14 (7)	-.03
Late Luteal	-.42 (6)	.75 (5)	.15
Premenstrual	-	-.47 (8)	-.09
Menstrual	-	-.18 (9)	-.04
	MDQ Negative Affect/MHPG		
Follicular	-.69 (4)	-.28 (7)	-.21
Ovulatory	.35 (6)	-.58 (5)	-.39
Luteal	-	-.32 (7)	-.33
Late Luteal	-.73 (6)	-.32 (5)	-.05
Premenstrual	-	-.28 (8)	.17
Menstrual	-	.01 (9)	-.11
	MDQ Arousal/MHPG		
Follicular	.31 (4)	-.27 (7)	-.21
Ovulatory	-.07 (6)	.73 (5)	.16
Luteal	-	-.28 (7)	-.26
Late Luteal	.56 (6)	.43 (5)	-.04
Premenstrual	-	.26 (8)	-.03
Menstrual	-	-.11 (9)	-.06

Note: Parentheses indicate N of pairs in correlation.

* $p<.05$.

CHAPTER V

DISCUSSION

In summary of the major findings, urinary MHPG peaked at ovulation and the late luteal phase of the menstrual cycle. The psychological measures, state-anxiety and MDQ Total peaked at ovulation and premenses. The MDQ Negative Affect and Arousal (pleasant affect) did not show phase related changes during the menstrual cycle. Correlations between urinary MHPG and the psychological variables suggest a complex relationship between urinary MHPG and the psychological variables.

Variations in MHPG

The elevation of urinary MHPG during the ovulatory phase supported the theory that the neurotransmitters of the CNS play a significant role in stimulating ovulation in the human female. Since 63% of urinary MHPG has its source in the brain (Maas, 1979), measurement of MHPG is a particularly direct measure of CNS activity during the menstrual cycle. Earlier studies of plasma and urinary NE during the menstrual cycle reflected the peripheral pools of NE.

Animal research has dealt directly with brain monoamines including NE and their effects on ovulation.

Rubinstein and Sawyer (1970) blocked ovulation by depleting hypothalamic catecholamines in proestrus rats. Sawyer et al. (1974) induced ovulation with an intraventricular dose of NE. Kalra et al. (1972) blocked ovulation in estrogen-primed rats with injections of drugs known to block brain catecholamines.

Measurement of plasma NE in humans, also indicated increases at ovulation (Rosner et al., 1976; Zacur et al., 1978; Zuspan and Zuspan, 1972). Badano et al. (1978), taking blood samples every eight hours for the three days before ovulation, found an estrogen peak, followed by a peak in NE, followed by an LH surge. In this same study, two anovulatory women had higher and more variable NE levels during the follicular phase than ovulatory women. Apparently, an increase in estrogen followed by an elevation in NE induces an LH surge. The increase in MHPG levels at the ovulatory phase in this study is added evidence for the involvement of brain NE in ovulation.

In this study, urinary MHPG also peaked significantly at days -5,-4, and -3 before menses which had previously been reported by DeLeon-Jones et al. (1978). Progesterone is known to increase during the luteal phase. Estrogen also shows a secondary rise at this time.

A preliminary investigation of the relationship between MHPG and progesterone, as estimated by pregnanediol measurement, was undertaken. Since this study did not

take all pregnanediol levels from ovulation to menses, the composite is only suggestive of the relationship between increased progesterone and MHPG (Figure 5). It can be seen by inspection that progesterone peaked during the luteal phase sometime after the sixth day post ovulation. Progesterone began its descent during the late luteal phase. All women maintained relatively high levels until premenses. Two women maintained high levels until menstruation.

The MHPG levels peaked after the progesterone levels began to decline. Other studies have also found a postovulatory elevation in NE (Zuspan & Zuspan, 1973; Zuspan & Rao, 1974). Also increased MAO activity has been related to increased progesterone levels during the late luteal phase (Southgate et al., 1968). Progesterone therapy increased MAO activity in amenorrheic and post-menopausal women (Klaiber et al., 1971). Oral contraceptives with progesterone compounds produced high MAO activity in endometrial tissue (Grant & Pryse-Davis, 1968). Furthermore, MHPG results from the deamination of NE by MAO enzymes. Therefore increases in MHPG during the late luteal phase may reflect the same interaction between NE and progesterone as the increases in MAO activity during the luteal phase.

In conclusion, MHPG levels peaked at ovulation when the estrogens are known to peak and rapidly decline

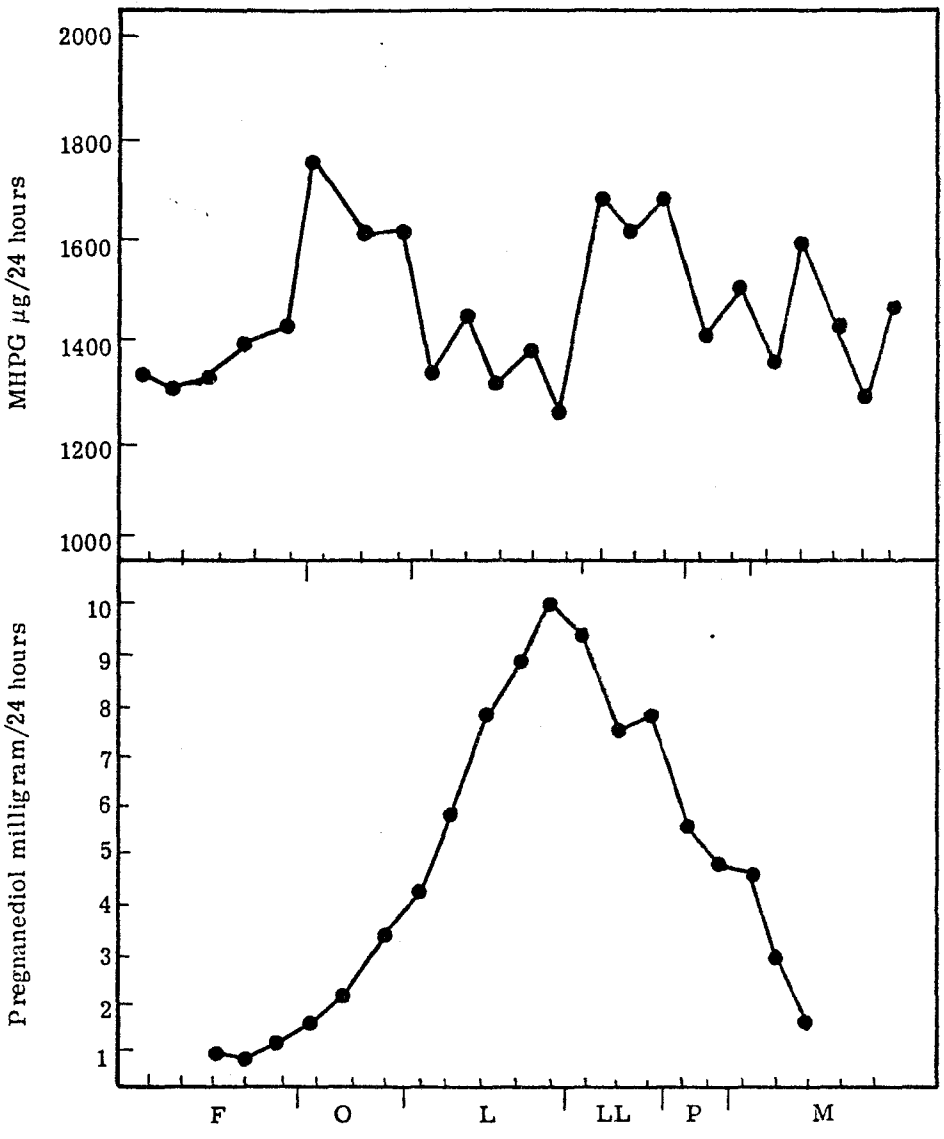

Figure 5. A composite of daily urinary excretion of MHPG and pregnanediol excretion during the menstrual cycle. Each value is the mean for 11 subjects.

Note: Abbreviated M=menstrual; F=follicular; O=ovulatory; L=luteal; LL=late luteal; P=premenstrual.

and when progesterone is known to increase. This is followed by a secondary rise in estrogen and a rise in progesterone during the luteal phase. MHPG levels appeared to peak after the ovarian hormones began to decline in the late luteal phase. Explanation for this apparent relationship must be found in future research on neurotransmitter involvement in the hypothalamic-pituitary-ovarian system.

Psychological Variation

The psychological variables of state-anxiety and MDQ total showed significant peaks at ovulation and premenses. State-anxiety is a measure of awareness of tension and heightened autonomic nervous system activity. The MDQ total score is a measure of symptoms popularly associated with menstruation.

The premenstrual peak in state-anxiety and MDQ total substantiated most of the literature of the variations in mood during the menstrual cycle. Correlational studies have repeatedly shown exacerbation of symptoms at premenses (Dalton, 1960; Dalton, 1961; Dalton, 1964; Glass et al., 1971; Mandell & Mandell, 1967; Ribeiro, 1960; and Tonks et al., 1967). Many studies have contrasted midcycle to premenses or menses. They have frequently found a U-shaped curve of increased symptoms at menses, low at midcycle and high at premenses. For

anxiety, Ivey and Bardwick (1968), Moos et al. (1969), and Silbergeld et al. (1971) found increases at the premenses. Using the STAI, Golub (1976) found significantly higher premenstrual state-anxiety scores than intermenstrual score. For MDQ total, Moos (1977) showed higher premenstrual scores than intermenstrual scores.

The MDQ negative affect, however, did not significantly peak at premenses as was hypothesized. Paige (1971) found a premenstrual increase in negative affect with another measure. Golub (1976) found an increase in depression at premenses on the DACL (Lubin, 1967) when comparing premenses with intermenses. Moos (1977) reported elevated negative affect at the premenses from retrospective questionnaries. On the other hand, Moos et al. (1969) reported no cyclic changes in depression as did Silbergeld et al. (1972) using the MDQ. In this present study, subjects did not have any history of depressive symptoms. They also scored highest on MDQ arousal, a measure of pleasant affect, throughout the cycle. Perhaps since the scale contains only eight items, it would be relatively insensitive to daily changes. Golub (1976) reported changes in depression levels using the DACL (Lubin, 1967) which has been shown to be sensitive to daily changes in depression. Among other differences from the MDQ negative affect scale, the DACL has 18 items.

On the other hand, evidence for increase in depression at premenses is insubstantial. Golub (1976) compared single measures from the premenses and intermenses. A valid comparison cannot be made to intermenses, since the term intermenses could refer to follicular, ovulatory or luteal activity, all of which have different hormonal balances. In addition, Moos (1977) who reported changes in negative affect was reporting data collected from retrospective questionnaires which were strongly subject to cultural stereotypy about the menstrual cycle.

Contrary to earlier findings in the psychological studies mentioned above, the present study found a peak in state-anxiety and MDQ total at ovulation. Altman et al. (1939) had found that 67.5% of their subjects retrospectively reported experiencing ovulation with elation, with only 31% reporting some tension at ovulation. Also increased sociability and sexual arousal have been found during the ovulatory phase (Moos et al., 1969; Luschen & Pierce, 1972). However, Benedek and Rubenstein (1939) did note increased tension and irritability as ovulation approached which would support these present findings of increased anxiety and menstrual distress.

In the past, many studies of psychological changes during the menstrual cycle have compared menses and premenses to intermenses. This can obscure difference since those measures could have been taken during the follicular,

ovulatory, or luteal phases. Both the follicular and luteal phases appear to have lower levels of symptoms. Other studies have used a particular day prior to menses such as -14 as ovulation which because of individual differences in time of ovulation, would be inaccurate for many subjects. Another method has been to divide the cycle into equal segments and compare these segments statistically. All these methods could miss an elevation in anxiety and menstrual distress symptoms which occurs at a very short time at ovulation. In general, documentation of ovulation by means of basal body temperature, hormone determinations, or LH levels must be done in order to carry out menstrual cycle research.

The MDQ water retention was the only factor on the MDQ which changed significantly during the cycle, showing a gradual rise from the follicular to the premenstrual phase. The women reported an increase in all symptoms within the factor-weight gain, skin disorders, painful breasts, and swelling. Janowsky et al. (1973) also reported significant weight gain at the premenstruum. Furthermore, Wilcoxon et al. (1976) found significant increase in the physiological symptoms of pain and water retention at premenses.

Pearson product-moment correlations between state-anxiety and the three MDQ variables--total score, negative affect and arousal--were significant. State-anxiety was positively correlated with MDQ total and

and negative affect. State-anxiety was negatively correlated with MDQ arousal (pleasant affect). That these relationships occurred lends concurrent validity to the measures as one would expect them to correlate. Correlations were first computed for each individual and then averaged by means of a Fischer's r to z conversion. Hence, the final correlation coefficient reflects the inner consistency within each subject as well as the relationship between state-anxiety and the MDQ variables.

The results of the statistical analyses of these psychological variables indicated that normal women have changes in levels of state-anxiety and changes in a syndrome called "menstrual distress" at ovulation and premenses. Both measures, the STAI and the MDQ, measure negative affect, tension, and heightened physiological activity. It would appear from this study that the incremental accumulation of symptoms both psychological and physiological rather than any particular measure such as negative affect accounts for the elevations at ovulation and premenses.

Each variable on the MDQ remained consistent from phase to phase. Across the cycle physiological measures accounted for from 40 to 45% of the total score; 42.5% of the items pertained to physiological symptoms.

Arousal accounted for about 17% of the total score with 10.6% of the items within the arousal factor. Negative affect accounted for 17% of the total score with 17% of the items. No one of these factors seemed to change the proportion alotted to that factor at any given phase. Therefore it appeared that psychological and physiological measures accounted for a consistent amount of the total score throughout the cycle. Hence MDQ total would represent a syndrome called "menstrual distress" which shows fluctuation during the cycle.

Although the elevations at ovulation and premenses for state-anxiety and MDQ total are statistically significant for the group, it must be noted that individuals do differ from the group patterns as was seen in Figure 4. On the STAI, only 18% peaked at both ovulation and premenses. On the MDQ, 45% showed these peaks. Only one subject has these elevations on both measures. As a result, these findings of a significant quartic trend for both measures must be interpreted with caution.

Correlations Between MHPG and the Psychological Variables

Correlations between MHPG and the four psychological variables were computed for each subject. The group correlations, averages of subjects' correlation coefficients computed by means of Fischer's *r* to *z*

conversion, were not significant. These findings suggest that the relationship between MHPG and each psychological variable is not a simple linear relationship within an individual. No other studies to date with either depressed or normal subjects have tested whether repeated measures of MHPG without a treatment intervention correlate with simultaneous repeated measures of a psychological variable. Hollister et al. (1978) reported a range of urinary MHPG between 1,003 to 6,276 µg per 24 hours when taking repeated measures of normal subjects. They were asked about their mood at each time of MHPG measurement. Their mood tended toward a middle range despite MHPG level.

Studies with depressed patients have shown that they have lower MHPG levels than controls (Maas et al., 1968; DeLeon-Jones et al., 1975). Also manic-depressives showed lower MHPG levels during the depressive phase of the illness than during the manic phase (DeLeon-Jones et al., 1973; Greenspan et al., 1970; Post et al., 1977). These studies suggest that when MHPG levels go down, depression increases.

Other studies, however, have found that depressives of various categories do not differ from normals when taking CSF MHPG measures (Shopsin et al., 1974; Wilk et al., 1972). In Fawcett et al. (1972) only three depressives were below the range in urinary MHPG found

in this present study of normal women. In Sweeney et al. (1978) no depressed subjects had lower means than the normal women in this study who had no depressive symptoms. These contradictory results indicate that low levels of MHPG are not necessarily related to increases in depression. The present study also found no direct linear relationship between urinary MHPG and negative mood.

One previous study (Sweeney et al., 1978) found a significant positive correlation between MHPG and state-anxiety (STAI). These correlations were based on change scores from a pre-experimental to an experimental condition. This present study, however, did not find correlations between MHPG and state-anxiety when taking repeated measures over a long period of time without treatment intervention. Nor did subjects' phase means of MHPG and state-anxiety correlated at each phase result in significant relationships. This additional evidence indicates that individuals do not exhibit a consistent relationship between MHPG and their moods.

When correlations within each subject across the cycle were not significant, it was suspected on investigation of means plotted across the cycle that the relationships between MHPG and the psychologicals would be different the first half of the cycle from the last half of the cycle. Correlations were computed with daily

group means for days 6-11 and days 14-21 (Table 5). These days represented the two halves of the cycle. The results of these correlations were only suggestive since the number of days in each correlation was small, N = 6 and N = 7. Also many correlations were done which increased the chance of a type I error.

Same-day correlations produced low nonsignificant correlations except for a significant positive correlation for days 6-11 for the MHPG-negative affect correlation. This was regarded as inconclusive when compared to the trends suggested by the time-lagged correlations.

When MHPG levels were time-lagged one day behind the psychological measures, the correlation coefficients increased. For days 6-11 they were positive; for days 14-21 they were negative. On days 6-11, the positive correlation between MHPG and MDQ total was significant. On days 14-21, the negative correlation between MHPG and MDQ negative affect was significant. The associations between MHPG and the affective measures were different depending on phase of cycle as had been suggested in Figure 1. It cannot be argued, however, that the nature of the affect is different at ovulation and premenses. All the psychological variables show peaks at ovulation and premenses. This suggests a similar reaction to ovulation and to the onset of menses. In addition, all the MDQ factors maintain a consistent percentage of the

MDQ total throughout the cycle. The explanation might be that both are correlated to another biochemical variable which also undergoes phasic changes, or perhaps these psychological measures do not differentiate an individual's experience at ovulation and at premenses.

The psychological variables were also time-lagged one day behind MHPG. These correlations between MHPG and the psychological variables were generally positive for days 6-11 and days 14-21. Only the state-anxiety correlations produced a negative correlation for days 6-11. When MHPG levels were correlated with negative affect, a significant positive relationship was found at days 14-21. When MHPG was correlated with MDQ total at days 14-21, the r was also positive and significant. These correlations suggest that an increase in MHPG would be followed within a day with an increase in negative affect and menstrual distress. One earlier study of a manic-depressive indicated that MHPG levels began to increase before a switch to mania (DeLeon-Jones et al., 1975). This might also indicate a time-lag of affective change behind a change in MHPG level. If after further investigation this positive association between MHPG levels and negative affect is substantiated, the theory that depression increases as MHPG levels decrease would be open to question.

Both methods of time-lagging suggested a possible relationship between MHPG changes and affective changes. With MHPG behind the psychological, it was suggested that the relationship was contingent on the subjects' psychological reaction to the phase of the menstrual cycle. When the psychological measures were lagged behind MHPG, a positive correlation was noted, especially with negative affect independent of the phase of cycle. These different results highlight the complexity of the relationship of biochemical factors with psychological factors. With present methods, it seems difficult to unravel these complexities.

Also to investigate the relationship of MHPG with the psychological measure at the various phases of the cycle, Pearson product-moment correlations were computed with means at each phase. All these correlations were nonsignificant. (Table 3) It was noted, however, when plotting means for each phase, that women having phase means of MHPG above 1700 µg per 24 hours displayed a different relationship with state-anxiety than those women with phase means below 1700 µg. When the group was divided into low and high excreters at each phase, correlation coefficients increased. For low excreters there was a significant negative correlation for state-anxiety at ovulation. There was also a significant positive correlation at premenses. High excreters produced

correlation coefficients which were in the reverse direction or extremely low. These findings suggest that the relationship between state-anxiety and MHPG levels is different for low and high excreters during the menstrual cycle. Level of MHPG excretion appears to be more closely associated to anxiety level in low excreters.

The nature of this difference is not clear from this study and warrants further investigation since the number of subjects was small. Also when a continuously high excreter and a continuously low excreter were compared, their correlations did not show the same directions as the group correlations for high and low excreters. This would also suggest the need for further study on excretion levels to verify the differences between high and low excreters suggested in this study.

Other studies with depressives also indicate that high and low excretion levels are associated with different responses, in particular, responses to drug treatments. Low baseling MHPG excreters responded to imipramine and showed increases in MHPG levels after treatment. High MHPG excreters responded to amitryptyline and showed decreases in MHPG after treatment (Fawcett et al., 1972; Beckman et al., 1975; Mass, 1975).

For STAI state-anxiety, Sweeney et al. (1978) found that those who showed increases in anxiety and in MHPG during an activity or a restricted activity

treatment had a lower baseline MHPG. Those with higher levels of MHPG showed decreases during the activity period. Therefore there is some earlier evidence which suggests that excretion level as such rather than diagnosis is associated with various patterns of affective response. Hence an individual would not show a significant correlation between MHPG and mood.

In conclusion, correlations between urinary MHPG levels and the psychological variables indicated that the relationships are not simple linear relationships. A number of intervening variables may exist. First, both MHPG and the psychological variables may be related to another biochemical variable which fluctuates during the menstrual cycle. Second, there was a large amount of individual variation in both psychological responses and MHPG excretion levels during the cycle. Third, the relationship between MHPG and the psychological variables may change depending upon the time of the cycle. Fourth, there might be a time-lag between MHPG and the psychological variables. Fifth, the interaction between affect and MHPG may be different depending on the existing MHPG level. And finally there were methodological limitations in this study because of the magnitude of other possible intervening variables such as psychological stress from sources other than the menstrual cycle or from other biochemical factors. All these factors should be taken into account in future studies of MHPG levels in relation to affective variables.

Conclusions

1. Increases in MHPG, the major brain metabolite of NE, at ovulation and at the late luteal phase support the hypothesis that neurotransmitters, in this case NE, are involved in the changes during the menstrual cycle within the hypothalamic-pituitary-ovarian system in women.

2. Increases in anxiety and "menstrual distress" at premenses support the popular theory that many women experience a "premenstrual syndrome"--more tension, irritability, negative mood, and water retention prior to the onset of menses. Increases in anxiety and menstrual distress at ovulation suggest that ovulation can also be a time of stress for many women. None of these increases in the psychological variables, approach pathological levels when compared with normative data.

3. Affective changes during the menstrual cycle are related to changes in MHPG in a complex way. The relationship might depend on the phase of cycle, time-lagging of the psychological and biochemical variables, and the existing MHPG excretion level. These parameters reflect the intricacy of relating any psychological variable to a biochemical variable.

4. The catecholamine hypothesis did not find support. No direct linear relationship was found between MHPG and negative affect and anxiety as measured with standardized scales. Repeated measures were taken for 23 days with no

drug treatment. It was suggested that a cut-off of 1700 µg per 24 hours differentiated two excretion levels which are related to different patterns of affective reaction. It was suggested also that negative affect and anxiety increase as MHPG levels increase. More measures of spontaneous MHPG excretion and psychological self-reports would help clarify whether MHPG levels are actually lower with increased depressive mood or whether that only applies to an individual with a clinical diagnosis of depression.

A number of suggestions for further research on the menstrual cycle arise from this study. Since there were 11 women with no depressive symptoms in this study, a comparison with women who experience depression could assist in determining whether depressive women experience more acute symptoms at ovulation and premenses than non-depressive women. Also a standardized measure of daily events and their associated stress levels could be an additional measure for clarifying the high degree of individual variation in mood during the cycle.

Methods which were effective in this study and warrant repetition were: (1) the use of daily self-reports to avoid cultural stereotypy about the menstrual cycle and (2) the accurate determination of ovulation which is absolutely essential when comparing differences across phases of the cycle.

Mood changes and variation in MHPG levels were statistically supported in this study of 11 women. As in all research using group statistics, however, it must be emphasized that there is individual variation. Also these statistically significant differences are not necessarily noticeable or substantial in everyday life. These qualifications are especially important when conducting menstrual cycle research because of its impact on the current re-evaluation of women's roles in society.

SUMMARY

Daily 24-hour urine collections were taken in order to measure MHPG, the major brain metabolite of NE, during one menstrual cycle of 11 normal free-cycling women. The psychological variables of state-anxiety (Spielberger et al., 1970), MDQ total, a measure of menstrual distress, MDQ negative affect, and MDQ arousal (Moos, 1977) were assessed daily. The purpose of this research were (a) to assess the role of NE by means of MHPG levels in the human reproductive cycle, (b) to assess fluctuation in mood often attributed to biochemical changes during the menstrual cycle, (c) to relate MHPG levels to psychological variables as was suggested by the catecholamine hypothesis of affective disorders.

Trend analysis indicated that MHPG levels peaked at ovulation and the late-luteal phases. State-anxiety and MDQ total peaked at ovulation and premenses. Pearson product-moment correlations indicated that there were no direct linear relationships between MHPG and the psychological variables within individuals. Other Pearson product-moment correlations indicated that phase of cycle, level of MHPG excretion, and a time-lag effect may be intervening variables within the MHPG-mood relationship.

The following conclusions were drawn from this study: (1) fluctuations in MHPG during the cycle indicate the involvement of the neurotransmitter NE in the human reproductive cycle; (2) women experienced heightened anxiety and menstrual distress at ovulation and premenses which is within a normal range; (3) low MHPG levels are not directly related to an increase in depressive mood which would be expected according to the catecholamine hypothesis of affective disorder. In fact, the relationship between MHPG levels and mood appears to be quite complex.

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APPENDIX

SUBJECT 1

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	1640	09	08	11	058	21	06	08	05	04
02	1506	08	10	06	058	34	06	10	05	04
03	1874	09	11	11	068	37	06	15	05	04
04	2108	08	10	15	063	38	06	08	05	04
05	1664	09	08	13	064	36	06	12	05	04
06	1930	08	09	15	066	38	06	12	05	04
07	2410	07	14	17	071	46	06	11	05	04
08	1808	08	10	16	066	39	06	10	05	04
09										
10										
11										
12										
13										
14	1901	08	09	13	062	31	08	08	05	04
15	2107	09	08	11	060	39	06	10	05	04
16	2035	10	16	16	089	41	08	14	08	06
17	1394	11	08	14	090	29	18	14	13	05
18	1756	12	10	20	084	40	06	13	05	07
19	1967	09	08	16	063	22	06	08	05	04
20	2112	09	08	14	064	22	06	08	08	04
21	1063	11	08	17	073	35	09	12	05	04
22	1505	09	08	11	058	22	06	08	05	04

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 2

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	1950	04	11	12	075	32	21	08	05	07
02	1724	04	11	14	071	30	15	08	08	04
03	1438	06	15	13	088	30	21	15	07	04
04	2104	04	10	14	063	32	11	08	05	04
05	1986	07	09	11	075	32	17	12	07	05
06	2403	05	25	12	093	46	15	16	09	04
07	1888	04	11	13	077	42	19	12	06	05
08	1927	05	11	12	073	28	20	08	05	05
09	2314	06	10	17	070	34	10	10	06	04
10	1647	04	09	14	074	32	20	11	05	04
11	2626	13	09	15	086	30	19	11	06	06
12	2138	09	18	09	080	49	19	14	07	04
13	1479	04	13	16	073	23	11	10	08	04
14	1983	07	11	12	077	30	16	11	07	04
15	1954	05	14	15	070	37	10	09	06	04
16	2228	09	11	15	075	31	16	08	05	04
17	2016	06	09	14	064	34	11	08	05	04
18	2100	12	16	13	090	31	14	16	08	04
19	1125	06	12	13	085	33	22	13	05	04
20	2447	07	13	10	075	33	15	12	07	04
21	1362	05	17	13	074	34	14	08	06	04
22	1527	04	12	16	065	34	09	08	05	04
23										

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHGP; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 3

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	1121	04	09	09	057	35	09	08	07	04
02	1272	04	08	09	052	30	06	09	05	04
03	1713	04	08	14	056	32	06	08	05	04
04	0915	04	14	06	057	44	09	10	05	04
05	1697	04	13	06	068	51	08	12	10	06
06	1807	06	08	13	057	30	06	08	05	04
07	1249	06	08	10	057	31	06	08	05	04
08	1604	06	08	12	056	31	06	08	05	04
09	0657	05	08	09	056	31	07	11	05	04
10	1096	05	08	07	051	32	10	08	05	04
11	1123	05	08	08	053	41	08	08	05	04
12	1354	05	10	09	054	51	06	08	05	04
13	1176	05	08	09	053	31	07	08	05	04
14	1272	06	08	10	056	33	08	08	05	04
15	1414	06	10	08	058	35	08	10	05	04
16	1254	06	10	08	057	36	08	08	05	05
17	1237	08	08	09	060	32	09	08	05	06
18	1119	08	13	06	073	42	16	08	08	05
19	1044	06	09	07	067	37	13	10	11	04
20	1225	08	08	12	059	31	07	08	05	04
21	1394	06	08	10	056	30	07	09	05	04
22	1810	06	08	08	057	30	11	08	05	04
23	1450	06	09	08	057	31	09	08	06	04

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 4

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01										
02	0874	05	14	09	067	43				
03	0848	05	08	09	060	34				
04										
05	1140	04	09	10	061	36	10	10	07	04
06	1150	04	14	08	066	30	09	10	10	04
07	1115	04	08	16	067	24	08	08	08	04
08	1082	06	14	09	064	48	07	09	04	04
09	1096	08	08	11	062	29	10	08	05	04
10	0971	08	13	11	069	41	09	08	09	04
11	0997	08	14	08	079	48	10	16	10	06
12	1135	05	14	09	065	48	10	09	07	04
13	1148	08	09	12	067	39	09	11	07	04
14	1057	10	09	10	063	32	07	08	06	04
15	1175	07	13		065	46	08	11	06	04
16	0927	11	13	11	072	42	10	08	07	04
17	1071	11	14	09	082	55	11	16	09	04
18	0850	12	09	14	092	34	10	21	13	04
19							09	19	12	04
20	1595	09	08	15	084	32	08	10	05	04
21	1656	10	08	10	062	30	15	08	05	04
22	1016	07	11	11	068	38	08	10	07	06
23	1261	04	10	10	056	42	12	08	05	06

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 5

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	1275	06	19	12	108	63	16	24	16	04
02	1354	09	16	17	103	40	15	20	10	04
03	1149	08	14	14	092	44	12	21	09	04
04	1058	07	13	14	086	33	14	20	09	04
05	1786	11	11	18	089	37	10	19	07	04
06	2232	11	11	15	082	33	10	14	05	05
07	2021	10	15	15	085	36	10	13	06	05
08	2182	07	16	15	084	27	11	11	09	04
09										
10										
11										
12										
13										
14	1783	11	10	14	083	35	16	12	07	04
15	2185	11	10	14	090	30	14	17	10	04
16	1909	09	12	17	076	33	09	10	07	04
17	1960	08	14	15	076	42	09	10	06	04
18	2187	06	25	10	084	59	09	10	12	04
19	2130	08	17	10	103	55	15	17	21	04
20	2305	08	13	15	082	41	10	11	14	04
21	2121	07	11	15	076	50	11	13	06	05
22	1555	08	12	15	079	40	11	10	08	05
23										

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 6

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	1356	04	10	07	052	39	07	08	05	04
02	2062	04	10	08	053	39	07	08	05	04
03	2072	04	08	09	051	39	06	08	05	04
04	1401	04	09	07	052	35	07	08	06	04
05										
06	1905	04	08	06	051	46	06	11	05	04
07	2168	05	10	07	054	43	07	08	06	04
08	2245	04	09	09	053	41	07	08	05	04
09	1767	04	08	08	052	36	06	10	05	04
10	1861	04	10	07	052	37	07	08	05	04
11	1509	04	08	07	050	39	07	08	05	04
12	1819	04	08	06	049	39	07	08	05	04
13	1141	04	08	08	050	46	06	08	05	04
14	2164	04	08	07	053	48	06	12	05	04
15	2008	04	12	08	056	48	07	08	05	04
16	2188	07	09	05	059	41	10	11	06	04
17	1910	09	12	06	064	41	13	08	05	04
18	1935	08	11	06	066	46	12	09	06	04
19	1849	07	08	06	058	36	12	08	06	04
20	1901	07	09	08	062	25	11	08	06	04
21	1680	04	08	07	061	39	12	08	06	04
22	1881	06	09	07	056	41	09	08	06	04
23	2214	05	08	07	056	36	11	09	05	04

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 7

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	0987	06	15	09	075	34	17	10	06	04
02	1283	05	28	10	081	40	13	09	05	04
03	0577	07	25	08	080	60	10	12	07	04
04	1101	06	11	16	064	37	06	08	06	04
05	1025	05	14	16	069	31	10	08	05	04
06	1444	05	16	16	074	44	09	10	06	05
07	1251	07	17	15	073	33	08	11	05	04
08	1486	07	22	11	077	35	08	11	05	04
09	0888	04	14	10	065	41	06	10	05	04
10							07	09	05	04
11	0486	07	11	11	061	30	09	14	05	04
12	0586	05	20	13	077	33	11	10	06	04
13	0927	07	21	14	081	33				
14	1117	06	13	14	070	31	13	08	05	04
15	1196	08	14	11	067	46	10	08	05	04
16	0946	13	16	08	070	49	07	09	06	04
17	0842	10	12	12	066	44	08	08	05	04
18	1384	05	17	10	071	36	12	11	05	04
19	0923	09	08	11	063	28	11	08	05	04
20							09	11	05	07
21	1274	10	12	16	077	32	10	08	05	06
22	0877	05	16	12	070	32	10	09	05	04
23	1234	04	14	10	067	30				

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 8

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	0750	04	10	16	065	39				
02	0665	04	08	18	062	22	08	08	05	04
03	0741	04	08	17	061	21	08	08	05	04
04	0661	04	08	16	052	24	06	08	05	04
05	0556	05	10	19	066	34	08	08	05	04
06	0742	04	13	05	113	51	24	13	29	13
07	0714	04	26	10	101	67	20	17	09	06
08	0678	04	15	13	076	36	17	08	07	05
09										
10										
11										
12	0801	04	08	20	062	26	06	08	05	04
13	0868	05	12	16	071	32	12	10	05	04
14	0851	05	08	17	062	24	08	08	05	04
15	1382	04	08	19	063	24	08	08	05	04
16	1282									
17	1293	09	24	10	096	65	19	12	07	04
18	1121	05	08	17	063	21	08	08	05	04
19	0917	05	08	18	061	20	06	08	05	04
20	0953	06	18	08	089	40	20	09	14	07
21							11	08	07	04
22	0795	05	09	14	065	37				
23										

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 9

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	1286	04	08	05	047	29	06	08	05	04
02	1113	04	10	08	055	22	06	08	08	04
03	1329	04	14	10	063	37	11	08	05	04
04	1008	04	10	09	060	28	13	08	05	04
05	1132	04	21	10	074	42	09	10	09	04
06	2583	04	14	11	062	34	08	08	05	04
07	1437	04	11	08	063	32	12	08	09	04
08	1898	06	10	08	063	31	11	10	07	04
09							10	13	09	04
10							08	13	05	04
11	1289	07	08	10	068	28	09	08	07	04
12	2236	09	10	06	062	36				
13	1809	09	08	08	060	32				
14	2081	08	14	08	062	27	07	08	07	04
15	1930	06	13	10	060	32	06	08	07	04
16	1747	10	12	08	067	25	06	08	06	04
17	1749	13	08	11	068	37	10	11	05	04
18	0974	07	25	10	082	47	07	08	06	04
19	1122	06	22	08	088	38	10	11	08	04
20	1462	04	29	12	085	29	14	12	15	04
21	1490	05	24	09	071	41	11	11	07	04
22	1347	07	21	12	078	32	09	08	05	04
23	1406	04	14	10	060	36	06	09	06	04

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 10

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	1685	06	09	13	078	33	13	13	07	06
02	1178	07	10	15	076	35	09	12	07	04
03	1406	07	12	14	081	34	11	12	08	04
04	1477	07	12	15	081	33	09	11	08	05
05	1298									
06	1526	07	10	16		31	09	14	07	04
07	0952	07	12	15		33	09	12	09	04
08	1780	06	12	15		31	08	08	10	04
09	0924	10	11	18	096	35	17	17	08	05
10	1621	09	12	16	087	27	16	14	07	05
11	1236	08	10	15	081	36	14	11	08	04
12	1011	11	15	17	096	36	13	12	16	04
13	1232					29	14	12	09	05
14	2073	09	17	15	102	30	16	13	10	06
15	1175	08	12	14	084	34	11	13	05	04
16	1807	11	15	18	096	43	13	12	08	06
17	0844	09	12	16	088	37	12	14	06	04
18	2100	10	12	15	083	41	08	13	08	04
19	1182	08	12	14	088	33	13	12	07	08
20	0978	07	11	14	083	32	11	12	08	07
21	1407	11	09	14	085	31	13	11	09	07
22										
23										

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

SUBJECT 11

Day	MHPG	WR	NA	AR	TOT	ST-A	P	CO	BC	AU
01	1346	04	14	19	079	28	06	11	05	07
02	1586	04	08	08	063	26	08	11	07	05
03	1557	04	08	10	060	34	08	08	07	04
04	2173	04	14	14	079	26	12	09	09	06
05	1967	04	17	21	082	25	06	11	05	06
06	1703	04	13	16	076	28	10	08	07	06
07	2333	05	10	13	085	27	18	08	10	07
08	1263	05	08	12	066	27	10	11	05	05
09	1533	05	10	21	077	25	06	12	07	04
10	1623	04	17	14	081	41	11	08	07	06
11	1196	04	19	13	090	46	11	14	08	04
12										
13										
14	2571	04	08	09	066	22	07	13	10	04
15	1324	04	11	07	072	44	12	10	07	06
16	2416	04	11	09	063	34	07	08	09	04
17	1527	04	11	13	069	37	11	08	05	04
18	1679	05	12	08	070	39	11	12	05	04
19	1541	07	15	09	073	31	10	13	07	07
20	1617	06	14	14	077	41	11	10	08	04
21	1094	05	16	10	081	30	12	14	07	06
22		05	11	14	068	22	07	08	07	05
23	1457	04	35	14	100	30	13	14	05	05

NOTE: Abbreviated 3 methoxy-4-hydroxyphenylglycol=MHPG; water retention=WR; negative affect=NA; arousal=AR; total=TOT; state-anxiety=ST-A; pain=P; concentration=CO; behavior change=BC; autonomic response=AU.

APPROVAL SHEET

The dissertation submitted by Merrily O'Connor-Miller has been read and approved by the following committee:

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The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the dissertation is now given final approval by the Committee with reference to content and form.

The dissertation is therefore accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

12/6/79
Date

Alan S DeWolfe
Director's Signature