HYSTERECTOMY AND THE PREMENSTRUAL SYNDROME.

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ABSTRACT.

This study reviews the literature in two major areas of Premenstrual Syndrome research. Firstly, the literature on the Premenstrual Syndrome itself is reviewed with the focus on such issues as syndrome definition, symptomatology, methodological problems, and etiological theories. Also outlined here are the hormonal events of the menstrual cycle with a review of the literature on premenstrual symptoms in relation to the menstrual cycle. The general conclusion here is that this area of premenstrual syndrome research has yielded confusing and often inconclusive results. Further well controlled research seems needed here. Secondly, the literature on the more specific area of the Premenstrual Syndrome and hysterectomy is reviewed. Research into ovarian function and its methods of detection post hysterectomy is discussed, as is research into PMS and anovulation. The specific focus of this section is the review of the research of Backstrom, Boyle, and Baird (1981), and Beumont, Richards, and Gelder (1975) whose studies on PMS and hysterectomy have yielded contradictory results. It is concluded that both studies are beset with methodological problems making valid interpretation of their results difficult, and their application to clinical practice questionable.

The aim of this study was to collect daily affective, somatic, and hormonal data from women who had undergone hysterectomy and who believed they experienced PMS. Ovarian function was determined by the calculation of urinary pregnanediol levels. Spectral analysis was used to analyse the significance of this data.

Of the thirteen subjects who finally took part in this

study, six showed significantly cycling mood and/or physical symptoms that were significantly related to the premenstrual phase of their cycle. The remaining seven subjects demonstrated significant cyclicity of mood and/or physical symptoms that were not related to their underlying hormonal cycle. It was concluded that there is some evidence to support the hypothesis that PMS can exist after hysterectomy, but more sophisticated research is suggested to further validate these findings.

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SECTION ONE: LITERATURE REVIEW.

CHAPTER ONE: THE PREMENSTRUAL SYNDROME.

1-1: INTRODUCTION.

For many years physical and affective fluctuations have been associated with the menstrual cycle. Clinical interest in these changes was initially aroused by the varied complaints women presented to their physicians, and it is Frank (1931), who is generally believed to have coined the term "Premenstrual Tension" (PMT) in what is marked as the first modern "scientific investigation" of premenstrual symptomatology. According to Frank, emotional symptoms of PMT consist of

> "a feeling of indescribable tension....unrest, irritability...and a desire to find relief by foolish and ill-considered actions." (Frank, 1931; p1054).

Since 1931 however, there has been a huge amount of interest in this condition, which in turn has generated a vast but confusing body of literature.

1-2: COMMON SYMPTOMS OF PREMENSTRUAL SYNDROMES.

Table 1-2: Common symptoms of Premenstrual Syndromes.

AFFECTIVE	COGNITIVE	PAIN
Sadness	Decreased Concentration	Headache
Anger	Indecision	Breast tenderness
Anxiety	Paranoia	Joint and Muscle
Irritability	"Rejection Sensitive"	Pain
Labile Mood	Suicidal Ideation	
NEOROVEGETATIVE	AUTONOMIC	CNS
Insomnia	Nausea	Clumsiness

Hypersomnia	Diarrhea	Seizures
Anorexia	Palpitations	Dizziness
Craving for certain foods	Sweating	Vertigo
Fatigue		Paresthesia
Lethargy		Tremors
Agitation		
Libido Change		
FLUID/ELECTROLYTE	DERMATOLOGICAL	BEHAVIOURAL
Bloating	Acne	Decreased Motivation
Weight Gain	Greasy Hair	Poor Impulse Control
Oliguria	Dry Hair	Decreased Efficiency
Edema		Social Isolation

Rubinow D.R. and Roy-Byrne P, (1984). "Premenstrual Syndromes: Overview from a Methodologic Perspective", American Journal of Psychiatry, 141; p170.

Abraham (1980) divided the symptoms into four subgroups (with the range encompassing anxiety, irritability, weight gain, breast tenderness, carbohydrate craving, depression, and withdrawal), while Moos (1968; 1969) in an extensive study on menstrual cycle symptoms, derived eight symptom cluster scales of pain, concentration, behavioural change, autonomic reactions, water retention, negative affect, arousal, and control.

Traditionally symptoms range from one or two to eight or nine in number, but can include any of the large combination of symptoms outlined and more besides. However, the inclusion of some reported symptoms in the literature is not entirely substantiated. For example, Moos (1968) originally included an item about "change in eating habits" in his research, but found that it did not consistently locate with any of the other factors. Likewise, Silbergeld, Blast, and Noble (1971) failed to show any significant cyclical variation in appetite or food consumption. There has also been some disagreement in the literature regarding changes in sexual activity during the premenstrual phase of the menstrual cycle. Some have noted an

increase in sex drive during the first half of the cycle, peaking at ovulation (Benedeck & Rubenstein, 1939; Moos, 1968), others have noted a mid-cycle increase in sexual unterest followed by a post ovulatory decrease (Kane, Lipton, & Ewing, 1969), while Kinsey, Pomeroy, Martin and Gebhard (1953) found that 90% of American women experienced greater sexual arousal during the premenstrual phase. These conflicting reports are mainly due to the fact that the data from these studies were collected retrospectively through questionaires, and as a result are most likely to be reflecting remembered desire rather than actual significant changes in sexual interest or activity.

1-3: METHODOLOGICAL CONSIDERATIONS.

The existence of methodological flaws in design has by and large been responsible for the research literature dealing with this condition being confusing, inconsistent, and highly contradictory. In the last fifty years there has been a distinct lack of consensus over the definition of the syndrome, which has led to a significant variation between studies with regards to its cyclicity, severity, timing and course, although the emotional symptoms described by Frank have been consistently supported by a large body of research and clinical reports (Abraham, 1980, b); Dalton, 1980; Halbreich, Endicott, Schacht, & Nee, 1982; Israel, 1938; Moos, 1969). Additions to his list have also been made and an almost limitless number and variety of reported changes in mood states, behaviours, and somatic symptoms have since been connected with the premenstrual phase. Furthermore, since

tension and stress are no longer considered the only major symptoms of the condition, it is now commonly referred to as the "Premenstrual Syndrome". (Indeed, in some cases tension may be overshadowed by other complaints or be entirely absent.)

The actual severity of the symptoms was initially rarely considered by many researchers. This meant, for example, that the symptom of depression was, and could be, applied to women who felt sad premenstrually and to women who felt suicidal at this time. However, the symptoms can range from mild to incapacitating, and the need for some form of differential grading of them has since been recognized and utilized by subsequent researchers, although to date, there is no internationally accepted scheme for symptom grading and classification (Abraham, 1980, b); Steiner, Haskett & Carrol, 1980).

As for the cyclicity of the symptoms, again the literature here is confusing. Some have defined PMS on the basis of its symptoms (Reid & Yen, 1981), while Dalton (1980) believes the timing of the symptoms to be more important than their actual presence, duration, or severity. Dalton (1980) stated that symptoms should occur regularly in the same phase of each menstrual cycle, and should then be followed by a symptom-free phase in each cycle. Indeed, both approaches have their place in the study of PMS. On the one hand, it is important to consider the presence or absence of symptoms when assessing the syndrome in order to avoid confusion with other cycle-related conditions such as dysmenorrhea, while on the other hand, Dalton's point is clearly an important one, given the large number and variety of these reported symptoms. Some

of the symptoms that make up the syndrome (for example, tension, anxiety, and headaches) are not uncommon ailments and do occur intermittently in women regardless of their cycle phase (Clare, 1981; Moos, 1969).

Yet for the concept of the premenstrual syndrome to be of any clinical value, it is of the utmost importance to establish that there is a significant change (be it increase or decrease) in these symptoms during the premenstrual phase and that these changes are cyclic in nature, and do not occur regularly during other phases in the menstrual cycle (Cruikshank, 1983; Dalton, 1980). In spite of earlier findings to the contrary (Anderson, 1972; Paige, 1971; Parlee, 1973; Rossi & Rossi, 1977; Swandby, 1980), the cyclical occurrence of these symptoms has been well established (Abraham & Hargrove, 1980; Hudson, 1985; Moos et al., 1969; O'Brien, Craven, Selby, and Symonds, 1979).

The collection of accurate premenstrual data has also been a stumbling block in the study of the syndrome. For example, the term "premenstrual" can mean different things to different people- researchers and patients alike: Kramp (1968) included the last six days of the luteal phase and first two days of menstruation in his concept of premenstrual, Dalton (1964) encompassed four days prior to and four following the onset of menstruation, thereby allowing the separate condition of dysmenorrea to often be confused with PMS. However, Sutherland and Stewart (1965) postulated that the symptoms must, by definition, disappear with the onset of menses. Furthermore, many have collected data only once during the follicular phase, and once premenstrually (Andersen, Larsen, Steenstrup, Svendstrup, & Nielson, 1977; Golub, 1976; Silverman,

Zimmerman, & Silverman, 1974). The findings from such data are of questionable validity since it assumes data collected in one cycle is representive of every cycle, and that the premenstrual phase may be predicted in advance of the cycle. However, symptoms within subjects may vary (in both number and severity) across cycles, and variations in the follicular phase can make predicting the luteal phase problematic even for women who ovulate and menstruate regularly.

It is clear from this literature then, that the onset and timing of the premenstrual phase tends to reflect such things as the beliefs of the researcher about the length of this phase, the requirements of their particular experimental design, and designs employed by previous researchers. Yet physiological methods of determining cycle phase have become more refined and accurate. Developments in radioimmunoassay techniques allows the analysis of hormone levels from small quantities of serum or urine, and it is now possible to examine daily or hourly hormonal changes throughout the entire menstrual cycle (Metcalf, 1973). Researchers can therefore no longer continue to make assumptions about cycle phase based on such techniques as the number of days past menstruation, or temperature change. Generally however, the premenstrual phase commences soon after ovulation during the luteal phase, and encompasses a time span of approximately eight to one days prior to menstruation.

There are also such factors as experimenter expectancy effects, and the subjects' expectations about the purpose of the study that have been problematic, as have studies where subjects have been recruited from specific populations such as psychiatric wards, clinics, and gynecological surgeries whose

findings have then been generalized to a normal population. Similarly, in the past, both the utilization of control groups and double-blind studies have been sparse.

However, by far the two most serious methodological problems that have impeded the evaluation of PMS are the methods employed in the assessment of premenstrual symptomatology, and the methods used in its collection or recording. Overall, much of the early research used general assessment techniques such as standard mood questionnaires and personality inventories, rather than ones specifically designed for menstrual cycle reseasrch. These types of asessments may not have been specific enough to assess whether the symptoms were in fact regularly occurring in the premenstrual phase of their menstrual cycles. It is therefore possible that unsuitable women may have been included in the samples, while suitable women may have been excluded. In order to standardize menstrual cycle symptom assessment Moos (1968) developed a Menstrual Distress Questionnaire (MDQ) which has since been used extensively. Steiner et al. (1980) employed a modified MDQ and several psychiatric rating scales, Abraham (1980,a) utilized a 19-item questionnaire, and Halbreich et al. (1982) developed the Premenstrual Assessment Form (PAF). This assessment form has categories for several different types of premenstrual mood, behaviour, somatic, and motor function changes, and allows for bi-directionality of symptom change. Yet even these assessment techniques have their methodological shortcomings. Moos' MDQ was initially retrospective in nature (but has since been modified), half his subjects were taking oral contraceptives, and nearly 10% were pregnant. His sample was therefore hardly representative

of the general population, and his findings are limited. Steiner et al. allowed only a very narrow definition of the syndrome by failing to include somatic symptoms in their assessment, thereby excluding from their sample many women with premenstrual symptoms such as weight changes, fluid retention and breast tenderness. Similarly, Abraham's scale was constructed without using standard psychometric procedures, resulting in questionable internal consistency and reliability.

The validity of research findings have been further compromised due to the retrospective method of data collection employed by most of the early studies. This method usually involved the completing of assessment-type forms based on interviews, and the self report of symptoms experienced in previous cycles. Such responses are based on memory and as such, are influenced by such factors as expectation, and cultural beliefs and attitudes, and therefore may not be an objective measure of symptom change (Abplanalp, Donnelly, & Rose, 1979; Brooks-Gunn & Ruble, 1980; Rubinow & Roy-Byrne, 1984). Recently however, prospective methods of data collection have been employed by many researchers and, by obtaining daily reports of moods and physical symptoms over several cycles, have noted discrepancies between retrospective and prospective accounts of symptomatology (Abplanalp et al., 1979; Brockway, 1975; May, 1976; Swandby, 1979; Vila & Beech, 1980). This lends support to the view that retrospecive data is of questionable value to those concerned with the diagnosis and treatment of PMS.

Upon considering these methodological issues, it becomes clear that the findings in any piece of research on PMS must

be interpreted in the light of the strengths and weaknesses of the particular research method employed.

1-4: The MENSTRUAL CYCLE.

Cyclic ovarian function during the menstrual cycle involves the interaction between the ovaries and the hypothalamic-pituitary system. The interval between the first day of menstruation and the first day of the next menses constitutes one menstrual cycle. Cycle length varies from 20-45 days, with the average length being 28 days. Ovulation usually occurs mid-cycle, thus dividing the cycle into the follicular (pre-ovulatory), and luteal (post-ovulatory) phases. The length of the follicular phase ranges from 10-17 days, with an average of 12.6 days, while the length of the luteal phase is relatively fixed at approximately 14 +/- 2 days (Baird, Baker, McNatty, & Neal, 1975). Estrogen, progesterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH) are the major features of the control system of the menstrual cycle. LH and FSH are both gonadotrophic hormones and are synthesized and released by gonadotropin-releasing hormone (Gn-RH). Gn-RH itself is secreted by the hypothalamus.

At the beginning of the menstrual cycle during menstruation (the early follicular phase) estrogen and progesterone concentrations are low, and Gn-RH begins to release LH and FSH. In response to these increasing FSH levels several ovarian follicles, each containing an ovum, begin to develop. After 5-6 days one of these follicles develops more rapidly than the others, while inside, the

maturing ovum begins to release small quantities of estrogens into the blood stream. This is followed by a progressive increase in estrogen levels during the mid follicular, and a sharp increase during the late follicular phases, thereby inhibiting the further secretion of FSH. FSH levels then begin to fall which in turn leads to the regression of the other developing ovarian follicles. Estrogen levels peak just before mid-cycle, and by exerting a positive feedback effect on the pituitary system, initiates a mid-cycle peak in LH. This LH peak then initiates ovulation by stimulating the growth of the ovarian follicle to the point where it eventually ruptures, releasing the mature ovum.

Soon after ovulation FSH levels rise again, while estrogen and LH levels decline sharply, and the cycle enters the luteal phase. The ovum enters the fallopian tubes where fertilization is to occur and, whether fertilized or not, then moves on into the uterus. The follicle from which the ovum was released changes and becomes the corpus luteum. The corpus luteum then secretes progesterone, (causing basal body temperature to rise), and a small quantity of estrogen. Together they function to equip the uterus for a fertilized ovum and to inhibit the further release of LH and FSH. Luteal phase levels of LH and FSH then decline to a nadir three to four days prior to menses, and are generally lower than those in the follicular phase. The corpus luteum itself regresses and, within approximately 12 days after ovulation, ceases to function. Progesterone and estrogen are then no longer released, and levels begin to decline approximately four days prior to menstruation. FSH levels at this point begin to rise again, although LH levels remain low and relatively stable,

and if fertilization has not occurred, menstruation begins.

As well as progesterone, estrogen, LH, and FSH, there are also other hormonal changes accompanying the menstrual cycle. Prolactin secretion is generally higher during the luteal phase than the follicular phase (Steiner & Carroll, 1977), aldosterone levels peak 9-10 days prior to menstruation then drop rapidly 3-4 days later (Katz & Romfh, 1972), and plasma angiotensin level are elevated in the luteal phase compared to the follicular phase (Sundsfjord & Aakvaag, 1970).

1-5: THE MENSTRUAL CYCLE AND PREMENSTRUAL SYMPTOMS.

The appearance of premenstrual symptoms has been closely linked to the luteal phase of the menstrual cycle, rather than specifically to ovulation (Backstrom et al., 1983; Brush, 1977; Clare, 1979,a); Cruikshank, 1983; Haskett, Steiner, Osmun, & Carroll, 1980; Reid & Yen, 1981; Steiner & Carroll, 1977). The symptoms usually appear soon after ovulation and gradually increase (in number and severity) in parrallel with corpus luteum development, and increasing progesterone levels. They then peak during the last five days of the luteal phase, past the point where estrogen and progesterone levels fall, and decrease rapidly with the onset of menstruation.

More recently, Rubinow et al. (1986) reported on characteristic patterns of affective and somatic changes in women who did not experience PMS. While their research supported the observations reported here, they also identified two different groups of non-PMS women, and hence, two different affective and somatic patterns. The first group consisted of women who presented with a retrospective history

of PMS, who subsequently failed to meet the confirmed prospective requirements of the syndrome. The second group were comprised of women who believed themselves to be asymptomatic who subsequently exhibited relatively stable mood patterns with small affective and somatic fluctuations. The former group however, exhibited more frequent mood changes, fluctuating from one extreme to another. Yet neither groups' affective and somatic fluctuations displayed any evidence of cyclicity, nor were they linked in any way to the premenstrual phase of the cycle. Although further research is necessary to validate these findings, Rubinow et al. have provided the clinician with useful information on the symptom profiles on non-PMS women, which may aid in the future selection of subjects for treatment and control trials.

CHAPTER TWO: THE ETIOLOGY OF PREMENSTRUAL SYNDROME.

2-1: INTRODUCTION.

The etiology of PMS, like its definition and diagnosis, has been the subject of much debate in the past fifty years. Theories are numerous and have been reviewed extensively (Backstrom, 1983; Clare, 1979; Steiner et al., 1977; Reid & Yen, 1981). Generally there are two major theoretical stances in the etiology of PMS: Psychological and Biochemical.

2-2: PSYCHOLOGICAL THEORIES OF PMS.

2-2-1: Evolution and PMS.

The evolutionary theory of PMS proposed by Rosseinsky and Hall (1974) postulates that PMS is an infertility indicator and has the evolutionary value of the propagation of the human race. However, while this is certainly a novel theory, the evidence to support it is, at best, extremely tenuous and can be questioned on a number of points. Their argument rests upon the hypothesis that there is a premenstrual increase in adrenalin which, in turn, causes premenstrual aggression. This then signals the woman that ovulation has recently occurred and she is now entering her infertile phase. Thus, by being hostile to her mate during this premenstrual infertile phase, and attentive at other non-premenstrual fertile times, the sexual desire of the mate is increased during those fertile periods, thereby increasing the probabilty of conception. Yet Rosseinsky and Hall provide no empirical support for this premenstrual increase in adrenalin

that is supposed to preclude this chain of events. Similarly, evidence of menstrual synchrony among cohabiting women is cited as evidence for the frustrated males not turning to other women during these infertile premenstrual times. While there is some evidence for menstrual synchrony (McClintock, 1971), Rosseinsky and Hall admit that they have no statistics available on women cohabiting in mixed male and female groups. However they go on to speculate that such synchrony could well occur there. Again their argument rests upon speculation with no empirical data to support it. Furthermore, while they explain how PMS may have served some evolutionary purpose in prehistoric times, they fail to address the issue of its evolutionary value in the 1980's.

Finally, the implication of this theory is that PMS is both innate and ineradicable. Yet again, what evidence is there to support the concept of the genetic inheritability of PMS? This issue is too confused with social-expectation factors for a clear genetic component to be identified. Similarly, if PMS is ineradicable, this approach is of little, if any, clinical value in terms of the treatment of the syndrome, and offers no practical support to those women who find this condition debilitating.

2-2-2: PMS and Personality.

Much of the early work in this area took a psychoanalytic approach to PMS, regarding it as a reflection of unconscious conflicts about the acceptance of the menstrual function and the female role, while menstruation was seen to symbolize a lost child or feminity (Benedeck, 1952; Deutsch, 1944; Israel, 1938). However, although the symptoms occurred prior to

menstruation, this highly speculative theoretical position gives such a central role to menstruation itself, that it is probable that menstrual complaints could have become confused with the premenstrual complaints that constitute the premenstrual syndrome.

Some authors have regarded PMS patients as women with many family conflicts and who regard menses as a stressful and negative event (Paulson, 1961). Others have built on this framework by relating such negative attitudes about menstruation to personality models (Levitt & Lubin, 1967; Paige, 1971).

Furthermore, there are some authors of the view that PMS is somehow associated with deficiencies in a woman's personality growth and structure (Morton, 1950). Some even hint at the possibility of a relationship between menstrual or premenstrual complaints and a general "neurotic" tendancy (Coppen, 1965; Coppen & Kessel, 1963; Kramp, 1968; Levitt & Lubin, 1967; Smith, 1976), and this viewpoint is, by and large, reflected in the methods used to study the association between PMS and personality.

Such methods have included the analysis of admissions to psychiatric units in relation to the phase of the menstrual cycle at the time of admission (Dalton, 1959; Janowski, Gorney, Castelnouo-Tedesco, & Stone, 1969; Kramp, 1968; Torghele, 1957; Wakoh et al., 1960), the comparison of women with previously diagnosed affective disorders with a control group (Diamond, Rubenstein, Dunner, & Fieve, 1976), and the diagnosis of the syndrome based upon the administering of various personality tests (Coppen & Kessel, 1963; Rees, 1953; Taylor, 1979).

Both Rees (1953), and Coppen and Kessel (1963) found a significant positive correlation between PMS and neurosis. Irritability was seen by Coppen and Kessel as being the key psychological symptom of the syndrome, and found women who were irritable premenstrually were more likely to be irritable at other times during the cycle as well. Thus they saw these premenstrual symptoms as being an exacerbation of already existing personality traits that were related to neuroticism. Gough (1975) reported that women who showed signs of being eager to seek help and were self-doubting tended to report more premenstrual symptoms, while Coppen (1965) reported that there was also a high incidence of menstrual disorders among the neurotic patients he studied. Furthermore, when compared with controls, these patients complained more frequently of irritability, depression, and pain. Similarly, Gruba and Rorhbaugh (1975) confirmed these findings by reporting subjects' scores on the MMPI were significantly correlated with their subjective reports of cycle-related pain, behaviour change, negative affect, and autonomic reactions.

This literature then, has centered upon the association between affective disorders and PMS, and neurosis and PMS. The reason for this association lies in the fact that symptoms such as irritability, depression, tension, and swelling, are both premenstrual phenomena and are also significantly correlated with neuroticism. Yet this association is by no means absolute. Golub (1976) could find no significant correlation between anxiety, a relatively stable baseline personality characteristic, and premenstrual anxiety or depression. Similarly, Rees (1953) also noted the presence of PMS in women with little or no evidence of instability in

personality adjustment or neurosis, or in women with a predisposition to neurosis. Furthermore, he also found many women with severe neurosis who did not actually experience PMS.

Thus it appears there is no simple relationship between PMS and personality in general, and neurosis in particular. The literature so far has had several crucial methodological flaws. Firstly there appears to be no uniform standardized definition of "neurosis" and thus there is no way of measuring how it was assessed, or the way in which the presence or absence of premenstrual symptoms were established. Secondly, regarding psychiatric ill-health, there are few, if any, details provided of how the clinical diagnosis was made. Thirdly, there appears to be confusion between menstrual and premenstrual symptomatology, although Coppen and Kessel (1963) claimed menstrual pain was not associated with neuroticism but premenstrual pain was. Fourthly, the range of premenstrual symptoms assessed were too limited and narrow. For example, the only psychological symptoms generally enquired about were irritability, depression, anxiety, and nervous tension. The only somatic complaints were headaches and swelling. No assessment was made of complaints such as food cravings, poor cognitive functioning, and poor coordination to name a few. Fifthly, there also appears to be sampling flaws in some of these studies. For example, Coppen's findings were based upon a sample of only 49 women and his controls used were matched for age and parity but not social class. Similarly, this sample consisted of both in-patients and out-patients but no mention is made of whether the patient's admission status affected the significance of the results. Reliable

conclusions regarding personality and PMS therefore require both a knowledge of the presence of menstrual and premenstrual symptoms, and the correlation of such symptoms with personality type in a sample derived from the general population.

In a noteworthy study Taylor (1979), using the Eysenck Personality Inventory, Cattell's 16 Personality Factor questionnaire, and a daily symptom rating scale, found that there was a strong association between neuroticism and high levels of premenstrual symptoms. He also proposed a personality profile of high premenstrual complaint scorers, and although this research also has its methodological problems, it represents a more thorough attempt to clarify the relationship between personality and PMS.

On the basis of this literature then, it is difficult to assess whether personality traits in general, and neurotic traits in particular covary with the cyclical occurrence of premenstrual symptoms. The personality of the women may indeed be an important factor and personality instability may act as an intervening variable between severe neurosis and PMS. It is possible that there may be an etiologic factor common to both. However, it is also possible that this apparent association may be due to the same symptoms being common to both premenstrual and neurotic disorders. This could then have resulted in an artificially inflated pattern of correlations.

2-2-3: Social-Expectation Theories of PMS.

In recent times there has been a shift in emphasis away from the personality theories of PMS to focus on the extent to

which PMS is mediated by beliefs and attitudes about menstruation and a woman's perception of the menstrual cycle. Within a social-learning framework, both the premenstrual phase and menstruation are viewed by many cultures as a negative and often debilitating emotional and physical event. Proponents of these theories postulate then, that social factors such as emotional conditioning, cultural beliefs and stereotypes may aggravate the severity of the premenstrual symptoms, thereby exacerbating the experience of the syndrome.

Yet research on the influence of such attitudes and beliefs on PMS is actually sparse. Paulson (1961), using a 180-item Menstrual Attitude Inventory, noted that many women with severe PMS also had mothers who experienced PMS and dysmenorrhea, and concluded from this that it may well be possible for attitudes about menstruation to be transmitted from one generation to the next. He also reported a significant correlation between attitudes towards menstruation and the degree of symptoms reported. The greater the severity, the greater the negative attitudes towards menses. Parlee (1974) found that both male and female subjects attributed negative emotions in premenstrual women to the phase of the cycle, whereas any positive emotions were attributed to situational factors. Kelley's covariation principle proposes that symptoms that covary with a particular cycle phase will tend to be attributed to that phase, especially if they do not covary with other plausible causes (Kelley 1973). Women may therefore attribute their symptoms to their menstrual cycle rather than to the situations that may have induced them. This then sets off an attribution pattern

linking their negative mood swings (for example) to the approach of menstruation (Compos & Thurow, 1978).

In order to demonstrate the sensitivity of premenstrual mood changes to expectations and beliefs, Ruble (1977) altered subjects' perceptions of their cycle phase by convincing them that they were either in their premenstrual phase (with menses due in one or two days), or in their intermenstrual phase (with menses due in seven to ten days). By rating the extent to which they had experienced any menstrual symptoms in the last day or two, those assigned to the premenstrual group reported significantly higher symptom ratings for water retention, pain, change in eating habits, and sexual arousal than those assigned to the intermenstrual phase. However, there was no significant difference between the groups for negative affect. From this Ruble concluded that learned associations or beliefs may lead a women to exaggerate what she is actually experiencing or to be more sensitive to naturally fluctuating bodily states (such as water retention and weight change) when she believes she is premenstrual.

Yet this literature has so far also been beset with methodological issues that cast some doubt on the strength of these conclusions. For example, Paulson's Attitude Inventory was utilized by few researchers, and never submitted to rigorous testing (Paulson, 1961). Its validity therefore has not been established. Similarly, while limited support was found for the covariation principle (Compos & Thurow, 1978), it did not hold for the symptoms of depression, irritability, and tension. For covariation to be perceived then, there must be some cue that distinguishes between the cycle phases, and that these symptoms can frequently occur during other phases

of the cycle, could have resulted in them not actually being perceived as covarying with any one particular phase in the cycle. Furthermore, all were based upon data obtained retrospectively through questionnaires and self reports. Thus, women with no or minimal symptoms may have exaggerated when reporting retrospectively, and similarly, women who were unaware of the temporal relationship between their affective and somatic fluctuations and their menstrual cycle may have underestimated them, or not reported them at all. However, while awareness of a particular phase of the menstrual cycle may alter a woman's perception of, or sensitivity to, PMS, it has already been established that retrospective reports of menstrual mood variations often fail to match actual prospective reports of mood at different times during the cycle (Abplanalp et al., 1979; May, 1976; Swandby, 1979).

The effects of placebo treatments on premenstrual symptoms in prospective studies are perhaps one of more sound methods of assessing the role of psychosocial factors in PMS. Marked placebo effects have been noted, especially in relation to premenstrual irritability, and depression (Cullberg, 1972; Goldzieher, Moses, Averkin, Scheel, & Taber, 1971). Metcalf and Hudson (1985) noted a significant placebo response for mood related PMS only in eight out of thirty one women who were observed for six menstrual cycles. However, they also noted that there were 13 women who experienced premenstrual symptoms in every cycle, and a total of 21 who had PMS in five of the six cycles and were thus placebo resistant. Given such a finding, it cannot be concluded that psycho-social factors such as expectation, cultural beliefs, and stereotypes alone are responsible for the manifestation of premenstrual

symptoms, although it does lend support to the earlier reports that their interpretation and expression are sensitive to such factors.

2-2-4: Conclusions.

In spite of the methodological problems that have hampered the research on the psychological theories of PMS, there can be little doubt that both personality and psychosocial factors are implicated in its etiology. However, as yet, there is no conclusive evidence to suggest that these factors alone are responsible for the condition.

2-3: BIOCHEMICAL THEORIES OF PMS.

These theories relate premenstrual symptoms to a set of covarying biochemical imbalances, deficiencies, or fluctuations.

2-3-1: Estrogen/Progesterone Theories.

Estrogen and progesterone regulate the menstrual cycle and, since the symptoms are so closely related to this cycle, the role of these two hormones in the etiology of PMS has often been addressed (Abraham, 1980, a; Dalton, 1959; Frank, 1931; Morton, 1950). Indeed, Frank (1931) first proposed that PMS was the result of excessive estrogen levels in the blood. Since then theories have hypothesized 1: an estrogen: progesterone ratio imbalance, 2: an excessive and/or deficient production of one or both hormones, 3: an abnormal sensitivity to estrogen and 4: a response to the withdrawal from either estrogen or progesterone as possible causes of the

premenstrual symptoms.

2-3-1-A: Progesterone Therapy for PMS.

The rationale for the use of progesterone in the treatment of PMS was first advocated by Israel (1938) who postulated that premenstrual symptoms were caused by the defective functioning of the corpus luteum, resulting in a progesterone deficiency. Others have endorsed this idea by adding that this deficiency in turn results in estrogen being inadequately countered or opposed by progesterone. Excessive estrogen levels can cause fluid retention, and breast complaints, and the CNS effects through accumulating levels in the limbic system (Backstrom & Mattson, 1975; Israel, 1938; Morton 1950). Similarly, progesterone therapy was eagerly supported by Dalton (1977) who found lower levels of plasma progesterone during the luteal phase in PMS patients when compared to controls.

However, subsequent research has yielded inconsistent and contradictory evidence to support this premise. While Dalton's findings were supported by some (Backstrom, Wide, Sodergard, & Carstensen, 1976; Munday, Brush, & Taylor, 1981), there were also others who failed to establish superiority over placebo when treating a variety of common premenstrual symptoms with progesterone (Andersch, Abrahamsson, Wendestam, Ohman, & Hahn, 1979; Sampson, 1979; Smith, 1976; O'Brien, Selby, & Symonds, 1980), although they did note that some women with PMS had lower plasma progesterone levels compared to non-PMS patients. Similarly, many have also failed to find any evidence of deficient corpus luteum functioning (Andersch, Hahn, Andersson, & Isaaksson, 1978; Backstrom et al., 1983;

Bickers & Woods 1951; Greenblatt, 1940).

2-3-1-B: Oral Contraceptives.

Oral contraceptives have been found to significantly decrease the severity of some premenstrual symptoms (Herzberg & Coppen, 1970; Mears & Grant, 1962; Moos, 1969), thereby appearing to support the hypothesis that estrogen and progesterone levels may be implicated the etiology of PMS. However, these studies were uncontrolled, and may have actually confused premenstrual symptomatology with dysmenorrhea, a condition clearly relieved by this type of therapy (Cullberg, 1972). Cullberg (1972) identified a small group of women whose symptoms were relieved by highly progestogenic oral contraceptives, and were made worse by highly estrogenic ones. Morris and Udrey (1972) in a double blind controlled study showed no significant difference in the premenstrual symptomatology of oral contraceptive and non oral contraceptive users at all. Again little agreement regarding the effectiveness of this type of therapy on premenstrual symptoms has been reached.

2-3-1-C: Estrogen: Progesterone Ratio.

Backstrom and Carstensen (1974) noted women exhibiting premenstrual anxiety had depressed progesterone and raised estrogen luteal levels, and an estrogen: progesterone ratio level significantly elevated in the last 3-6 days of the cycle. Similarly, Abraham (1980, a) found decreased luteal estrogen: progesterone ratios in women with premenstrual anxiety, irritability, and nervous tension, but increased ratios in women with premenstrual depression. It has also been

suggested that premenstrual symptoms were provoked by progesterone withdrawal, since symptom severity peaks at a time when both estrogen and progesterone levels are falling (Greene & Dalton, 1953; Kutner & Brown, 1972), while Somerville (1972) postulated that estrogen withdrawal could be implicated in the onset of premenstrual migraines.

Yet again research findings in this area are unclear and inconclusive. During the follicular phase PMS patients are generally feeling at their best, and are symptom free. Yet estrogen levels during this phase are much higher than progesterone levels, and when they fall off rapidly at ovulation, migraines, if Somerville is correct, should also be expected to occur at this time. Similarly, while the late luteal phase estrogen: progesterone ratio may be changing and falling the premenstrual symptoms are already present and well established by the time this occurs, leaving it unlikely that PMS is due to these changing ratios alone, although it is possible that the symptoms may be aggravated by them.

2-3-2: Prolactin and PMS.

Raised levels of the pituitary hormone prolactin (PRL) has also been suggested as an etiological factor in PMS (Carroll & Steiner, 1978; Horrobin, 1973) and have been reported in PMS patients (Brush, 1977; Halbreich, Assael, Ben-David, & Bornstein, 1976; Kullander & Svanberg, 1979). Yet the treatment of premenstrual symptoms with a PRL suppressant, bromocriptine, has at best, yielded limited and indirect support for this theory.

In a double-blind trial, Benedeck-Jaszmann and

Hearn-Sturtevant (1976) demonstrated the superiority of bromocriptine over placebo in alleviating premenstrual mood disturbances, edema, breast tenderness, and weight gain, and subsequently claimed they had discovered the key to the etiology of the syndrome. However, this study was comprised of women attending an infertility clinic, and were thus hardly representative of the general population. Graham, Harding, Wise, and Berryman (1978), reported a significant improvement in affective symptoms compared with placebo, and decreased breast tenderness and weight gain, although treatment was administered during two luteal phases and data collected during the last five days of each cycle only. The report of Andersch et al. (1979) of beneficial effects from bromocriptine on premenstrual irritability and breast symptoms was confounded by the absence of a placebo trial, while Elsner, Buster, Schindler, Nessim, and Abraham (1980) found bromocriptine to be superior to placebo on only three of the eight premenstrual symptoms monitored. Similarly, Andersen et al. (1977) noted the only symptom significantly improved through this therapy was mastodynia (breast pain).

Indeed, this was the one consistent finding from all of these bromocriptine trials, in spite of their methodological problems. However, it can not be concluded from this literature that it was bromocriptine's effects on PRL levels that brought this about. For, although bromocriptine was shown to reduce PRL levels, there was no evidence to suggest that they were abnormally elevated to begin with. Recently Backstrom and Aakvaag (1981) found no PRL level difference between PMS patients and controls, nor were the levels cited by Brush (1977), Halbreich et al. 1976, or Kullander and

Svanberg (1979) outside the "normal" range.

Bromocriptine treatment then, has shed very little light on the role of PRL in the etiology of PMS, although as a dopamine agonist, its apparent therapeutic effects on mastodynia may well be mediated through direct dopaminergic action at central nervous and peripheral sites. Further research is neccessary before such a relationship can be established.

2-3-3: Nutritional Theories of PMS.

Generally it is believed that premenstrual symptoms may be the result of a deficiency in some nutrients causing a hormonal imbalance and diminished stress threshold (Abraham, 1980, a, b; Block, 1960; Nicholas, 1973; Pagani, 1952; von Klein, 1954). On the basis of this, many nutritional theories of the premenstrual syndrome have been proposed, while almost every vitamin has been recommended at some time during the past fifty years as treatment.

Abraham and Hargrove (1980), and London, Sundaram, and Goldstien (1982) found vitamin E significantly reduced mastodynia, while Nicholas (1973), and Michaelson, Juhlin, and Valquist (1977) in double blind trials, noted that vitamin A and zinc supplements alleviated premenstrual oily skin and acne. Abraham and Hargrove (1980) also postulated that a magnesium deficiency could be responsible for premenstrual anxiety, tension, and irritability. Previously Nicholas (1973) had noted a reduction in nervous tension, mastodynia, and weight gain when treating PMS patients with magnesium. However, the rationale behind this theory and treatment rests upon a tenuous link between stress, carbohydrate craving, and

a magnesium deficiency. There are also reports in the literature of success in the treatment of PMS with vitamin A (Argonz & Abinzano, 1950; Block, 1960; Michaelson et al., 1977; Nicholas, 1973; Pagani, 1952; von Klein, 1954). It was postulated by Argonz and Abinzano (1952) that deficient estrogen metabolism may be corrected by vitamin A, while Pagani (1952) thought it prevented thyroid hyperfunction. Von Klein (1954) on the other hand, postulated that vitamin A had direct anti-estrogenic and diuretic properties which thereby alleviated premenstrual symptoms.

The use of pyridoxine (vitamin B6) has probably been the most common vitamin treatment for PMS to date. Its use was first advocated because it was postulated that PMS resulted from a B-Complex deficiency causing aberrant estrogen metabolism (Biskind, Biskind, & Biskind, 1944). PMS patients were reported to respond well to vitamin B therapy, following which, estrogen levels returned to 'normal'. A second line of reasoning behind the treatment of PMS with pyridoxine came through the discovery that it acts as a coenzyme in the biosynthesis of dopamine and serotonin. These brain monoamines have been implicated in the modulating of memory, mood, behaviour, and motor coordination. Therefore a deficiency in B6 leading to a deficient biosynthesis of serotonin from tryptophan and impaired dopaminergic function, could well be an etiologic factor in the mood changes associated with PMS (Adams, Wynn, Seed, & Folkard, 1974; Andersch et al., 1978; Judd & McMurdo, 1960; Rose, 1978). Furthermore, there has been immense interest in its use, and a vast body of literature to attest to its therapeutic value. (Abraham & Hargrove, 1980; Barr, 1984; Snider & Dietman,

1974).

However, in spite of this, a large gap between theory and supporting evidence is still apparent. The magnesium deficiency and vitamin A hypotheses and treatments are, by and large, unsubstantiated, and many of these treatments, although amenable to double blind placebo trials, were not well controlled. Similarly, the vitamin B6 and B-Complex rationale was challenged as early as 1948 with the discovery of women with apparently normal estrogen metabolism yet suffered from a severe vitamin B deficiency (Zondeck & Brezezinski, 1948). In a double blind placebo controlled study, Stokes and Mendels (1972) failed to establish the superiority of vitamin B6 over placebo in relieving premenstrual symptoms, while subsequent studies have also failed to reveal any consistent or significant dopaminergic effects of B6 (Canales, Soria, Zarate, Mason, & Molina, 1976; DeWaal, Stevn, Harms, Slabber, & Pannell, 1978; Husami, Idriss, Jewelewicz, Ferin, & Vande-Wiele, 1978; Peters, Zimmerman, & Breckwoldt, 1978; Tolis, Laliberte, Guyda, & Naftolin, 1977).

2-3-4: Fluid Retention.

A great deal of attention has focused on the possible etiological factors of premenstrual fluid retention, and the effectiveness of diuretic treatments for symptoms related to this. However, when administered in controlled double-blind trials, diuretics have failed to significantly alter weight or total body water, thereby affording no significant relief from the symptoms (Reid & Yen, 1981). Similarly, some have failed to establish a cyclical pattern of premenstrual weight gain or

body water and sodium changes (Andersch et al., 1978; Mattson and von Schoutz, 1974), while others, with the exception of premenstrual edema, could find no significant relationship between fluid retention and the severity of the premenstrual symptoms (Appleby, 1960; Golub, Menduke, & Conley, 1965). Such studies therefore, do not support the advocacy of diuretic treatment for PMS based on the premise that fluid retention plays a major role in the manifestation of premenstrual symptoms.

2-3-5: The Renin-Angiotensin-Aldosterone (RAA) Axis.

Janowski, Berens, and Davis (1973) postulated on the basis of the relationship between body weight and negative affect, that the underlying mechanism in the etiology of PMS was the RAA axis. However, in view of the doubt in the literature reviewed here on the role of fluid retention in PMS, this has not been established with any degree of certainty.

2-3-6: Endogenous Opiates and PMS.

Recently, Reid and Yen (1981) have proposed that cyclical changes in endogenous opiate activity may be the neuroendocrine event underlying the manifestation of premenstrual symptoms. This hypothesis cites the abnormal release of, or heightened sensitivity to, the neuropeptides beta-endorphin and alpha-melanocyte stimulating hormone during the luteal phase as causing an excessive exposure to, and subsequent withdrawal from, endogenous opiate peptide (EOP) activity, thereby triggering the premenstrual symptoms. Neuropeptides, by their ability to alter neurotransmitter activity, can cause mood and behaviour changes, as well as

affecting pituitary hormones such as PRL and vasopressin release.

Increased EOP activity during the luteal phase is associated with increased appetite, and the inhibition of the biogenic amine systems, thereby decreasing the release of dopamine or norepinephrine, and causing fatigue and depression. Raised EOP levels are also thought to inhibit prostaglandin-E1 (PG-E1) in the bowel, and decrease muscular propulsive activity, causing constipation and fluid retention. Acute withdrawal from EOP activity, and the return to normal neurotransmission of the biogenic-amine systems is hypothesized to occur during the late luteal phase, and coupled with the possibility of a slowly acquired sensitivity to this normal neurotransmission, results in rebound hyperactivity, leading to premenstrual anxiety, irritability, and aggression. Increased PG-E1 activity following this withdrawal results in premenstrual diarrhea. Furthermore, variations in the degree or duration of this EOP exposure, and the rapidity of withdrawal are thought to account for differences in the severity of PMS from one month to the next (Reid & Yen, 1981; 1983).

As evidence for this position Reid and Yen (1983) draw parrallels between premenstrual symptoms and those commonly evoked by exogenous opiate exposure and wthdrawal. Constipation and diarrhea are common features of opiate exposure and withdrawal (Coupar 1978), as is dopaminergic hyperfunction and the resulting hostile and irritable behaviour (Gianutsos & Lal, 1978; Reid & Yen, 1981; Schwartz, Pollard, Llorens et al., 1978). Furthermore, the decreased neurotransmission by biogenic amines is also implicated in

depression (Adolphe, Dorsey, & Napoliello, 1977; Van Praag, 1978). Further support is provided by research into the effects of the opiate receptor antagonist naloxone. By blocking endogenous opiate peptides, this drug can produce premenstrual type symptoms (Cohen et al., 1981; Quigley & Yen, 1980). However, apart from Peck's study (1982), no confirmation has been provided for these comparisons and conclusions, and evidence of aberant neuropeptide activity in PMS patients and its underlying mechanisms is yet to be demonstrated. Yet it is nevertheless, a plausible theory, and should not at this stage be discounted since further naloxone studies may provide the necessary empirical evidence.

2-3-7: Summary.

Again, given the methodological problems already addressed it is no surprise that the literature on these biochemical theories of PMS is also in a state of disarray and confusion. These issues have diminished the strength of the etiological conclusions derived from the treatment literature, and to date, none of these treatments or theories have withstood double blind trials.

CHAPTER THREE: PREMENSTRUAL SYNDROME AND HYSTERECTOMY.

3-1: PMS AND ANOVULATION.

A finely integrated pattern of hormone secretions from the ovary and hypothalamic-pituitary systems is necessary for regular ovulation. As has already been mentioned, the ovary controls the timing of the cycle, and appears largely to be endogenously driven. However, variations altering this rhythm can spontaneously occur in a normal menstrual cycle. This most frequently occurs for example, following pregnancy, during early and late productive years, and during lactation. Ovulation can also be affected by stress, and major dietary and weight changes. Anovulation and amenorrhea can have a number of origins although it is beyond the scope of this thesis to review each possible cause. Generally, anovulation is due to acyclic gonadotrophin release resulting in the lack of corpus luteum development, and the absence of menstruation (Rebar, 1983; Schneider & Leyendecker, 1983). However, there is little evidence to suggest whether women with PMS experience their symptoms during anovular cycles, and few studies have been undertaken to investigate this.

Adamopolous, Loraine, Lunn, Coppen, and Daly (1972) in a study of 8 chronic PMS patients, observed seven anovular cycles out of fifteen, concluding that PMS could exist in the absence of ovulation. Similarly, Andersen et al. (1977) reported the presence of premenstrual complaints in two anovular control cycles. On the other hand, Backstrom et al. (1983) reported no cyclical mood changes, and only a slightly stastically significant premenstrual increase in breast

tenderness in three women over five anovular cycles. Magyar, Boyers, Marshall, and Abraham (1979), after monitoring 40 women, concluded that an indication of an ovulatory cycle were the presence of regular cycles, and consistent premenstrual symptoms.

Again the conflicting evidence can be put down to methodological issues. Adamopolous et al. (1972) estimated ovulation on the basis of pregnanediol levels, yet gave no specific criteria by which ovulation (or rather, anovulation) was determined. Nor was any mention made of whether the symptoms were prospectively recorded, and seven of the eight subjects indicated the presence of an underlying psychiatric background. Their symptoms could easily have been a function of this rather than related to the menstrual cycle. Similarly, Andersen et al. (1977) also failed to elaborate on the criteria by which ovulation was determined, nor were details supplied on the type of premenstrual complaints that were present. However, if premenstrual symptoms do in fact fail to appear during anovular cycles, then relief from the syndrome would be afforded by suppressing ovarian activity.

Studies on the effects of oral contraceptives on PMS , as has already been discussed, have yielded conflicting results. More recently however, attention has focused on the effects of antigonadotrophic agents which suppress ovarian activity. These agents act by preventing the mid-cycle LH surge, thereby preventing follicle growth and subsequent ovulation. Post ovulatory FSH levels are also inhibited, and since there was no follicular development, there is also no corpus luteum or menstruation. Day (1979) found Danazol to be effective in treating PMS, whereas Mansel, Wiseby, and Hughes (1982) found

that it was superior to placebo only in the treatment of breast tenderness. Furthermore, they could find no evidence of a temporal relationship between the symptoms and cycle phase during the administering of Danazol, and its side effects outweighed any therapeutic value it may have held. Preliminary results from the administration of Buserelin revealed that premenstrual symptoms were aggravated if initially administered during the follicular phase (Bancroft, Boyle, Davidson, Gray, & Fraser, 1984). However, its therepeutic effects were not evident until the second month of treatment, and then was only effective in controlling PMS in some women. Similarly, Muse, Cetel, Futterman, & Yen (1984) noted a marked attenuation of premenstrual symptoms with the administration of a GnRH agonist. After one month, both physical and affective symptoms had decreased in severity to follicular phase levels.

Research into the effects of naturally occurring and medically induced anovulation on PMS is, at present, in its early stages, and is marked by a lack of clear evidence one way or the other. With regards to naturally occurring anovulation, such research is hampered by the necessity to establish the mechanisms leading to its absence. Furthermore, it is important that these be considered when deriving conclusions about the hormonal fluctuations and apparently covarying premenstrual symptoms during these anovular cycles, since it is possible that these symptoms may in fact be a function of the mechanisms underlying the anovulation itself. However, by medically inducing anovulation in normally menstruating PMS patients and controls, the clinician will be able to control the ovarian cycle, and then evaluate in a

placebo-controlled fashion, both the effects of this anovulation, and the effects of exogenously administered steroids (such as estrogen), on the premenstrual symptoms. Such a technique may be of great practical interest to all concerned with menstrual research, and if pursued, may provide valuable information on the etiology of PMS whatever the outcome.

3-2: PMS AND HYSTERECTOMY.

The literature has so far suggested that the presence of ovarian activity, the corpus luteum, and accompanying hormonal events are all implicated in the etiology of PMS. As well as this, psychological factors such as personality, cultural beliefs, and expectations about menstruation can influence a woman's interpretation and reporting of her symptoms. In an attempt to control for the expectation effects regarding awareness of cycle phase and approaching menstruation, and to gain further evidence of the role of ovarian steroids in PMS, attention has recently focused upon the presence and/or persistence of premenstrual symptoms in women who have undergone a simple hysterectomy, whose ovaries have remained intact.

Beumont, Richards, and Gelder (1975) in a study of seven hysterectomized women, found no significant differences in symptoms between two phases of the menstrual cycle, although they showed evidence of ovarian function. However, while data was collected prospectively, this was only done so for approximately thirtyfive days. This barely covers one menstrual cycle, hardly providing adequate information about

the persistent cyclical mood and somatic changes that constitute PMS. Similarly, no mention was made of whether these women had ever experienced cyclical premenstrual changes prior to their hysterectomy. If they had not, there was no reason to expect that they would do so after hysterectomy. If however, they had retrospectively reported having experienced PMS prior to their hysterectomy, these negative results could have been due to the well documented inadequacies of retrospectively selected subjects. No firm conclusions about the role of expectation, or hormonal influences in the etiology of PMS can therefore be drawn from this research. Nor on the basis of these findings, can one speculate on the existence of premenstrual symptoms post hysterectomy.

Backstrom, Boyle, and Baird (1981) studied seven women who had been prospectively diagnosed as experiencing PMS and who had then undergone a hysterectomy. Daily records of moods and physical symptoms were recorded, and ovulation was indicated from the change in excretion of pregnanediol and total estrogen. They noted the persistence of the cyclical affective and physical symptoms of PMS in the presence of ovarian function in these women. The presence of these symptoms, although less severe than prior to their hysterectomy (but not significantly so), led Backstrom et al. (1981) to conclude that the presence of the uterus was neither necessary for ovulation, nor for the formation or regression of the corpus luteum.

However, like Beumont et al. (1975), these findings must be interpreted in the light of several methodological considerations. Firstly, diagnosis prior to hysterectomy was, with the exception of one subject for whom a menstrual history

was available, made on the basis of data obtained from one cycle only. While it was fortunate that all of these subjects ovulated during that cycle, their ages ranged from thirty to fortynine years. Some of these subjects were therefore in an age group where, approaching menopause, anovular cycles are common. Secondly, after the hysterectomy, data was collected over two cycles for four subjects, and over only one cycle for the remaining three subjects, making a total collection period of two to three cycles for the entire study. This is hardly sufficient time to assess a) the existence of cyclical premenstrual symptoms prior to the hysterectomy, and b) their persistence (and any changes in severity etc.) post hysterectomy. Thirdly, the collection of the hysterectomy data began immediately after surgery, allowing little time for recovery from any post operative trauma. Similarly, relief from fibromyoma and menorrhagia afforded by the surgery could well have resulted in the subjects being better able to tolerate their premenstrual symptoms, which could account for reported changes in symptom severity.

3-3: OVARIAN FUNCTION POST HYSTERECTOMY.

The continued functioning of the ovaries after hysterectomy has now become an important concern to those who, like Backstrom et al. (1981) and Beumont et al.(1975), take the study of the premenstrual syndrome into this realm. Similarly, the prediction of cycle phase in the absence of menstrual markers is also crucial in this area of research.

It has been demonstrated that the uterus plays an important role in the functioning of the corpus luteum in some

non-human species (Anderson, Bland, & Melampy, 1969; Fischer, 1967; Neill, Johansson, & Knobi, 1969), and it is postulated that such functioning is due to the secretion by the uterus of luteolysin. (Anderson, Neal, & Melampy, 1962; Gardner, First, & Casida, 1963; Hansel, 1966; Short, 1964). Although hysterectomy is known to prolong the luteal function in guinea pigs (Loeb, 1927), pigs (Duncan, Bowerman, Anderson, Heam, & Melampy, 1960), and cows (Wiltbank & Casida, 1956), its effects upon the quality of continuing ovarian function in humans, where it exists, has been the subject of much debate.

Stone, Dickey, and Mickal (1975) examined the immediate effect of abdominal and vaginal hysterectomy on estradiol-17-beta (E2) and progesterone levels, noting a drop in circulating steroids on the second post operative day. They found that all those whose hysterectomy had been performed during the follicular phase of the cycle exhibited no significant variation in progesterone levels, while all those performed during the luteal phase exhibited a significant and persistent decrease. Furthermore, the E2 levels of both the follicular and luteal phase patients were significantly lower than the preoperative levels, although there was no change in LH and FSH levels. The control group, (women who had undergone a routine laparoscopy), exhibited no significant variation or changes in E2, progesterone, LH, or FSH levels other than those fluctuations observed during normal menstrual cycles, thereby eliminating the possibility of the changes observed in the hysterectomy patients being a function of surgical technique and/or the anaesthetic employed. However, similar studies have yielded contradictory results. Neither Doyle, Barclay, Duncan, and Kirton (1971),

nor Beling, Marcus, and Markham (1970) found hysterectomy performed during the early luteal phase prolonged the functioning of the corpus luteum, while Andreoli (1965) noted that it was not effected by hysterectomy performed on the twentyfourth day of the cycle (i.e. during the late luteal phase), but was prolonged when performed on the seventeenth to the nineteenth day of the cycle (i.e. during the mid luteal phase). It is possible then that the timing of the operation is important for hysterectomy to have an immediate effect on corpus luteum function, and that that effect is only apparent during the cycle in which the operation is performed, since normal cyclical ovarian function was subsequently observed by these researchers. (Stone et al., 1975; Doyle et al., 1976; Beling et al., 1970; Andreoli 1965).

Backstrom, Smith, Lothian, and Baird (1985) compared the post hysterectomy steroid levels in women with and without PMS (who acted as controls) noting that follicular development and ovulation resumed less quickly in the PMS women. Furthermore, their FSH levels were significantly lower than those of the controls in the late follicular phase, although there was no difference in estrogen levels during this phase. However, Backstrom et al. (1985) did not carry this study on beyond the first postoperative cycle. The permanency of such differences between the PMS group and controls then, cannot be ascertained. Similarly, it can only be inferred from this study that follicular development and ovulation occurred more quickly in the non-PMS control group, although no mention is made of whether this was significntly different in any way to follicular development either prior to their hysterectomy, or in normal women. Corson, Levinson, Batzer, and Otis (1981)

found no statistical differences in E2 and progesterone values between hysterectomized women and normal controls (i.e. women who have not undergone hysterectomy, and who ovulate and menstruate regularly). Similarly, continuing ovarian function was demonstrated in 80% of the subjects of Ellsworth, Allen, and Nisker (1983), in 64% of the sample of de Neef and Hollenbeck (1966), while Kaiser, Geiger, and Kunzig (1979) also found evidence of normal ovulatory cycles in 70% of their hysterectomy subjects. A difference in the incidence of normal ovulatory cycles between women with one or two remaining ovaries has also been suggested and reported (Beavis, Brown, & Smith, 1969; Leverton, 1958), although de Neef and Hollenbeck (1966) failed to find any such differences. Beavis et al. did report however, that one remaining ovary may function less efficiently than two with increasing age.

Furthermore, there is little evidence in the literature to suggest that hysterectomy with ovarian tissue remaining intact hastens the onset of menopause. Whitelaw (1958) found evidence of estrogenic activity in hysterectomized women (comparable to age-matched normal women) up to six years after hysterectomy had been performed, thereby suggesting that the ovaries may continue to function for a considerable amount of time after the operation. Leverton (1958) found evidence of ovarian function as long as seven years after hysterectomy, while Beavis et al. (1969) observed that 75% of their sample ovulated regularly with normal cycle lengths for between one and thirteen years after hysterectomy. Likewise, of the total sample hysterectomized women studied by Bancroft-Livingston (1954), 95% exhibited active vaginal smears (reflecting

ovulation) less than three years after hysterectomy, and 60% continued to exhibit active smears more than five years after the operation. These figures were also found to be comparable to a matched control group of normal women. Whitelaw also noted that only 30% of his subjects over the age of fortyfive years with ovarian tissue intact exhibited menopausal symptoms, and that those subjects who did exhibit signs of decreased estrogenic activity were of an age when the onset of menopause was expected. Similarly, Bancroft-Livingston found that ovulation occurred less frequently in hysterectomized women with advancing age, but comparisons with age-matched normal women yielded no significant differences between the two groups.

The literature then has, by and large, failed to reveal any long term effects of hysterectomy on the quality of the functioning of the remaining ovaries. The immediate effects on E2 and progesterone levels noted by Stone et al. (1975) appear to be temporary and confined to the operative cycle, with normal ovarian function resuming fairly quickly for most women and continuing until the expected time of menopause.

3-4: METHODS OF DETECTING OVARIAN FUNCTION.

Methods of detecting ovarian function have included monitoring basal body temperature (BBT) for the post ovulation increase (Corson et al., 1981; Kaiser et al., 1979; Whitelaw, 1958), gonadotrophin and estrogen activity from vaginal smears (de Neef & Hollenbeck, 1966; Whitelaw, 1958), and menopausal symptomatology (de Neef & Hollenbeck, 1966; Whitelaw, 1958). The more accurate and frequently used indices of ovarian

activity however, are the measurement of plasma and urinary hormone levels (Backstrom et al., 1981; Beling et al., 1970; Beumont et al., 1975; Corson et al., 1981; Doyle et al., 1976; Ellsworth et al., 1983; Kaiser et al., 1978, 1979; Metcalf, Evans & Mackenzie, 1984; Stone et al., 1975). Since regular venepuncture is both painful and distressing and twelve hour urine samples inconvenient, Metcalf (1973) demonstrated that the measurement of the pregnanediol:creatinine ratio in small samples of urine provided the clinician with the same information about ovarian activity as did the individual measurement of changes in other plasma and urinary hormone levels. Thus, less frequent samples are adequate to assess ovarian function, making the participation in longitudinal menstrual research less demanding. It must be noted however, that these assessments of ovarian activity only indicate that ovulation may have occurred. For absolute proof of ovulation, pregnancy or the removal of the mature oocyte must first occur.

The precise day of ovulation, or the expected day of menstruation have not been specifically addressed in the literature assessing ovarian activity after hysterectomy, thereby implying that they are not neccessary to such assessment. Yet while this may be so, the accurate prediction of cycle phase (including the expected day of menstruation) is crucial to long term research on PMS after hysterectomy. It is extrtemely important to be able to distinguish clearly and accurately between the phases of the menstrual cycle in order for the cyclicity of the physical and affective symptoms of PMS to be established in the absence of menstrual markers. However, although Backstrom et al., 1981, and Beumont et al.,

1975 attempt to identify the day of ovulation, neither adequately address these issues. Both derived the cycle phases from their predictions of the day of ovulation, and the days of the studies were numbered using the day that hysterectomy was performed as the reference point. Beumont et al. predicted ovulation as occurring on the day LH levels peaked, whereas Backstrom et al. predicted it occurred on the day of the LH surge also, or on the day between the estrogen peak and the rise in pregnanediol. Backstrom et al. used pregnanediol levels as reference points for the end of the luteal phase, although no specific attention was paid by either Backstrom et al. or Beumont et al. to specifying the expected day of menstruation. Their methods of predicting the phases of the cycle could therefore be subject to considerable error. Given that samples were collected twice weekly by Backstrom et al. and three times a week by Beumont et al., the days of LH, FSH, estrogen, and progesterone fluctuations may have occurred in between these collections. Predictions of the day of ovulation and the end of the luteal phase need only be slightly inaccurate for the corresponding assessment of tne cyclicity of the premenstrual symptoms to also become inaccurate.

It seems then, that this area of premenstrual research, like others, is not without its problems, and as yet, there is no clear evidence supporting the findings of either Beumont et al. (1975) or Backstrom et al. (1981).

SECTION TWO: THE STUDY.

CHAPTER FOUR: METHODOLOGY.

4-1: AIMS.

In the light of the contradictory findings of Beaumont et al. (1975) and Backstrom et al. (1981) reviewed here in Section One, chapter 3-2, this experiment aimed to retrospectively recruit a sample of women, who having undergone hysterectomy and having at least one ovary intact, believed they still continued to experience premenstrual symptoms. The purpose of this was to prospectively collect mood, physical symptom, and ovarian data from these women over a period sufficient in length to enable the use of spectral analysis, a statistical technique of particular relevance in the context of PMS research, and the assessment of ovarian function.

The specific aim of this study was to firstly establish the existence of ovarian activity in the subjects, and to secondly assess whether they exhibited significantly cycling affective and/or somatic symptoms, and to then establish whether these cycling mood and physical symptoms were significantly related to the premenstrual phase of their menstrual cycle.

4-2: INSTRUMENTS.

Prospective daily recording of physical and affective symptoms beginning the day after the initial interview was to be

carried out by subjects each morning and was to reflect their status of the previous day. Upon its completion each daily diary was to then be sealed in an envelope. They were also required to collect a urine sample upon rising on Thursday and Monday mornings. The diaries and samples were collected on Monday, the Thursday urine sample being frozen until its collection. The necessary information and apparatus for the recording of the diaries and the collection of the urine samples was therefore provided for each participant at the commencement of the study. Consent was also obtained from each subject regarding the future use of their data at this time. The study was to initially continue for 14 weeks, thereby covering at least three menstrual cycles. At the end of 14 weeks, each subject was assessed for such things as evidence of ovulation (as indicated by the analysis of the urine samples), commitment to the study, and available time on the part of the researcher. It was then decided on the basis of these factors whether each subject continued to participate in a second 14 week phase of the study.

4-2-1: Daily Diary.

The daily diary (Appendix 7) comprised of 4 sections:

A: General information relating to name, date, and any medication being taken (including dose and time taken where applicable).

B: Eight bi-polar visual analogue scales (VAS) 100mm in length. The anchors were happy/unhappy, exhausted/full of energy, confident/not confident, very tense/calm and relaxed, friendly/hostile, very poor concentration/very good concentration, irritable/unflappable. In order to minimise

the probability of stereotypic responding, the direction of the poles was alternated for each subsequent scale. A score of 100 indicated a maximum negative mood, while the sum of the eight scales provided a daily mood score. Subjects were required to mark moods at their best, worst, and in general for each day. Clear instructions were given to place the 'general' marker between the 'best' and 'worst' marker but not necessarily at mid-point.

C: A checklist of six physical symptoms. They were breast tenderness, swelling, constipation, food cravings, headaches, and stomach cramps. Subjects responded no, mild, moderate, or severe, and were scored as 0, 1, 2, or 3 respectively. The sum of these ratings provided a daily physical symptom score.

D: An opportunity to add further comments regarding the previous day if necessary.

4-3: PROCEDURE.

4-3-1: Selection Interviews.

4-3-1-A: Initial Phone Check.

With the aid of a phone-check form (Appendix 1) all subjects were screened by telephone to gain brief details of menstrual cycles, health, age, hysterectomy, and occurrence of their premenstrual symptoms pre and post hysterectomy.

4-3-1-B: Initial Interview.

From the phone check women were then selected to be interviewed prior to the commencement of the study in order to acquire more detailed information about menstrual cycle

history, current health status, dietary and sleep patterns, and stress level. Information about gynecological history was also required, including fertility and associated problems, and methods of contraception. Subjects were also required to provide details of their hysterectomy such as dates and reasons for it. They were also asked to relate details of their premenstrual symptoms prior to and post hysterectomy. This information was collected with the aid of the initial interview form. (Appendix 2). The women were asked to describe their symptoms in detail while a 10-item observer scale was used by the interviewer to rate them. (Appendix 3). They then completed two 36-item self-rating scales, one indicating their symptoms prior to hysterectomy, and the other their symptoms since hysterectomy (Appendix 4). These scales, designed by Steiner et al. (1980), retrospectively sample the somatic and affective symptoms of the syndrome.

4-3-1-C: Mid-Study Interview.

All subjects regardless of whether they were to continue with the second phase or not were interviewed at this point. With the aid of the Mid-Study Interview form (Appendix 5), subjects were questioned regarding any changes that may have occurred in their lifestyle (such as stress levels, occupation, health, diet etc.) during the time of the study. They were also asked to indicate their stress level during this period, and the severity of their premenstrual symptoms generally and during the previous cycle. This was carried out in order to get an overall picture of each woman's lifestyle during this period.

Each subject was given the information about her ovarian

cycle length and incidence of ovulation that had been analysed from the urine samples gathered during the previous 14 weeks. For those subjects who continued on the study for a further 14 weeks, the second phase proceeded as follows: At various intervals during this phase, each was given a calendar of the following month on which the predicted dates of ovulation and menstruation were marked. The premenstrual phase was also marked on these calendars. The purpose of this excercise was to assess whether this informaton about their ovulatory cycle would have any expectancy effects on the perception of their premenstrual symptoms.

The collection of urine samples and completion of the daily diaries continued during this phase as before.

4-3-1-D: End of Study Interview.

At the end of the second phase of the study, each subject was again interviewed regarding changes in lifestyle during this phase. With the aid of the End of Study Interview form she was asked to give an indication of a) the severity of her premenstrual symptoms both during the previous cycle, and during the second phase of the study in general, b) both her current stress level and her stress level in general during that phase of the study, c) her current stress level in comparison to her stress level at the mid-study point and at the beginning of the study. Subjects were then asked to report whether they had noticed any discrepancies between the marked dates on the calendars they were sent and whether they felt that this had altered their expectations about subsequent predicted ovulation dates. (Appendix 6).

4-4: ANALYSES.

4-4-1: Statistical Analysis.

As the use of visual analysis and verbal description is of questionable validity (Sharpley 1981), one of a group of statistical techniques, namely time-series analysis, was used in this study. Spectral analysis, analysis in the frequency domain used here, has been used in the past in other contexts and disciplines, (Luce, 1970; Gottman, 1979; Jenkins & Watts, 1968), and is of particular relevance in the context of PMS research. It has two main advantages over other analyses in the time-series domain such as sample autocovariance function. Firstly interpretation is easier, and secondly the variance associated with various frequencies is of direct interest. (Hudson 1985) The Fourier Transform allows the variance at each frequency of any time-series to be calculated (at a discrete set of frequencies known as the overtone series). The spectral density function is the final product of these calculations and is a measure of the variance or power at each of the frequencies of the overtone series.

When a bivariate case is involved as with PMS research, two additional statistics can be derived: 1, Coherence, the best linear relationship between the two series at each frequency, and 2, Phase, which is a description of the temporal relationship between the two series at each frequency. At a particular frequency, if the spectral density is low, and coherence is high, the linear relationship is likely to be trivial. Phase can only be interpreted if coherence reaches significance, since the variance of phase increases dramatically as coherence approaches zero. Further,

the response time between the two series can be examined by inspecting the slope of the phase over the range of significant coherence. A negative slope indicates the two series are out of phase, with the first slope leading, while a positive slope indicates the second series leads. (Gottman, 1979).

4-4-2: Urinary Analysis.

Pregnanediol (metabolized progesterone), in urine was measured as was creatinine, a progesterone waste product. Metcalf et al. (1984) found that pregnanediol excreted in a 24 hour period was reflected in the ratio of pregnanediol to creatinine. The measurement of this ratio was therefore used as an index of ovulation. Ovulation was judged to have occurred if one urine sample yielded a pregnanediol:creatinine ratio of > or = 5 mmol, or if the sum of two consecutive samples' ratios were > or = 7 mmol. If a sample yielded a ratio of less than these limits, then it was considered to be a follicular phase sample. (Metcalf, 1979; Metcalf et al., 1984; Metcalf & Sanders, 1981.)

CHAPTER FIVE: RESULTS.

5-1: OVERVIEW.

Thirteen Pakeha women were finally selected to take part in this study. Of those who requested to take part and were not selected, reasons given were age was outside the 25-45 year range, poor health, types of medication being used (such as hormonal preparations), and the presence of symptoms such as hot flushes that were indicative of the onset of manopause. Similarly, women with current psychiatric problems or undergoing traumatic life experiences were also excluded from this study. Those selected had undergone hysterectomy and maintained they still experienced PMS. All completed the first phase of the study, and four went on to complete the second phase. Of the nine who did not continue into the second phase, five did so due to lack of time on the experimenter's part, one was about to move out of the city, and three were not accepted due to concerns about their commitment to the study, and their stress levels.

The age of these women at the time of the study ranged from 30-42 years (mean, 37.2 years; SD, 3.4). The elapsed time between hysterectomy and the commencement of the study ranged from 4 months to 6 years, 7 months (mean, 2.8 years; SD, 2.5). All thirteen women had had a vaginal hysterectomy and three had had one ovary removed, while the remaining ten had retained both ovaries. All had had children. Six women had two children, six had three, and one woman had four children. Two were on medication for asthma, while another three took daily doses of vitamin B6 and efamol. Of this

latter group, one woman agreed to discontinue this medication for the duration of the study, while the other two women taking it refused to stop. It was decided to accept them for the study on the basis of research findings failing to support the theory that vitamin B6 and efamol effectively reduce premenstrual symptoms. (Stokes & Mendels, 1972).

Eleven of the women reported they had menstruated regularly prior to hysterectomy, one reported she had never menstruated regularly, and the other reported she had menstruated regularly until she had had children. Her menstrual cycles had become irregular from then on.

5-2: INDIVIDUAL SUBJECT PROFILES: Information given at the Initial Interview.

Subject 1, aged 35 years, had had a vaginal hysterectomy four months previously to ameliorate excessive bleeding. Both ovaries remained intact. She began menstruating at the age of 11, and reported that her cycle was regular, between 27 and 32 days in length. From age 14-21 she was using the contraceptive pill to relieve dysmenhorrea. She has three children and used the rhythm method of contraception from the age of 21 until her hysterectomy. She was 1.57 metres (m) in height, and weighed 50.8 kilograms (kg). This 94% ideal body weight. (New Zealand Calorie Counter, 1987).

She reported that she was in good health, although she was taking ventolin for asthma approximately once a week. She jogs for twenty minutes daily, plays tennis twice a week, and cycles regularly. She eats three meals a day, does not smoke, and consumes little alcohol. Her stress level she described

as moderate, and she has about eight hours sleep a night.

She claims she suffered from PMS for twelve years prior to hysterectomy. Symptoms began at ovulation and would cease on menstruation. Since hysterectomy, these symptoms have continued to occur regularly, lasting approximately seven days, but are not as severe as they were prior to hysterectomy.

Subject 2, aged 40, had had a vaginal hysterectomy 3 years, 4 months previously at the age of 37. Hysterectomy was performed to ameliorate excessive bleeding, and one ovary, found to be enlarged, was removed. Menstruation began at the age of 13. This was fairly regular, with cycle length being 30-33 days. After her third child, 14 years previously she ceased using contraception as her partner had a vasectomy. Weighing 57.2 kg, and and standing 1.65m tall, she was 99% ideal body weight. She described her health as very good, in spite of taking ventolin for asthma on alternate days. She excercises frequently, jogging approximately 30 kilometres a week, eats three meals a day (mostly vegetarian), is a non-smoker, and drinks socially. She reported her stress level as being moderate, has a full time job, and sleeps well.

She claimed she experienced PMS for ten years up until her hysterectomy. The symptoms, lasting a total of seven days, began five days prior to menstruation and continued for two days during menstruation. However, since hysterectomy, she claimed she was unaware of the occurrence of these symptoms.

Subject 3 was 36 years old. She had a vaginal hysterectomy 6 years before at the age of 30 to correct a

hormonal imbalance, weight problems, and PMS. Neither of her ovaries were removed. Menarche was at the age of 12, and her cycles regular and of 28 days duration. Methods of contraception used over a six year period and in between pregnancies (and prior to hysterectomy) were the IUD, the contraceptive pill, and depo-provera. She reported her weight fluctuates between 60.7 kg and 66.5 kg, approximately 103% ideal body weight. She was 1.57 m tall. She reported she was in good health and not on any medication. She exercises occasionally, does not smoke, and eats regular meals. She drinks little, and sleeps about eight hours a night.

She described her stress level as mild, and said she experienced PMS for ten years prior to hysterectomy. These symptoms lasted for 25 of the 28 days of her cycle. Since hysterectomy, these symptoms last up to ten days during most months, and their severity has decreased.

Subject 4 was aged 38 and had had a vaginal hysterectomy 6 years, 7 months before aged 32. This was due to excessive bleeding, and it was found that her uterus was enlarged and hardened. Both ovaries remained intact. Menstruation began when she was 13, her cycles were regular, and lasted 28 days. She had two children and used the oral contraceptive pill for eleven years until she had the hysterectomy. She weighed 60 kg, 104% ideal body weight, and was 1.65m tall. She reported she eats two meals a day, choosing to miss breakfast, smokes at least one packet of cigarettes a day, and is a moderate drinker. Her stress level she felt was moderate, and she sleeps well. She was attending a fitness programme twice a week.

She has two children and reported she suffered from PMS since the birth of her second child four years prior to her hysterectomy. Since then the symptoms have continued regularly and last approximately fourteen days. She reported she was taking 200 miligrams (mg) vitamin B6 and 3000 mg efamol daily to alleviate the symptoms, which she found to be effective. She would not agree to cease taking this for the duration of the study.

Subject 5 was 37 years old. She had a vaginal hysterectomy 3 years, 11 months beforehand aged 34. She said that although she had had heavy periods, the main reason for the hysterectomy was because she suffered from PMS. Neither of her ovaries were removed. She began menstruating at the age of 12 years. Her cycles were regular and lasted 30 days. She had two children and conceived her second child with the aid of fertility drugs. She used the oral contraceptive pill and depo-provera until her partner had a vasectomy. She was 1.55m tall and weighed 62.5 kg, 118% ideal body weight. She reported that she has arthritis in her arm and took brufen daily. She also has hip problems and cannot excercise regularly. She does not smoke, she drinks socially, and and eats regular meals. At time the study began she was calorie counting in order to lose weight. She rated her stress level as severe as her marriage had recently broken up, and she was feeling the pressure of copng with a family alone. Her health problems and premenstrual symptoms also added to this strain. She sleeps lightly and for about eight hours a night.

She had suffered from PMS for seven years prior to her hysterectomy, with the symptoms lastng ten days. She felt she

still experienced these symptoms every 28-30 days, and they would last 8-10 days.

Subject 6 was 41 years old and had had a vaginal hysterectomy four months previously because of pelvic pain and excessive bleeding. One ovary was removed. Menarche was at the age of 11, and menstruation occurred regularly. She reported her cycle length was 35 days. She had two children, and except when pregnant, used the oral contraceptive pill over a ten year period. She ceased using contraception when her partner had a vasectomy seven years prior to her hysterectomy. She weighed 60 kg, 109% ideal body weight, and stood 1.60m tall. She felt her health was good. She eats three meals a day, is a non smoker, and rarely consumes alcohol. She described her stress level as between mild and moderate and gets about 7 hours sleep a night.

She reported she had experienced PMS regularly for ten to twelve days each cycle for seven years prior to hysterectomy. She felt she has continued to to experience these same symptoms of the same duration and severity since the hysterectomy.

Subject 7, aged 40, had had a vaginal hysterectomy ten months previously at the age of 39 due to excessive bleeding. One ovary was removed. She began menstruating at the age of 11, her cycles being regular and lasting about 28 days. She had two children, and used the oral contraceptive pill and depo-provera before having a tubal ligation, 11 years prior to hysterectomy. She weighed 59 kg, 104% ideal body weight, and was 1.63m tall. She reported her health to be excellent. She

eats three meals a day, mostly natural health foods, is a non smoker, a non drinker, and cycles daily. She described her stress level as mild and said she was a restless sleeper.

She had experienced PMS for about four years prior to hysterectomy, with symptoms lasting about twelve days. Since the hysterectomy she felt she still experienced these symptoms monthly although they were milder and of three to four days duration.

Subject 8 at the time of the study was 42 years old. She had a vaginal hysterectomy at the age of 36, 6 years, 6 months previously due to excessive bleeding. Neither of her ovaries were removed. Menstruation began when she was 13 years old. Her cycles were irregular, fluctuating between 10 and 24 days in length. Methods of contraception were the contraceptive pill and the IUD. She had difficulty in conceiving her third child and had a tubal ligation after that birth. She was 1.73m tall and weighed 67 kg, 107% ideal body weight. She described her health as good. She eats regular meals, does not smoke, and drinks socially. She does not excercise regularly. She rated her stress level as moderate, and generally sleeps well for about seven hours a night.

She reported she had experienced PMS for three to four days each cycle for five years prior to hysterectomy. She felt that since the hysterectomy these symptoms had continued in the same pattern as they had before. She was currently taking 200mg vitamin B6 and 3000mg efamol daily to alleviate these symptoms. She was not willing to cease doing this for the duration of the study.

Subject 9, aged 35 at the time of the study, had a vaginal hysterectomy thirteen months previously. She reported that the hysterectomy was performed for a number of reasons. She had had an embedded IUD, thrush infections, heavy bleeding, and a prolapse. Both ovaries remained intact. Menarche was at the age of 12. Her cycles were not regular until after the birth of her last child and they fluctuated between 14 and 35 days in length. She used the contraceptive pill and the IUD as methods of contraception in between four pregnancies, and up until she had the hysterectomy. She was 1.63m tall, and weighed 88.9 kg, 157% ideal body weight. She described herself as being very healthy, and feeling especially well since the hysterectomy. She eats regular meals, and tries to eat healthily. She consumes a moderate amount of alcohol, and gave up smoking just prior to the hysterectomy. She felt her stress level to be severe at the time as she and her family had recently returned to New Zealand from overseas. She felt she had been under a great deal of stress because of this.

She reported she had always had PMS before her hysterectomy with the symptoms lasting for seven days. Since then these symptoms had continued regularly, lasting five to nine days each month. She took vitamin B6 and efamol to alleviate the symptoms, but agreed to discontinue this for the duration of the study.

Subject 10, aged 38, had a vaginal hysterectomy 5 years, 8 months previously at the age of 33. Neither of her ovaries were removed, and hysterectomy was performed due to excessive bleeding. Menstruation began at the age of 13, and her cycles were regular and of 21-28 days duration. She had had three

children and one miscarriage, and had used the contraceptive pill. She described her health as good, although she did have an occasional problem with fluid retention. She took modiuretic tablets for 2-3 days every second month to alleviate this. She said she eats regular meals, does not smoke, and has the occasional drink. She was 1.57m tall, and weighed 47.5 kg, 87% ideal body weight.

She felt her stress level was mild and and reported she had experienced PMS for six years prior to hysterectomy, with the sympyoms lasting 3-4 days. For two years after the hysterectomy these symptoms ceased. They then began to recur, and she reported she had experienced them for 2-3 days each month for the past three years.

Subject 11, aged 33, had a vaginal hysterectomy 8 months prior to the study. The reason for this was excessive bleeding, and clotting. Neither of her ovaries were removed. She began menstruating when she was 13 years old. Her cycles were regular, and of 28 days duration. She had two children, one miscarriage, and a termination following an ectopic pregnancy. She had used the contraceptive pill for contraception. She reported her health was generally good, although she had had an operation on her wrist six months previously. She eats regular meals, exercises regularly, consumes little alcohol, and smokes approximately one packet of cigarettes a fortnight. She rated her stress level as moderate, and sleeps about nine hours a night. She was 1.55m tall, and weighed 60.7 kg, 115% ideal body weight.

Prior to the hysterectomy she experienced PMS every month which would last about seven days. Since then she felt this

pattern had continued unchanged.

Subject 12 was 30 years old and had had a vaginal hysterectomy 9 months previously due to acute pain, heavy bleeding and a prolapse. Both ovaries had remained intact. Menarche was at age 11, and her cycles were regular until she had children. the length then fluctuated between 21 and 30 days. She had three children and used an IUD until she had a tubal ligation five years prior to hysterectomy. She reported she was on ventolin for asthma, and has cortisone injections every six weeks in summer. She was 1.65m tall, and weighed 61 kg, 123% ideal body weight. She reported she has two meals a day, skipping breakfast, does not smoke, and drinks socially. She rated her stress level as moderate

She felt she had suffered from PMS since she began menstruating. The symptoms would last between seven and ten days, and became more severe as she got older. Since her hysterectomy she reports these symptoms have continued in the same pattern as before but they are not as severe. She also reported that following the hysterectomy she experienced severe fluid retention and hot flushes. It was thought that her ovaries had ceased to function. However these symptoms subsided quickly and had not recurred at the time of the study.

Subject 13, aged 39, had had a vaginal hysterectomy 12 months previously due to excessive bleeding. Neither of her ovareis were removed. She began menstruating at the age of 10, with cycle length being 21 days. She used depo-provera as a method of contraception, and had two children. Following the birth of her second child her cycles became extremely

irregular. She described her health as being good, and said she eats regular meals, is a non smoker, and consumes little alcohol. She was 1.68m tall, and weighed 76 kg, 124% ideal body weight.

She rated her stress level as mild and claimed she experienced PMS for five years up until the hysterectomy. The symptoms would last fourteen days. Since the hysterectomy she said the pattern of the symptoms have remained unchanged.

5-3: SPECTRAL ANALYSIS.

Results from all subjects will be presented along with spectral density analysis (Table 5-1). The spectral analysis graphs are presented in Appendices 8 and 9. .

Table 5-1: Spectral Density Analysis.

KEY.

SUBJECTS (S), SEGMENT (SEG), NUMBER OF DATA POINTS (T), BANDWIDTH (BW), MEAN SPECTRAL DENSITY AND SIGNIFICANT CYCLICITY (MSD), SUM OF PEAK (SP), PERIOD OF RANGE PEAK (PRP), DEGREES OF FREEDOM (DF), CHI SQUARED (CHI SQ), SIGNIFICANCE (SIG), MOOD/SPECTRAL DENSITY (MOOD/S), PHYSICAL SYMPTOMS/SPECTRAL DENSITY (PHYS/S), PREGNANEDIOL (P'DIOL).

S	SEG	T	BW	MSD	SP	PRP	DF	CHI SQ	SIG
1	MOOD/S	161	0.0556	17150	510300	26 20-54	18	108	.001
	P'DIOL	161	0.0556	3999	255020	26 18-81	18	144	.001
	PHYS/S	161	0.0309	2.10	64.2	29 20-54	10	60	.001
					19.9	13 9.5-13.5	10	60	.01
						27			

	P'DIOL	161	0.0309	4008	244039	18-54 13	10	70	.001
					39560	10-16 32.5	10	70	.05
2	MOOD/S	195	0.0462	3178	111276	16-& 11	18	234	.001
					39544	9.3-14 11	18	144	.001
					63779	7.2-14 28	18	252	.01
	P'DIOL	195	0.0462	1135	98465	18-196	18	198	.001
					8077	32.5	18	126	NS
	PHYS/S	195	0.0462	0.51	6.99	21.6-97 15	18	144	.005
					6.34	12-18 6.5	18	126	.005
					10.26	5-8 29.7	18	270	.005
3	MOOD/S	118	0.0420	13055	476490	17-60	10	60	.001
					79261	29.7	10	120	NS
	P'DIOL	118	0.0420	159.2	7592	13-119	10	90	.001
					863.01	29.7	10	90	.001
	PHYS/S	118	0.0420	4.86	146.07	17-119 13.3	10	70	.001
					42.1	9-145 29.7	10	60	.05
4	MOOD/S	119	0.0588	3342	47547	17-119 13.3	14	98	.001
					39351	6.6-14.8 29.7	14	154	NS
	P'DIOL	119	0.0588	1738	92011	13-119 39.7	10	70	.001
	PHYS/S	119	0.0420	4.83	142.9	19.8-119 29.7	10	60	.001
	P'DIOL	119	0.0420	1681	84054	15-59 94	10	70	.001
5	MOOD/S	188	0.0263	5893	292136	10.5-109 27	10	190	.001
	P'DIOL	188		9920	588320	21-37.8 27	10	50	.001
	PHYS/S	188	0.0476	0.53	24.33	17-108 27	18	198	.001
	P'DIOL	188	0.0476	9897		17-47 32.5	10	50	.001
6	MOOD/S	195	0.0256	13937	667570	18-65 15	10	90	.001
					111143	13-18 15	10	50	.01
					124970	13-18 32.5	10	70	NS
	P'DIOL	195	0.0256	5298	360698	21.6-65 16	10	70	.001
					98160	13-21 32.5	10	70	.001
	PHYS/S	195	0.0462	5.82	359.53	19-97 32.5	18	216	.001
	P'DIOL	195	0.0462	5297	392120	19-97	18	162	.001

						21.6			
7	MOOD/S	212	0.0231	25151	810100	15-43	10	100	.001
					134787				NS
						24			
	P'DIOL	212	0.0231	911.32	69106	18-42	10	100	.001
						24			
	PHYS/S	212	0.0417	1.31	66.1	15-108	18	252	.001
						27			
	P'DIOL	212	0.0417	906.38	72844	18-108	18	198	.001
						30			
8	MOOD/S	91	0.0549	8030	171100	15-91	10	60	.001
					49579		10	50	NS
						91			
	P'DIOL	91	0.0549	868	25172	18-91	10	50	.001
	PHYS/S	91	0.0549	1.79	11.21		10	90	NS
						16			
9	MOOD/S	129	0.0385	5106	201388	9-130	10	140	.001
					25276		10	50	NS
						32.5			
	P'DIOL	129	0.0385	1243	75053	12-130	10	100	.001
						43.3			
	PHYS/S	129	0.0385	2.29	71.5	13-130	10	100	.001
						8.6			
					40.25	5.4-13	10	150	NS
						18			
10	MOOD/S	108	0.0463	5983	61321	14-36	10	50	.001
						11			
					68899	7.7-14	10	70	.001
						27			
	P'DIOL	108	0.0463	1243	43468	16-108	10	70	.001
						18			
	PHYS/S	108	0.0463	2.29	92.37	7-108	10	160	.001
						22			
11	MOOD/S	110	0.0455	17541	329570	15-110	10	70	.001
						12			
					196990	9-15	10	60	.001
						27.4			
	P'DIOL	110	0.0455	532.4	23684	15-110	10	70	.001
						27.5			
	PHYS/S	110	0.0455	6.39	171.4	16-55	10	100	.001
						12			
					58.8	9-16	10	60	.01
					47.26			90	NS
						95			
12	MOOD/S	95	0.0526	11314	97910	23-95	4	40	.001
						14			
					180307	8-24	9	90	.001
						24			
	P'DIOL	95	0.0526	1268	51378	14-95	7	70	.001
						31.6			
	PHYS/S	95	0.0526	9.79	289.43	15-95	6	60	.001
						32			
13	MOOD/S	96	0.0521	1721	52330	12-96	10	80	.001
					116331		10	70	NS
	P'DIOL	96	0.0521	2712	5965.4				NS
						32			
	PHYS/S	96	0.0521	4.11	130.4	10-96	10	90	NS

Significance for coherence was established according to the

methods suggested by Jenkins and Watts (1968). A critical value of 0.56 was established to ensure that there was no overlap between a coherence of zero and the 95% confidence interval around this critical level. Provided coherence reached this critical value, and there were significant peaks within both of the spectral density functions, phase and slope of the phase graph could be interpreted. (Gottman, 1979; 1981).

5-4: DATA SUMMARY.

Subject 1.

Results for subject 1 shows significant cyclicity for mood, physical symptoms and pregnanediol. However when calculating the relationship between mood and pregnanediol, and physical symptoms and pregnanediol the coherence values fail to reach significance on both counts. Thus in each case no phase is able to be interpreted and no relationship between mood and pregnanediol, and physical symptoms and pregnanediol established.

Subject 2.

These results showed significant cyclicity for mood, physical symptoms and pregnanediol. Again significant coherence was not established for both the mood/pregnanediol and physical symptoms/pregnanediol relationships. In each case therefore, no significant relationship exists.

Subject 3.

Significant cyclicity for mood, physical symptoms, and pregnanediol was evident for subject 3. Coherence between the

mood/pregnanediol data was significant. Interpretation of the phase relationship reveals a 5 day lag. However it was not possible to determine a mood or pregnanediol-lead slope. Coherence between physical symptoms and pregnanediol was also established, with a 6 day lag and a slope suggesting that pregnanediol leads.

Subject 4.

Mood, physical symptoms and pregnanediol cyclicity was significant. Coherence failed to reach significance for mood and pregnanediol. However, coherence of 0.52 for the physical symptoms/pregnanediol relationship just failed to reach significance at 0.56. If this was accepted then phase interpretation suggests that pregnanediol leads by 0.5 of a day.

Subject 5.

Evidence of significant cycling mood, physical symptoms, and pregnanediol was established for subject 5. No significant coherence was established for the mood/pregnanediol relationship. Thus, phase was uninterpretable. Coherence did reach significance for the physical symptoms/pregnanediol relationship however, with a pregnanediol-lead approximately a day and a half phase shift.

Subject 6.

Results here showed significant cyclicity for mood, physical symptoms, and pregnanediol. Significant coherence was established for both the mood/pregnanediol and the physical symptoms/pregnanediol relationships. In each case a pregnanediol-lead phase lag of approximately 4 days was evident.

Subject 7.

Mood, physical symptoms, and pregnanediol cycled significantly. Coherence was just significant for the mood/pregnanediol relationship. Phase interpretation revealed a mood-lead slope with a 2.5 day lag. Physical symptoms/pregnanediol coherence was also significant with a 1-2 day phase lag. It is not clear however, whether physical symptoms or pregnanediol lead.

Subject 8.

For subject 8 evidence of significantly cycling mood and pregnanediol exist, although the cyclicity of pregnanediol seems questionable. There appears to be no real detectable cyclicity of physical symptoms. Despite this, coherence between mood and pregnanediol is significant. Phase interpretation reveals a 4 day lag although it is unclear whether mood or pregnanediol leads.

Subject 9.

Results for subject 9 reveal significant cyclicity for mood, physical symptoms, and pregnanediol. Coherence failed to reach significance for the relationship between both mood and pregnanediol, and physical symptoms and pregnanediol. No phase interpretation could therefore be calculated.

Subject 10.

Significant cyclicity for mood, physical symptoms, and pregnanediol was established, with no significant coherence noted for either the mood/pregnanediol relationship or the physical symptoms/pregnanediol relationship. Phase was therefore uninterpretable. However it is of interest to note that mood and physical symptoms were found to be cycling together.

Subject 11.

Cyclicity for mood. physical symptoms, and pregnanediol were found to be significant. However, coherence was not significant for either mood and pregnanediol, or physical symptoms and pregnanediol, and phase was not able to be interpreted.

Subject 12.

Significantly cycling mood, physical symptoms, and pregnanediol was found in subject 12. There was no evidence of significant coherence for the mood/pregnanediol nor the physical symptoms/pregnanediol relationships. Phase was therefore uninterpretable.

Subject 13.

In subject 13 significant cyclicity was established for mood, and physical symptoms only. Significant cyclicity could not be detected for pregnanediol and it was therefore impossible to estimate coherence significance.

5-5: SUMMARY.

Of the thirteen subjects, all showed evidence of significant cyclicity of mood. All but one (subject 8) had significantly cycling physical symptoms, while pregnanediol cycled significantly for all but subject 13.

A total of six subjects showed evidence of significant coherence for either the mood/pregnanediol relationship or the physical symptoms/pregnanediol relationship. The coherence for subjects 3, 6, and 7 reached significance for both mood and pregnanediol, and physical symptoms and pregnanediol.

Subjects 4 and 5 revealed significant coherence for the physical symptoms/pregnanediol relationship only, while

subject 8 revealed a significant coherence only for the mood/pregnanediol relationship. With regard to phase interpretation, of these six subjects, a pregnanediol-lead slope could be detected for subjects 4, 5, and 6, with a 0.5, 1.4, and 4 day lag respectively. Intrepretation of phase for subject 7 revealed a mood-lead mood/pregnanediol relationship, with a 2.5 day lag. It was not possible to determine which variable lead the physical symptoms/pregnanediol relationship for this subject, although there was a lag of 1-2 days. It was also not possible to determine which variable lead for subjects 3, and 8. A lag of 5 days for mood and pregnanediol, and 6 days for physical symptoms and pregnanediol was estimated for subject 3, while a lag of 4 days was estimated for subject 8.

CHAPTER SIX: DISCUSSION.

6-1: INTERPRETATION OF RESULTS.

Spectral analysis was applied to prospectively collected mood, physical symptoms, and pregnanediol data in order to determine the significance of their relationship. Six of the thirteen subjects showed evidence of significantly cycling mood and/or physical symptoms that were significantly related to the premenstrual phase of their menstrual cycle. These findings appear to be consistent with those of Backstrom et al. (1981) who also found evidence of cyclical affective and somatic symptoms in the presence of cyclic ovarian function.

Continuing ovarian function was found in all but one subject (13) thereby supporting the findings of Ellsworth et al. (1983), de Neef and Hollenbeck (1966), and Kaiser et al. (1979). Of these twelve subjects, subjects 2, 6, and 7 had only one ovary. Two of these women (subjects 6, and 7) showed significant mood and physical symptom cyclicity which significantly correlated to the premenstrual phase of their cycle. Subject 13, who failed to demonstrate any evidence of ovarian function, had reported that she had had extremely irregular menstrual periods prior to her hysterectomy, thus casting doubt on the functioning of her ovaries even then.

If PMS has an underlying hormonal substrate as is postulated in the biochemical etiological theories of the condition, then one could expect that in the six significant mood or physical symptoms/pregnanediol relationships found here, pregnanediol should be the leading variable. This is the case for three of these six subjects. For the remaining

three subjects it was not possible to determine which variable lead, although it is at least plausible that pregnanediol also leads in these cases.

With regard to the pregnanediol analysis itself, it must be noted that pregnanediol (metabolized progesterone) values are simply markers of the phases of the menstrual cycle. These values must reach a critical value before it can be concluded that ovulation has occurred, and that the hormonal events of the menstrual cycle are progressing as usual towards menstruation, whether menstruation is physically possible or not. It therefore cannot be assumed that although pregnanediol is the leading variable in these cases, that this is the underlying hormonal substrate of the syndrome. It may well be that other hormonal events that occur during this phase of the cycle are the underlying substrates of PMS.

The urinary analysis then merely measured the pregnanediol levels. It is therefore beyond the scope of this analysis to measure deficiencies or excesses of progesterone, or to examine hormonal imbalances or ratios as has been implicated in the etiology of PMS. Nor is it possible to relate this analysis to the various nutritional theories of the syndrome. It is therefore inappropriate for comment to be made regarding the biochemical etiological theories of PMS beyond saying that for at least some subjects (3, 4, 5, 6, 7, and 8) ovarian cyclicity is related to their symptoms.

For the remaining seven subjects, their affective and somatic symptoms bore no significant relationship to their menstrual cycle whatsoever. Significant cyclicity of mood was established for all seven subjects, with average cycle lengths of 26, 32, 16, 18, 12-22, 14-95, and 32 days being

noted for subjects 1, 2, 9, 10, 11, 12, and 13 respectively. Significant cyclicity of physical symptoms was also established for all of these subjects, with averege cycle lengths of 29, 32, 8-43, 18, and 12-27 days respectively. It is possible that these cyclical moods and physical symptoms could be totally unrelated to or independant of PMS. It may well be that their occurrence is related to psychological personality traits or neurotic tendancies, such as was proposed by Rees (1953), and Coppen and Kessell (1963). However, further assessment of these subjects must be conducted before any such conclusions should be made.

Similarly it seems that having been aware of their cycling affective and somatic symptoms, these women have assumed in the absence of menstrual markers that they have occurred during the premenstrual phase of their cycle. Thus attributional processes may well be implicated here. Each subject believed her symptoms occurred cyclically during the premenstrual phase of her premenstrual cycle prior to hysterectomy. When these symptoms recurred after hysterectomy, she continued to attribute their causation to the premenstrual phase of her cycle. This in turn leads one to question whether these symptoms were actually significantly related to their menstrual cycles prior to hysterectomy. As it was only possible to obtain prospective PMS data from one of the subjects in this group prior to hysterectomy, no firm conclusions can be made regarding this. For subject 10 and 13, their affective and somatic symptoms appear to be cycling together. It is therefore also possible that there may be a significant relationship between these two variables as has been found before (Hudson 1985). However, due to time

restrictions on the researcher, it was not possible to investigate this.

6-2: METHODOLOGICAL CONSIDERATIONS.

Methodological considerations for this study are as follows:

1: Subject Selection.

It is clear that this study has employed a biased sample of subjects. This study was limited to women between the age of 25 and 45, who had undergone hysterectomy, and had at least one ovary intact. This study focused specifically on evaluating the existence of PMS post hysterectomy. It has not sought to make any comparisons with or generalisations to the existence of PMS in the general population.

2: Data Collection.

A) The daily diary used in this study included 10 visual analogue scales and a six-item symptom checklist. The VAS was unmarked and the negative poles of the questions were alternated to minimise the impact of stereotypic responding.

B) The mood descriptor words on the daily diary rating scales may have forced women to rate their moods under labels that may not have been meaningful to them. However validity data suggest that this is acceptable (Hudson, 1985). Similarly, the physical symptom checklist required them to subjectively rate their symptoms as mild, moderate, or severe.

C) Subjects were required to mark moods at their best, worst, and in general for each particular day on the daily diary rating scale. Clear instructions regarding the placement of these markers were followed by all subjects and closely monitored by the researcher. In the final analysis the value

of the 'general' point only was used due to lack of time on the researcher's part. This data can be used in future research however.

D) Data for this study was collected prospectively each day and sealed in an envelope upon completion to prevent referral to it at a later time. While it could be argued that this was still retrospective given that self report is retrospective, and each daily diary recorded the previous day's events. However, this is still likely to be a more accurate indication of data than that which is collected later in time.

E) Data was collected over at least three cycles and was therefore (albeit barely) sufficient for spectral analysis to be employed. However it was very time consuming.

3: Ovarian Function.

Ovarian function was calculated from urinary pregnanediol levels. While the most accurate method of calculating this is from plasma analysis, urinary analysis is the next accurate and most convenient method (Metcalf 1973). The aim of this analysis was to calculate pregnanediol levels only. This study did not set out to test any of the etiological theories of PMS in relation to this.

4: Expectancy Effects/ Health.

A) This study attempted to exclude women who were on medication, were severely stressed, or who showed signs of poor physical and/or mental health. In this way attempts were made to minimise the effects these variables may have had on the collection of accurate premenstrual data.

B) Traditional expectancy effects were non-existent since the subjects initially lacked knowledge of their cycle phase due to the absence of menstual markers.

C) For obvious reasons this study was not beset with such problems as subjects taking oral contraceptives, or pregnancies as have beset other 'normal-subject' PMS research.

5: Retrospective Data.

Pre hysterectomy data was collected retrospectively for all but two subjects. The implication for this study is that it may have included women whose somatic and affective symptoms may not have been significantly related to their menstrual cycles prior to their hysterectomy. This could explain why seven of the subjects failed to show evidence of cyclicity of mood or physical symptoms that was significantly ralated to their cycle.

6-3: SUGGESTIONS FOR FUTURE RESEARCH.

Suggestons for future research include:

1) Analysis of the relationship between affective and somatic symptoms, irrespective of their relationship to the menstrual cycle which has not been able to be addressed in this study.

2) A prospectively conducted longitudinal study of women throughout their menstrual life would be ideal. However it is accepted that this type of study would need initially to be conducted on an immense scale, and would be fraught with difficulties. A more practical study would be one which prospectively recorded the premenstrual data of women about to undergo hysterectomy in order to initially test for the existence of significant cyclicity of affective and somatic symptoms that are significantly related to their menstrual cycle. This would mean delaying the operation in order to

achieve this. Once hysterectomy has been performed, it may then be possible to not only establish whether these symptoms continue to occur, but it may also be possible to identify two distinct subgroups from this sample: One whose affective and somatic symptoms are significantly related to their cycle in the absence of menstrual markers, and one whose mood and physical symptoms do not have any significant relationship to their cycle. These women's symptoms may be operating on the basis of a psychological marker. Retrospective comparisons could then be made between these subgroups regarding such things as symptomatology, severity, onset and duration. Comparisons could also be made between pre and post hysterectomy symptomatology.

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APPENDIX 1

NAME:

INITIAL PHONE CHECK

To identify women 25 - 45y, minus uterus, with at least 1 ovary, and in reasonable health.

Age (if not on reply form)	- How old are you?
Hysterectomy	- When?
	- For what reason?
	- Were your ovaries removed?
PMS - Pre-op	- How bad was your PMS?
	- How long did you have it?
	- When did it occur each month?
- Post-op	- How bad is your PMS now?
	- How often do you notice it?
	- How long does it last?
Health and medication	- State of health
	- Any medication? .....
	..... (give names and reasons)
	.....
Commitment	- Can you fill in a short form each day for 14 weeks and provide a urine sample x 2/week?
	- Can you forego the use of medication which might alter your moods during this time?
	- At the end of the 14 weeks we would tell you what your ovaries are doing and when you ovulate, and we would discuss with you what next to do in the PMS study.

Do you know anyone else?

For women meeting our needs:
Make an appointment to interview (allow approximately 1 hour).

Time of Interview .....
Date .....
Place .....

APPENDIX 2

PREMENSTRUAL SYNDROME : INITIAL INTERVIEW

Date.....

Full name (with title) .....

Address.....(home).....(work)

Telephone No.....(day) .....(evenings)

Age.....Date of Birth.....

Date of Hysterectomy.....

Name of Surgeon.....

Name of Hospital.....

Reasons for hysterectomy.....

Were any ovaries removed?.....

Have you had any other gynaecological surgery (give details)?

.....

.....

.....

How have you felt since the operation?.....

Menstrual cycle history

How old were you when your periods started? .....

Did they occur regularly? .....

How long were your cycles? average time .....
shortest .....
longest .....

Did you have any period pains? .....

Did you have mid-cycle pain (or discomfort)? **YES/NO**

Do you still have this pain? .....

If you do, how often do you feel it? .....

How heavy were your menstrual bleeds? .....

How long did the bleeding persist? .....

State of Health .....

.....

APPENDIX 2 (contd...)

Current drugs (medicines).....
.....

Non-gynaecological Operations (with dates).....
.....

Method of Contraception.....

If oral/injected contraceptives:-

(a) duration of treatment.....

(b) date on which it ceased.....

Reproductive History:-

Ages of children.....

Miscarriages .....

Fertility problems.....
.....
.....

Height .....

Weight .....

Diet:

(a) daily meal pattern (no. of meals/day).....

(b) food dislikes.....

(c) variability in food intake from day to day.....
.....

(d) alcohol intake .....

(e) smoking habits.....

(f) hours of sleep .....

Occupation:

(a) number of people cared for.....

(b) hours of paid employment .....

(c) extent of other time consuming occupations.....

(d) time spent on sporting activities/week (e.g. jogging etc).....

Recent changes:

(a) in residence.....

(b) in occupation.....

APPENDIX 2 (contd...)

(c) people lived with .....

(d) close friends.....

(e) responsibilities.....

Stress Level:- **MILD** **MODERATE** **SEVERE**

Premenstrual Tension

Duration (years).....

Duration each month before hysterectomy?.....

Do you get PMT now?.....

If you do, how often do you get it?.....

and how long does it last? .....

****

Specimens and records collected on .....

Arrangements for specimen collection .....

Appointment dates .....

.....

.....

Authority given to obtain surgical information .....

Enquiries to:-

Dr Glen Metcalf
Princess Margaret Hospital
Phone: 39-169 Ext 847

or Ms Lynette Bamber
Phone 884-322

or Mrs Di Skidmore
Phone 792-890/495 work
516-217 home

EVERY MORNING:

Before starting the day's activities, complete the questionnaire and seal it into the envelope provided; label the envelope with the date.

ON MONDAYS & THURSDAYS:

a. On waking, collect a urine specimen in the container provided.

b. Write your name and the date on the specimen container and the date on the urine form.
Put specimen and form together in the plastic bag, and place them in your freezer until they are collected.

ON MONDAYS:

Put the week's envelopes (containing the questionnaires) plus the 2 plastic bags (containing specimen and pathology form) in a brown paper bag; deliver the bag before 8.30 a.m. to:

.....

If you have any problems do not hesitate to phone.

APPENDIX 3 - STEINER OBSERVER RATING SCALE

RATING SCALE FOR PREMENSTRUAL TENSION SYNDROME

Name:_____ Rater: _____ Date:_____

Circle the most appropriate score for each item:

1. Irritability-Hostility (0-4)
   (Irritable, hostile, negative attitude, angry, short-fused, yelling & screaming at others)
   0. Not irritable.
   1. Doubtful, trivial. Not reported without direct questioning.
   2. Mild, Occasional outbursts of anger and hostile behaviour. Spontaneously reported.
   3. Moderate, Irritable behaviour evident. Frequent outbursts.
   4. Severe. Affects most inter-actions between patient and significant others.

2. Tension (0-4)
   (Tense, restless, jittery,upset, high-strung, unable to relax)
   0. Not tense.
   1. Doubtful, trivial.
   2. Mild. Reports occasional tension.
   3. Moderate. Tense, jittery, unable to relax. Restless behaviour evident.
   4. Severe. Constantly tense and upset.

3. Efficiency (0-4)
   (Decresed efficiency, easily fatigued)
   0. No disturbance.
   1. Doubtful, trivial.
   2. Mild. Somewhat reduced efficiency.
   3. Moderate. Easily fatigued, gets much less done than usual.
   4. Severe. Fatigue causes serious interference with functioning.

4. Dysphoria (0-4)
   (Dysphoric mood, distinguish from depression)
   0. Not dysphoric
   1. Somewhat blue, sad. Elicited only on direct questioning.
   2. Mild dysphoric and labile mood, spontaneously reported.
   3. Marked spontaneous emotional lability; occasional crying, feelings of loneliness.
   4. Severe, obvious and persistent.

5. Motor Co-ordination (0-4)
   (Clumsy, prone to accidents, lowered motor co-ordination)
   0. No disturbance.
   1. Doubtful, trivial.
   2. Mild clumsiness, feels awkward.
   3. Moderate. Frequent "accidents".
   4. Severe impairment in motor co-ordination, e.g. unable to write properly, sew, or unable to drive.

6. Mental - cognitive functioning (0-4)
   (Forgetful, poor concentration, distractable, confused, lowered judgement)
   0. No disturbance.
   1. Doubtful, trivial.
   2. Mild. Slight forgetfulness and distractability.
   3. Moderate. Performance impaired by poor concentration, cognitive disorganisation, forgetfulness, etc.
   4. Severe. Marked deterioration in cognitive capacity, poor judgement, leading to regrettable decision.

7. Eating habits (0-2)

   0. No change.
   1. Mild increase in food intake, eating at odd irregular hours, mostly snacks and sweets.
   2. Obvious, marked increase. Uncontrollable cravings for sweets, chocolate, etc.

8. Sexual drive and activity (0-2)

   0. No change.
   1. Mild but consistent increase or decrease in sexual drive, desire, libido.
   2. Marked change in sexual drive with definite change in sexual behaviour.

9. Physical symptoms (0-4)

   (Painful or tender breasts; swelling of abdomen, breasts, ankles, or fingers; water retention; weight gain; headaches, low-back pain etc.)

   0. No physical symptoms.
   1. Doubtful or trivial.
   2. Mild. Some symptoms, increased awareness of bodily changes.
   3. Moderate. Obvious changes and complaints.
   4. Severe. Physical symptoms are incapacitating. Pain and discomfort. Marked water retention and edema. Weight gain more than 5 lbs.

10. Social impairment (0-4),

    Avoidance of social activities and interactions with family, at home, at work, at school, etc.)

    0. No social impairment.
    1. Doubtful, trivial.
    2. Mild avoidance of social activity.
    3. Moderate but obvious impairment of social activity, mainly noticeable at home and with family.
    4. Severe. Marked impairment of most social interactions including at work or school. Withdrawal, isolation.

Total score .....

APPENDIX 4 - STEINER SELF RATING SCALE

SELF RATING SCALE FOR PREMENSTRUALTENSION SYNDROME

Name:..... Date:.....

Instructions: The following questions are concerned with the way you feel or act today (or the way you felt or acted during the week).

Please answer **ALL** questions by circling **YES** OR **NO** as indicated.

1. Do you find yourself avoiding some of your social commitments	YES	NO
2. Have you gained 5 or more pounds during the past week?	YES	NO
3. Is your co-ordination so poor that you are unable to use kitchen utensils, garden tools or unable to drive?	YES	NO
4. Do you feel more angry than usual?	YES	NO
5. Do you avoid family activities and prefer to be left alone?	YES	NO
6. Do you doubt your judgement or feel that you are prone to hasty decisions?	YES	NO
7. Do you feel more irritable than usual?	YES	NO
8. Is you efficiency diminished?	YES	NO
9. Do you feel tense and restless?	YES	NO
10. Do you feel a marked change in your sexual drive or desire during the last week. (If YES, is it increased or decreased?	YES	NO
11. Are your present physical symptoms causing so much pain and discomfort that you are unable to function?	YES	NO
12. Have you recently cancelled previously scheduled social activities?	YES	NO
13. Do you feel as if you were unable to relax at all?	YES	NO
14. Do you feel confused?	YES	NO
15. Do you suffer from painful or tender breasts?		
16. Do you have an increased desire for specific kinds of food(e.g. cravings for sweets, chocolate, etc.)?	YES	NO
17. Do you scream/yell at family members (friends, colleagues) more than usual? Are you "short-fused"?	YES	NO
18. Do you feel sad, gloomy, and hopeless most of the time?	YES	NO
19. Do you feel like crying?	YES	NO
20. Do you have difficulty completing your daily household/job routine?	YES	NO
21. Was there a marked change in your sexual drive with definite change in your sexual behaviour during the last week?	YES	NO
22. Do you find yourself being more forgetful than usual or unable to concentrate?	YES	NO
23. Do you happen to have more "accidents" with your daily housework/job (cut fingers, break dishes, etc)?	YES	NO
24. Have you noticed significant swelling of your breasts and/or ankles and/or bloating of your abdomen?	YES	NO
25. Does your mood change suddenly without obvious reason?	YES	NO
26. Are you easily distracted?	YES	NO
27. Do you think that your restless behaviour is noticeable by others?	YES	NO
28. Are you clumsier than usual?	YES	NO
29. Are you obviously negative and hostile towards other people?	YES	NO
30. Are you so fatigued that it interferes with your usual level of functioning?	YES	NO
31. Do you tend to eat more than usual or at odd irregular hours (sweets, snacks, etc.)	YES	NO
32. Do you become more easily fatigued than usual?	YES	NO
33. Is your handwriting different (less neat than usual)?	YES	NO
34. Do you feel jittery or upset?	YES	NO
35. Do you feel sad or blue?	YES	NO
36. Have you stopped calling or visiting some of your best friends?	YES	NO

Below are two statements concerning premenstrual tension syndrome. Please put a cross closest to the position you consider best describes your symptoms.

1. How severe were your PMT symptoms this last month?

absent_____very severe

2. How severe were your PMT symptoms over the past six months?

APPENDIX 5

PREMENSTRUAL SYNDROME: MID-STUDY INTERVIEW

Date.....

Full Name:.....

Interviewer:.....

(The interviewer should examine the information given at the first interview, the written comments on the daily diaries and the pregnanediol cyclicity before going to the interview).

The Study so far

How have you found the study?.....
.....

Questions

Since the study began, have you noticed any changes in the following (and if you have, please describe them):-

1. Your diet.....
2. Smoking habits.....
3. Alcohol intake.....
4. Hours of sleep.....
5. Daily Activities.....
6. Number of people cared for.....
7. Job.....
8. Other time consuming occupations.....
9. Residence.....
10. People lived with.....
11. Close friends.....
12. Responsibilities.....
13. Level of stress.....
14. Your PMT.....
15. General Health.....
16. Anything else.....

APPENDIX 5 (contd...)

Would you say your general level of stress during the study was:-

MILD **MODERATE** OR **SEVERE?**

Results

You ovulated ..... times during the study and are likely to do so again in about ..... days. The length of your ovarian cycle appears to be about ..... days.

Continuation of Study

Calendar

Are you willing to continue? .....

Urine Pack.

Specimens

Specimens and records to be collected from .....

by ..... each .....

Below are two questions concerning the premenstrual tension syndrome. Please put a cross closest to the position best describing your symptoms.

1. How severe was your PMT this last month?

absent very severe

---

2. How severe was your PMT in general, during the last 3 months?

absent very severe

APPENDIX 6

PREMENSTRUAL SYNDROME - END OF STUDY INTERVIEW

Date.....

Full Name:.....

Interviewer:.....

(The interviewer should examine the information given at the first interview, the written comments on the daily diaries and the pregnanediol cyclicity before going to the interview).

The study so far

How have you found the study?.....
.....

Questions

Since the study began, have you noticed any changes in the following (and if you have, please describe them):-

1. Your diet.....
2. Smoking habits.....
3. Alcohol intake.....
4. Hours of sleep.....
5. Daily activities.....
6. Number of people cared for.....
7. Job.....
8. Other time consuming occupations.....
9. Residence.....
10. People lived with.....
11. Close friends.....
12. Responsibilities.....
13. Level of stress.....
14. Your PMT.....
15. General Health.....
16. Anything else.....

APPENDIX 6 (contd....)

1. On a scale of 0 - 10, how would you rate your premenstrual symptoms:

   (a) during the last month?

   (b) during the last 3 months?

2. How would you rate your general level of stress during the last 3 months?

   mild - moderate - severe -

3. How would you rate your stress level now?

   mild - moderate - severe -

4. Would you say your stress level now was **greater/milder/the same as it was** (a) at the mid-study point?

   (b) at the beginning of the study?

APPENDIX 7

DAILY DIARY

Date ..... Name .....

Did you take any pills or medicine yesterday? .....

If you did, what was the name of the medicine (or pill)? .....

..... and the dose .....

and the times taken .....

Below are some statements concerning your feelings. Please put a cross at the position which is closest to the way you felt yesterday.

1. **How happy were you?**

happy ⊢——————————————————————————⊣ unhappy

2. **How tired did you feel?**

exhausted ⊢——————————————————————————⊣ full of energy

3. **How confident did you feel?**

confident ⊢——————————————————————————⊣ not confident

4. **How tense or worried were you?**

very tense ⊢——————————————————————————⊣ calm & relaxed

5. **How did you feel towards other people?**

friendly ⊢——————————————————————————⊣ hostile

6. **How was your ability to concentrate?**

very poor ⊢——————————————————————————⊣ very good

7. **How was your muscular co-ordination?**

very good ⊢——————————————————————————⊣ very bad

8. **How did you feel in yourself?**

irritable ⊢——————————————————————————⊣ nothing could upset me, unflappable

Some more questions. Please tick the box that applies to you.

	NO	YES		
		MILD	MOD	SEVERE
(a) Were your breasts tender yesterday?				
(b) Did you feel bloated or swollen?				
(c) Were you constipated?				
(d) Did you have any food cravings?				
(e) Did you have a headache?				
(f) Did you have stomach cramps or pain?				

Finally, is there anything else you would like to say about yesterday? Please write on the back of this form.

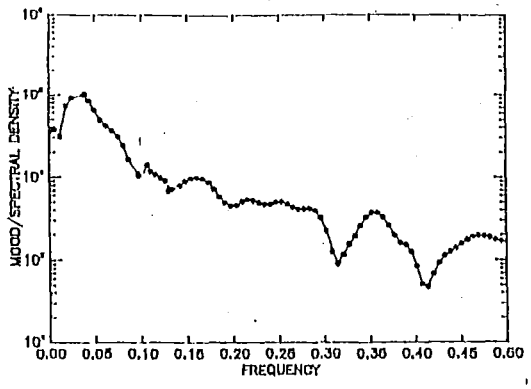
APPENDIX 8

MOOD AND PREGNANEDIOL LOG

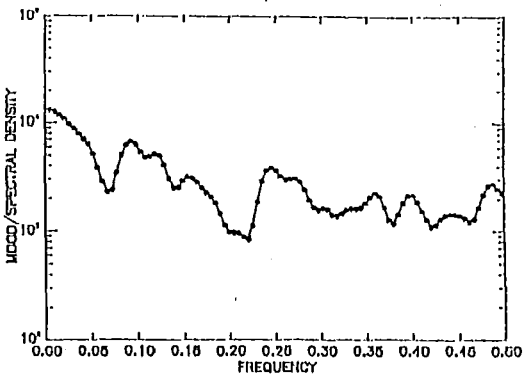
SPECTRAL DENSITY, COHERENCE AND PHASE FOR EACH SUBJECT

APPENDIX 8

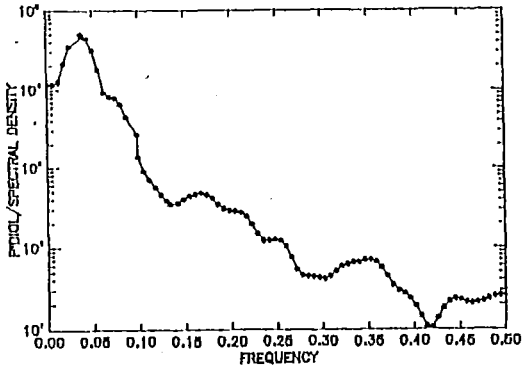
SUBJECT 1: MOOD/SPECTRAL DENSITY



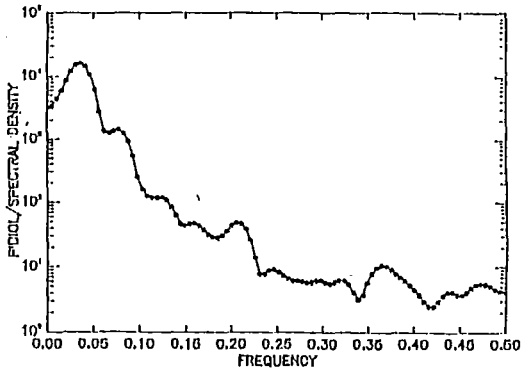
SUBJECT 2: MOOD/SPECTRAL DENSITY



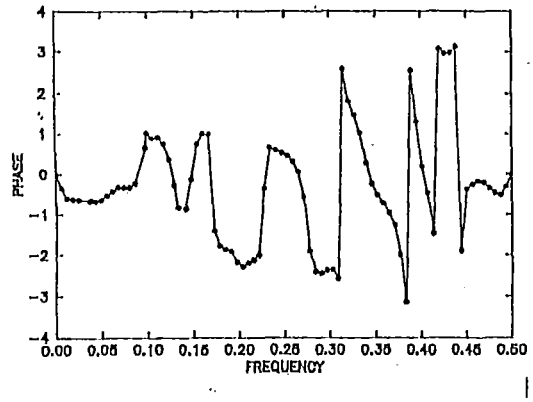
SUBJECT 1: P'DIOL/SPECTRAL DENSITY



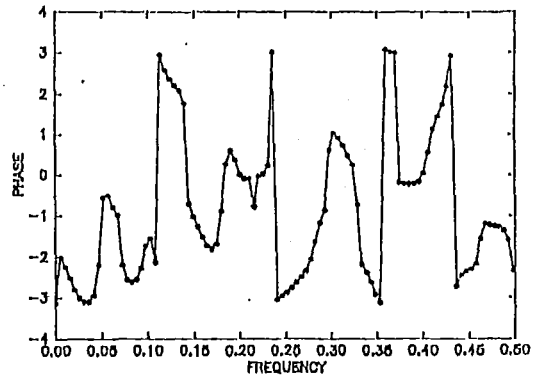
SUBJECT 2: P'DIOL/SPECTRAL DENSITY



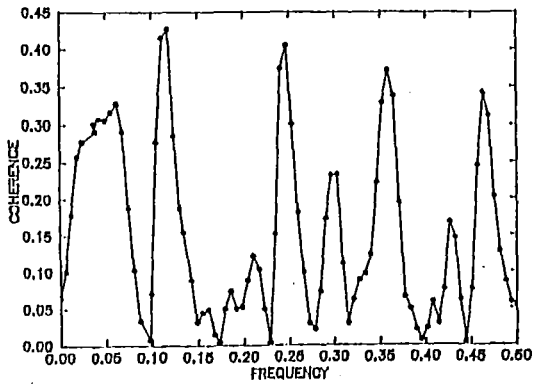
SUBJECT 1: PHASE



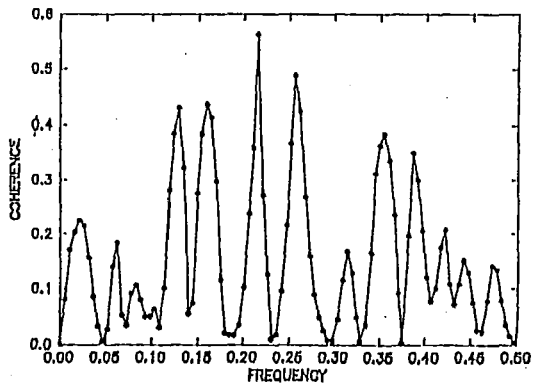
SUBJECT 2: PHASE



SUBJECT 1: COHERENCE

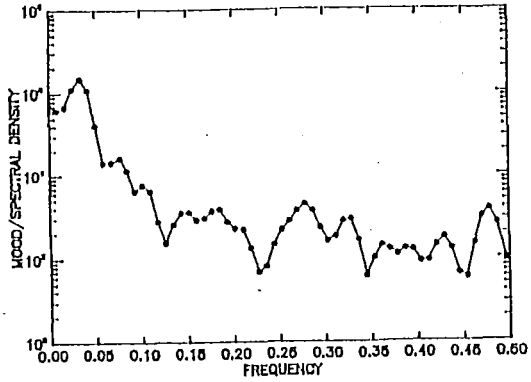


SUBJECT 2: COHERENCE

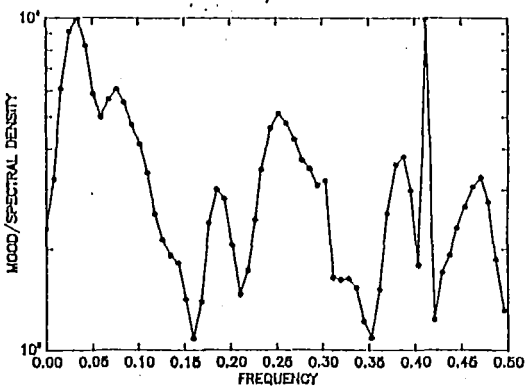


APPENDIX 8

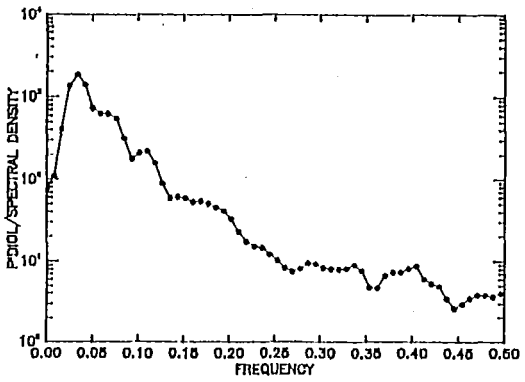
SUBJECT 3: MOOD/SPECTRAL DENSITY



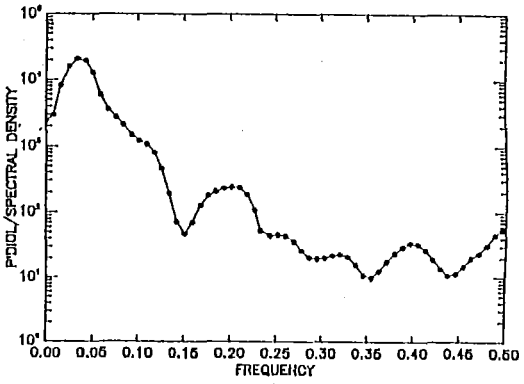
SUBJECT 4: MOOD/SPECTRAL DENSITY



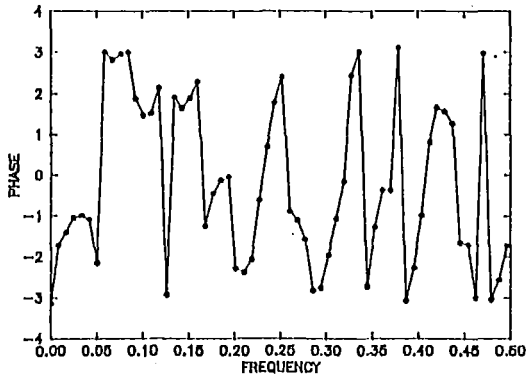
SUBJECT 3: P'DIOL/SPECTRAL DENSITY



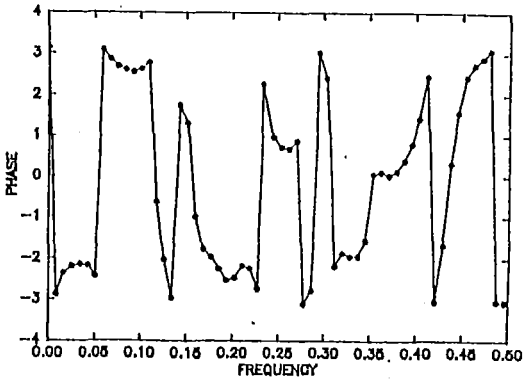
SUBJECT 4: P'DIOL/SPECTRAL DENSITY



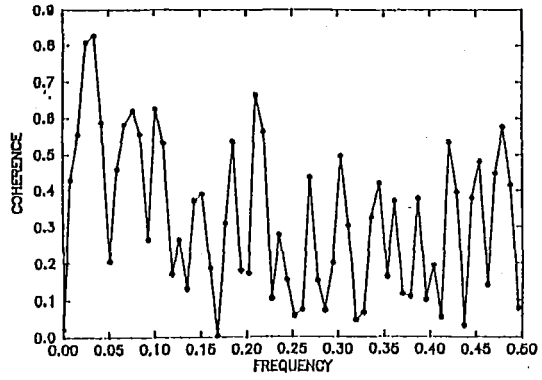
SUBJECT 3: PHASE



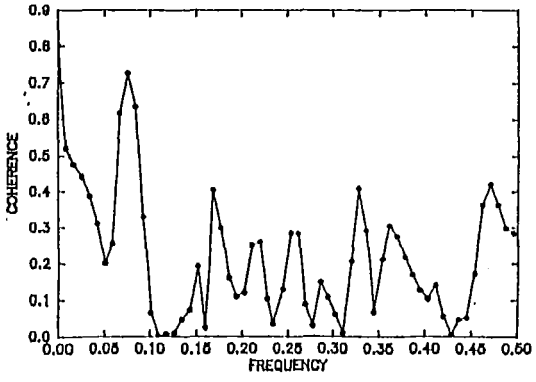
SUBJECT 4: PHASE



SUBJECT 3: COHERENCE

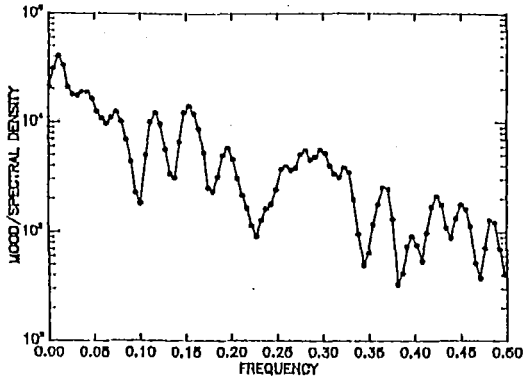


SUBJECT 4: COHERENCE

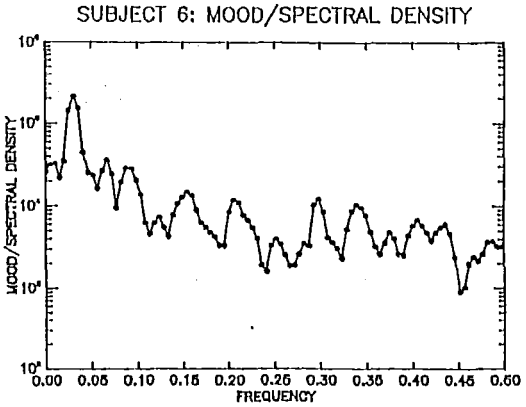


APPENDIX 8

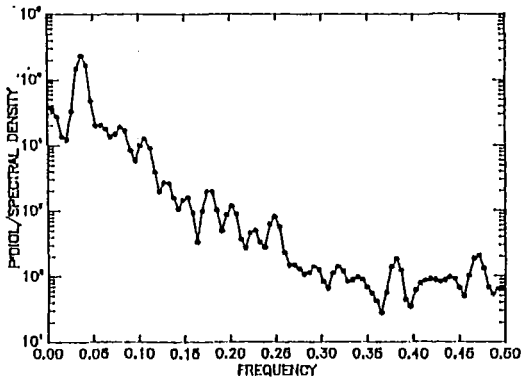
SUBJECT 5: MOOD/SPECTRAL DENSITY



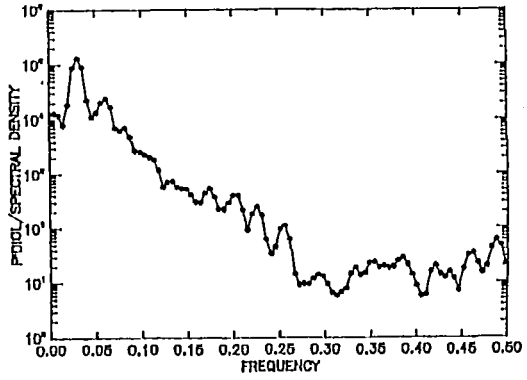
SUBJECT 6: MOOD/SPECTRAL DENSITY



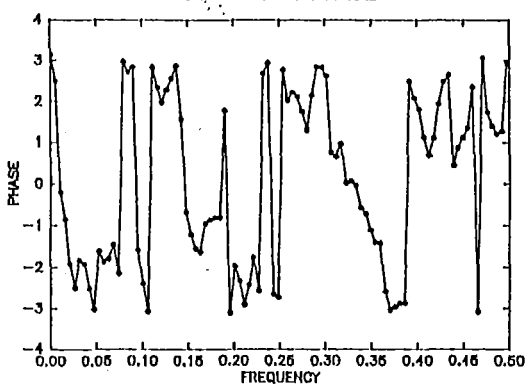
SUBJECT 5: P'DIOL/SPECTRAL DENSITY



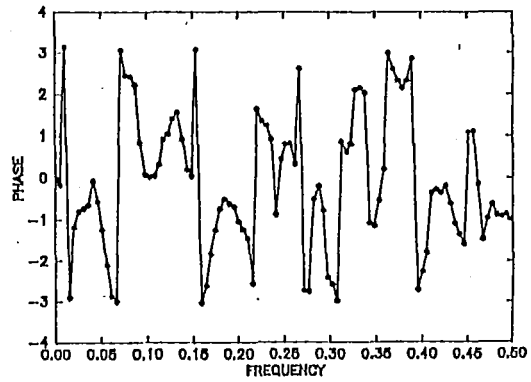
SUBJECT 6: P'DIOL/SPECTRAL DENSITY



SUBJECT 5: PHASE



SUBJECT 6: PHASE



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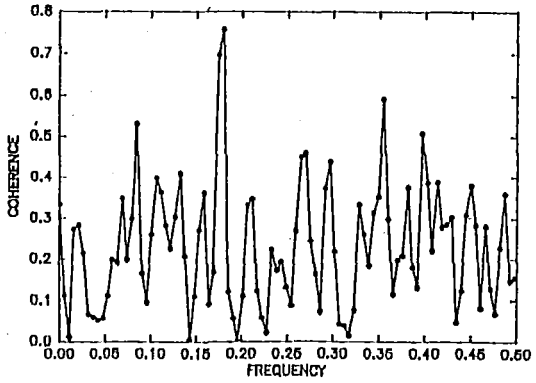

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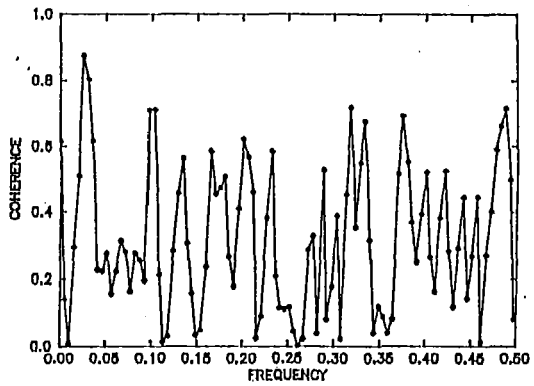
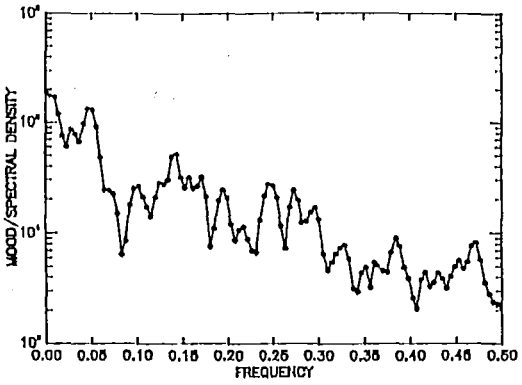
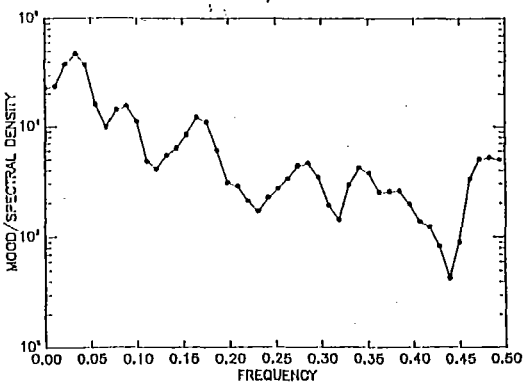


APPENDIX 8

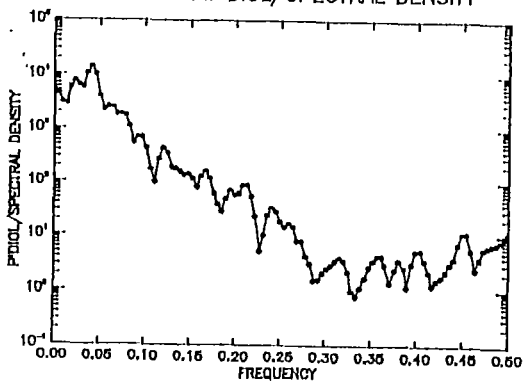
SUBJECT 7: MOOD/SPECTRAL DENSITY



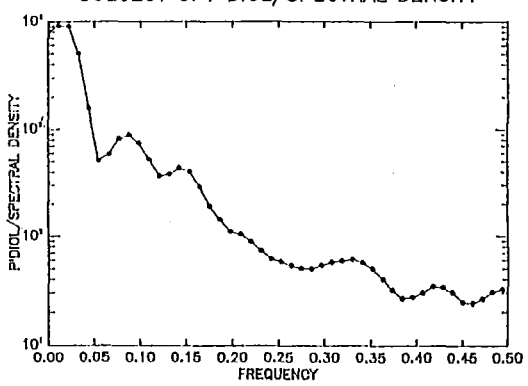
SUBJECT 8" MOOD/SPECTRAL DENSITY



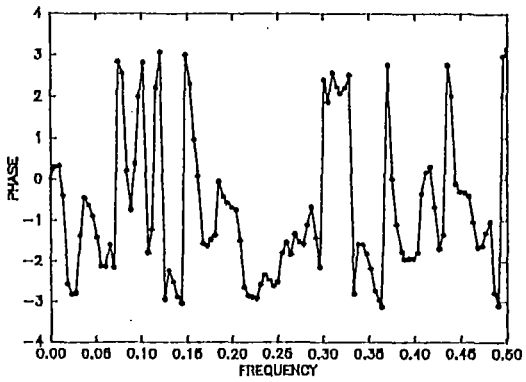
SUBJECT 7:P'DIOL/SPECTRAL DENSITY



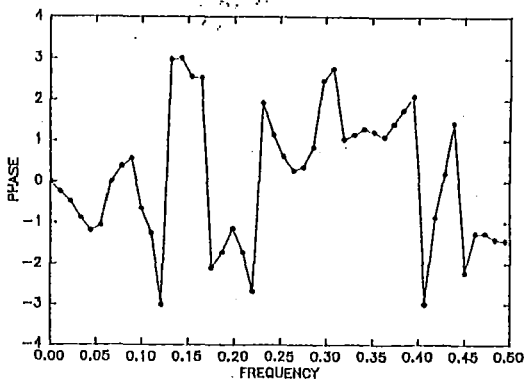
SUBJECT 8: P'DIOL/SPECTRAL DENSITY



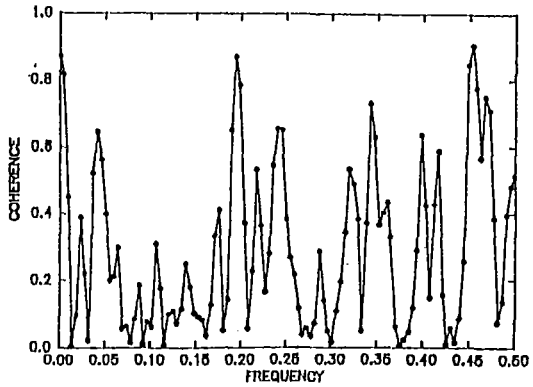
SUBJECT 7: PHASE



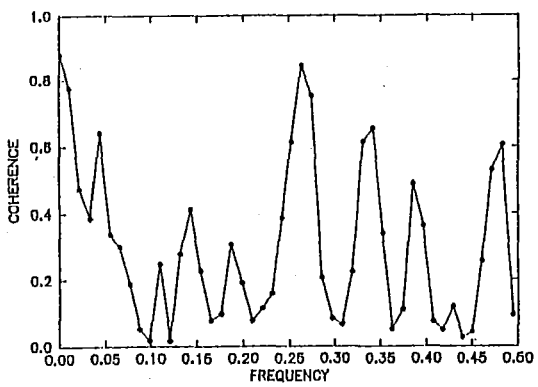
SUBJECT 8: PHASE



SUBJECT 7: COHERENCE

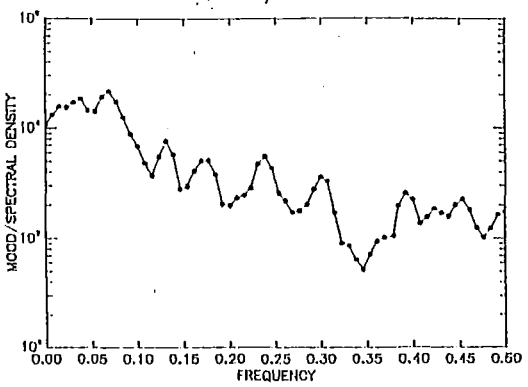


SUBJECT 8: COHERENCE

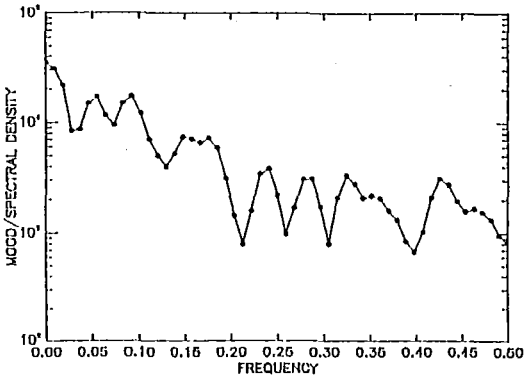


APPENDIX 8

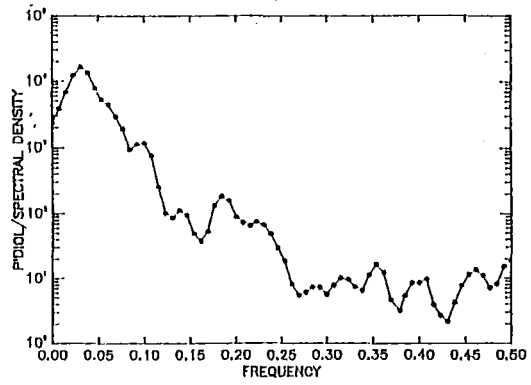
SUBJECT 9: MOOD/SPECTRAL DENSITY



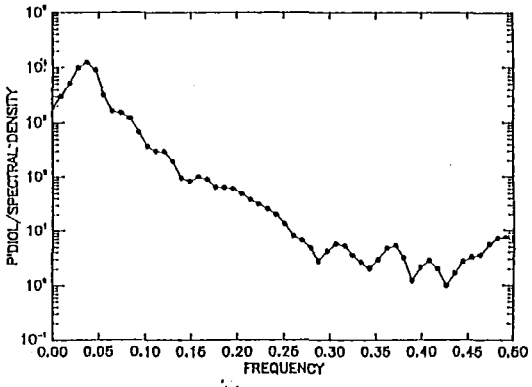
SUBJECT 10: MOOD/SPECTRAL DENSITY



SUBJECT 9: P'DIOL/SPECTRAL DENSITY



SUBJECT 10: P'DIOL/SPECTRAL DENSITY



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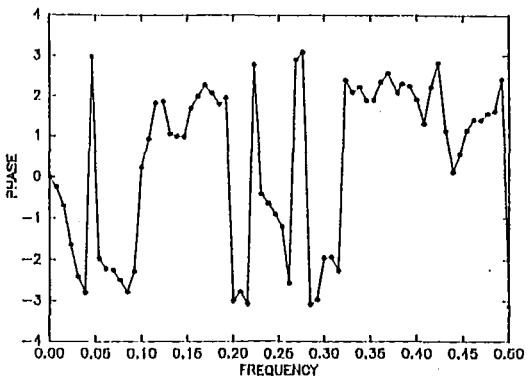
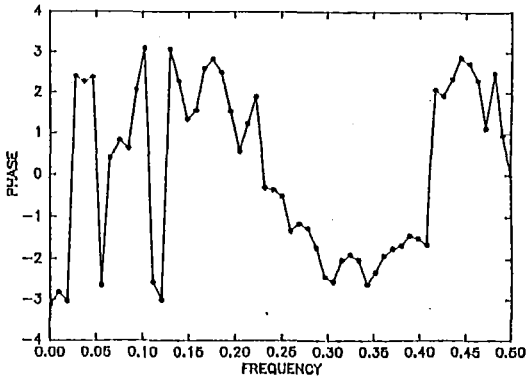
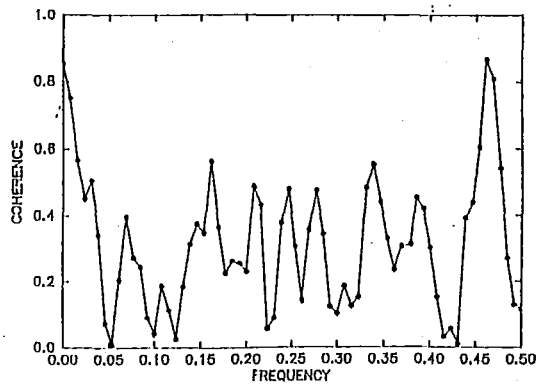


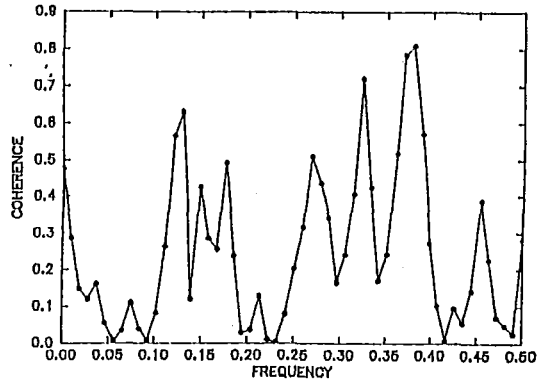
SUBJECT 10: PHASE



SUBJECT 9: COHERENCE

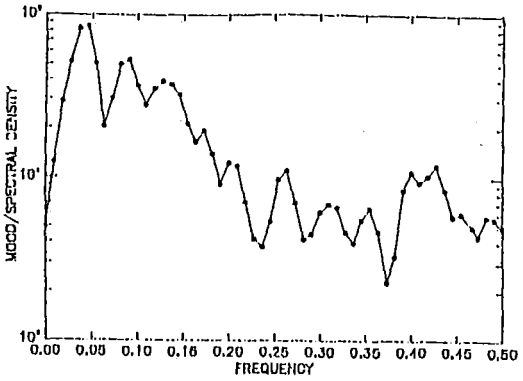


SUBJECT 10: COHERENCE

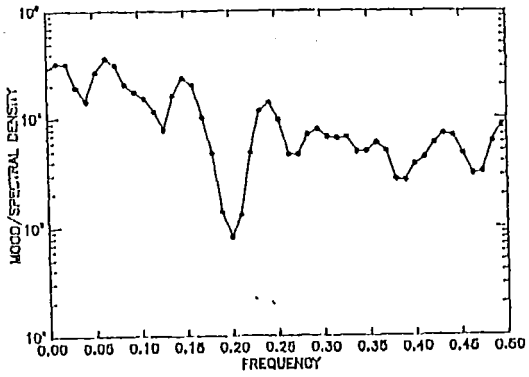


APPENDIX 8

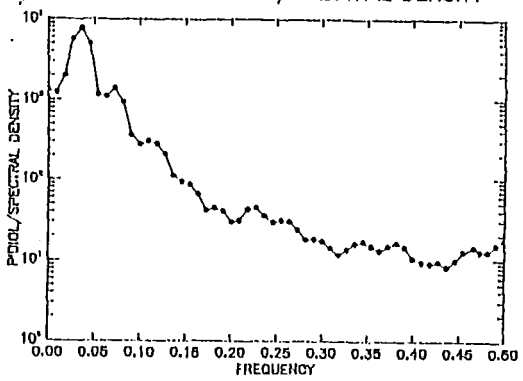
SUBJECT 11: MOOD/SPECTRAL DENSITY



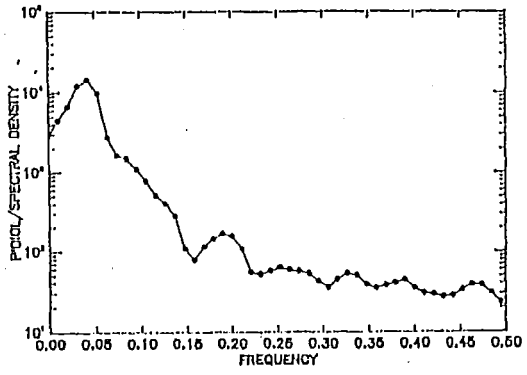
SUBJECT 12: MOOD/SPECTRAL DENSITY



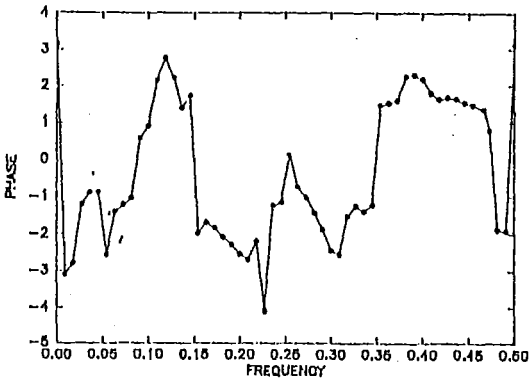
SUBJECT 11: P'DIOL/SPECTRAL DENSITY



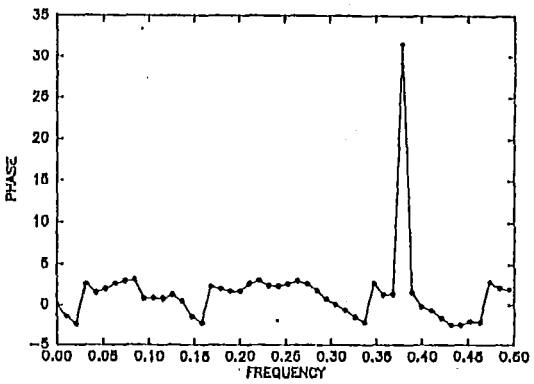
SUBJECT 12: P'DIOL/SPECTRAL DENSITY



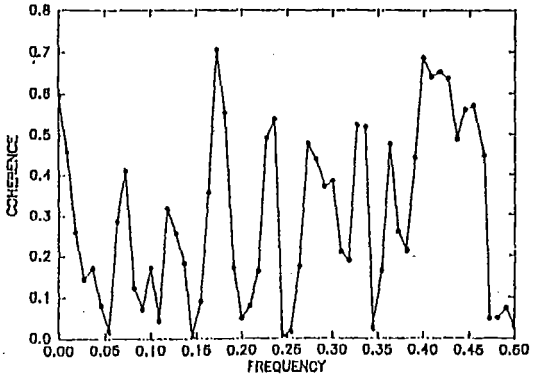
SUBJECT 11: PHASE



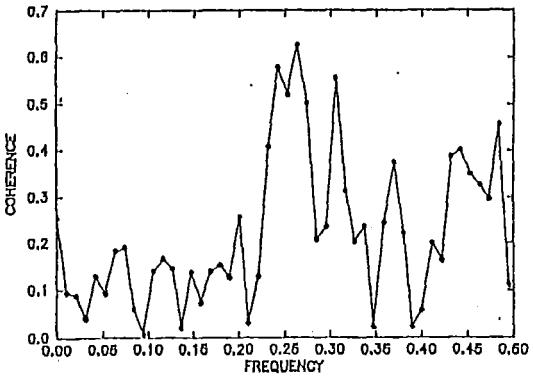
SUBJECT 12: PHASE



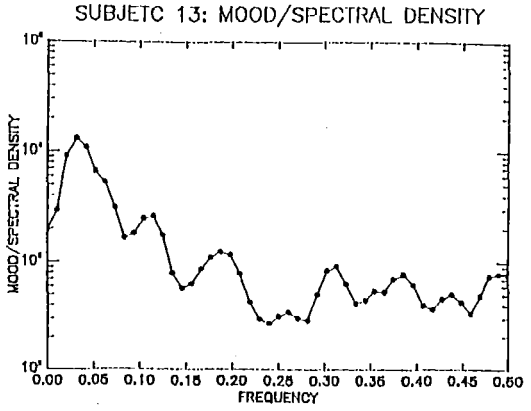
SUBJECT 11: COHERENCE

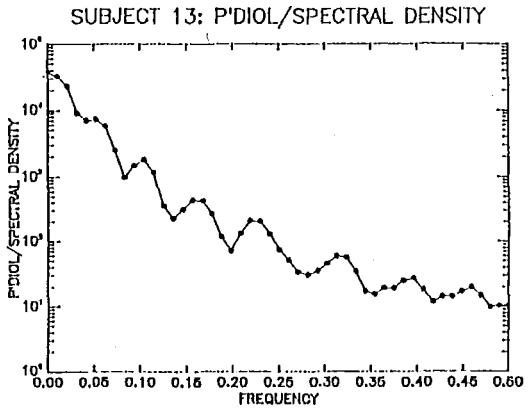


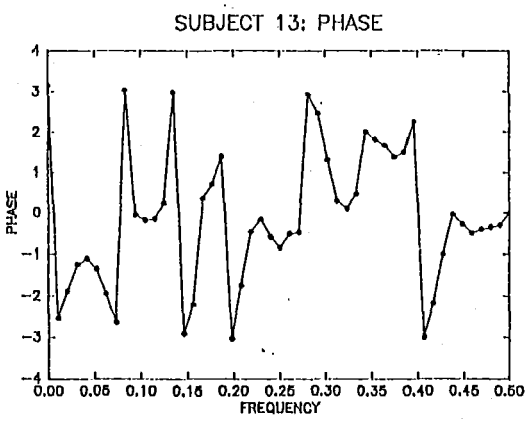
SUBJECT 12: COHERENCE

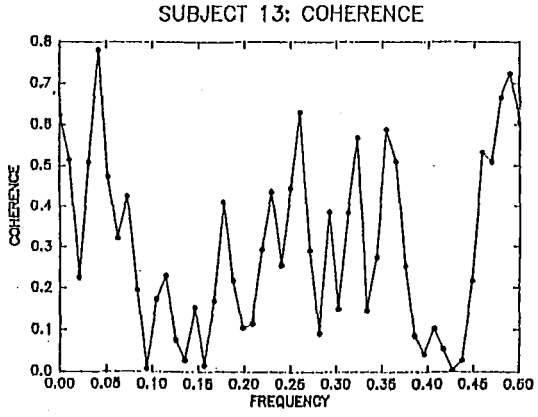


APPENDIX 8


SUBJETC 13: MOOD/SPECTRAL DENSITY
MOOD/SPECTRAL DENSITY
FREQUENCY


SUBJECT 13: P'DIOL/SPECTRAL DENSITY
P'DIOL/SPECTRAL DENSITY
FREQUENCY


SUBJECT 13: PHASE
PHASE
FREQUENCY


SUBJECT 13: COHERENCE
COHERENCE
FREQUENCY

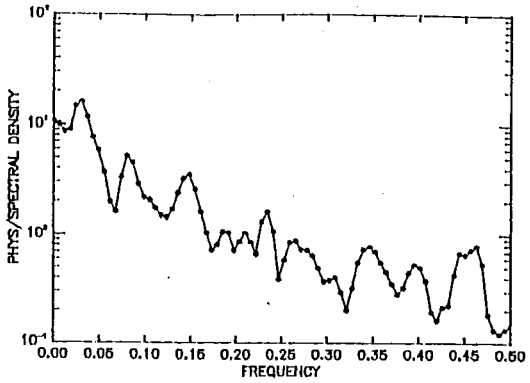
APPENDIX 9

PHYSICAL SYMPTOMS AND PREGNANEDIOL LOG

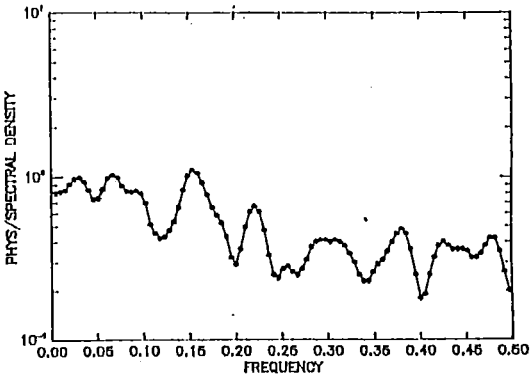
SPECTRAL DENSITY, COHERENCE AND PHASE FOR EACH SUBJECT

APPENDIX 9

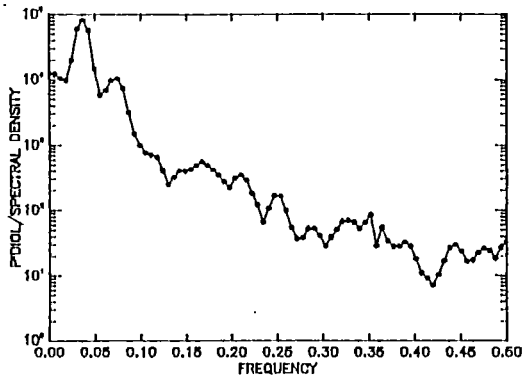
SUBJECT 1: PHYS/SPECTRAL DENSITY



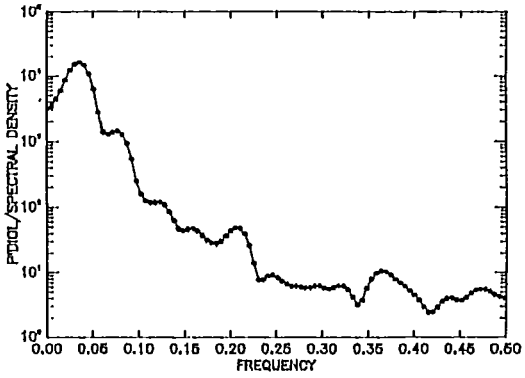
SUBJECT 2: PHYS/SPECTRAL DENSITY



SUBJECT 1: P'DIOL/SPECTRAL DENSITY



SUBJECT 2: P'DIOL/SPECTRAL DENSITY



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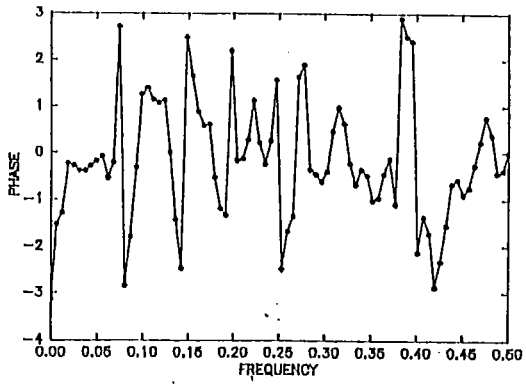

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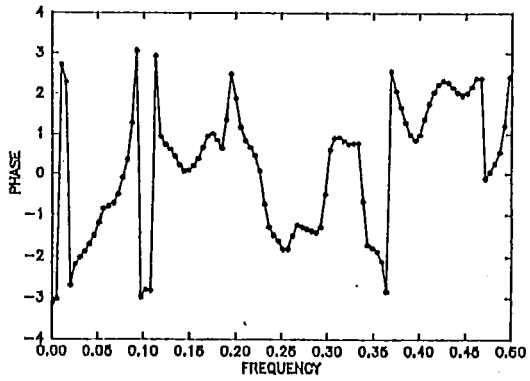

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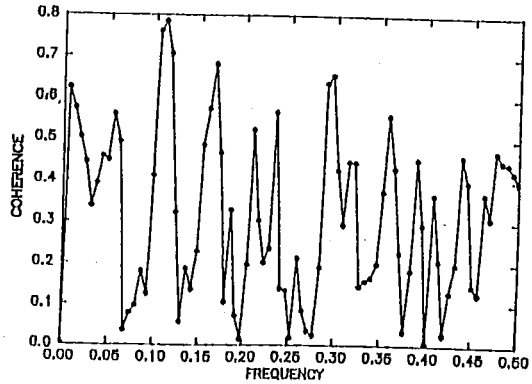

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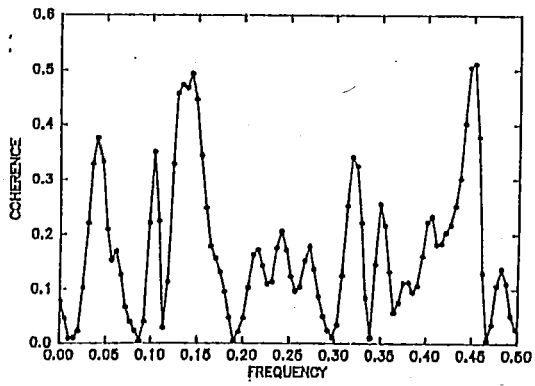

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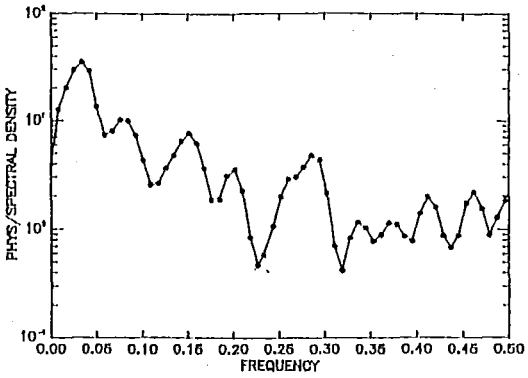
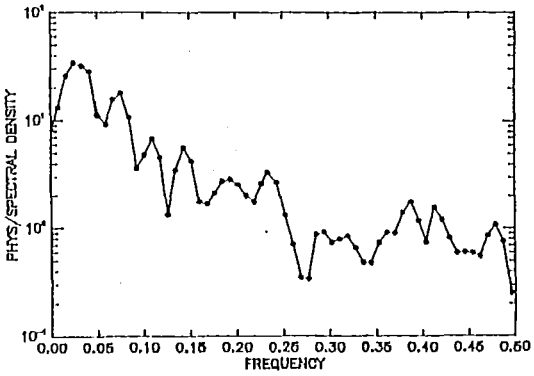
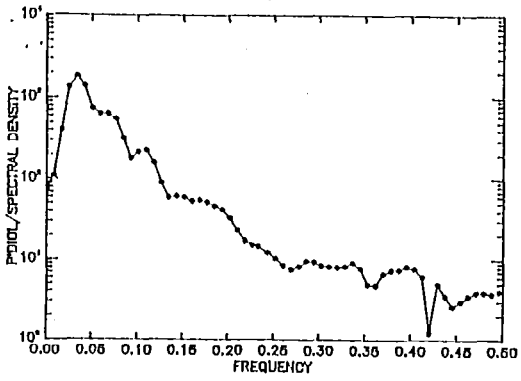
SUBJECT 3: PHYS/SPECTRAL DENSITY



SUBJECT 4: PHYS/SPECTRAL DENSITY



SUBJECT 3: P'DIOL/SPECTRAL DENSITY



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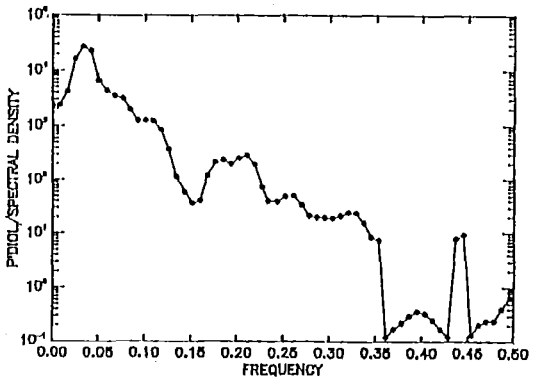

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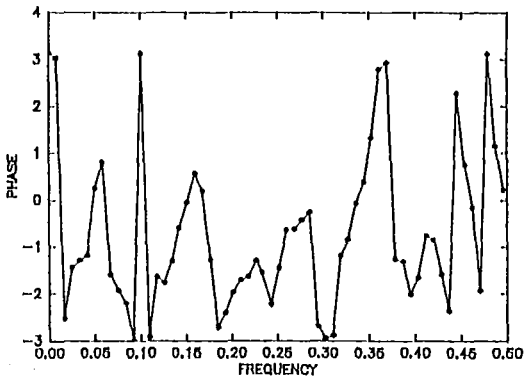

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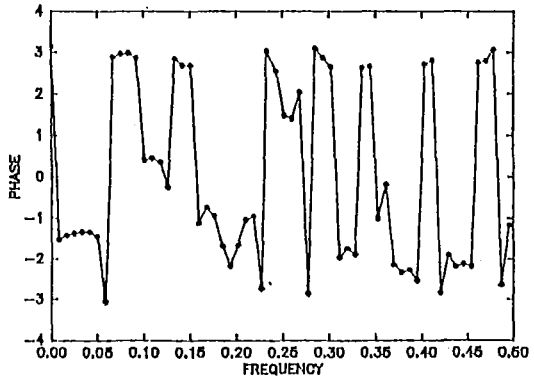

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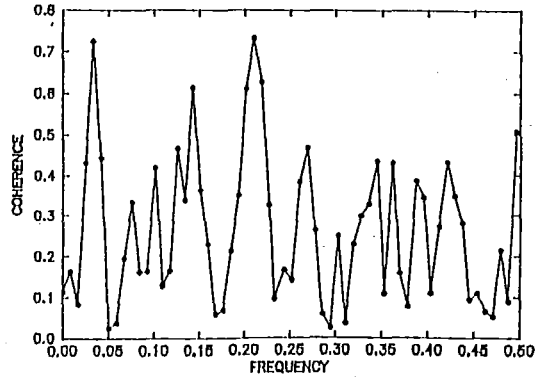

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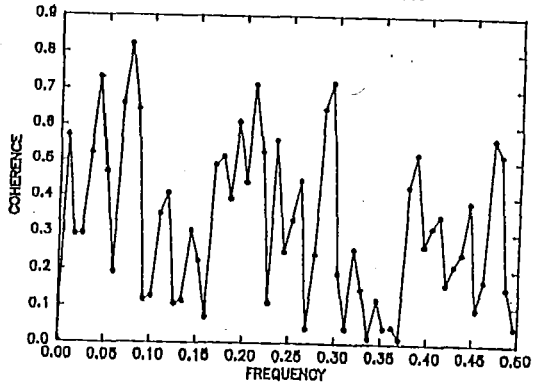

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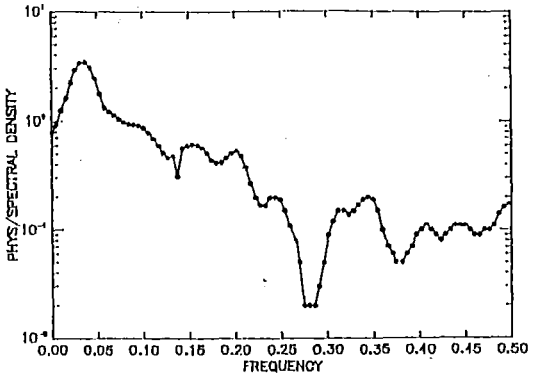
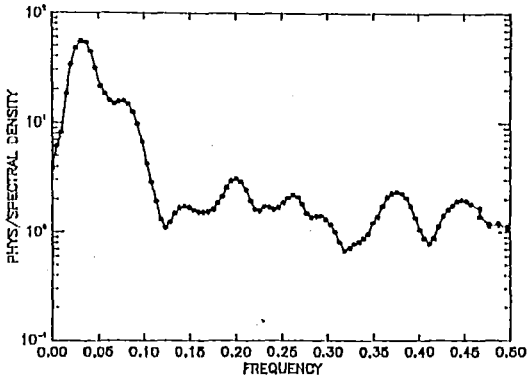
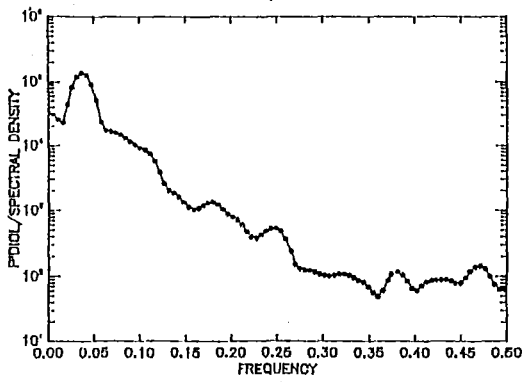
SUBJECT 5: PHYS/SPECTRAL DENSITY



SUBJECT 6: PHYS/SPECTRAL DENSITY



SUBJECT 5: P'DIOL/SPECTRAL DENSITY



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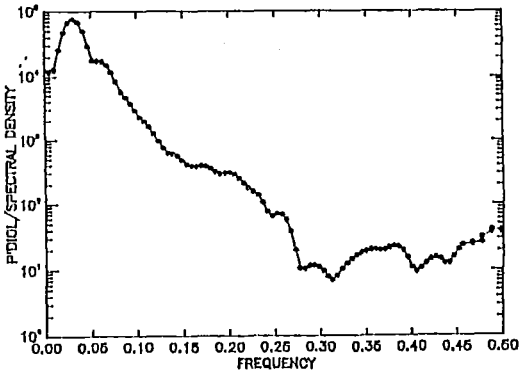

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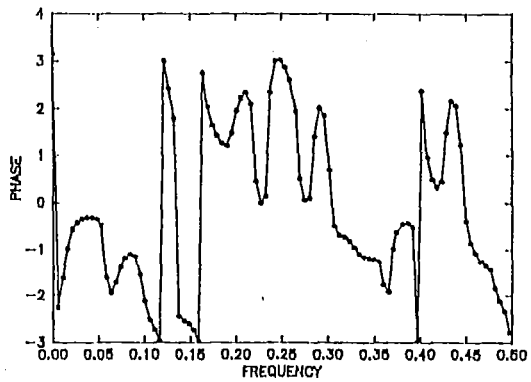

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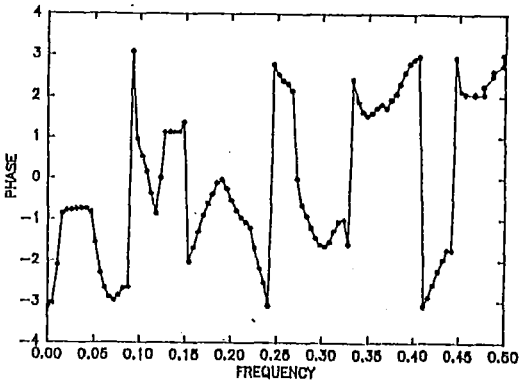

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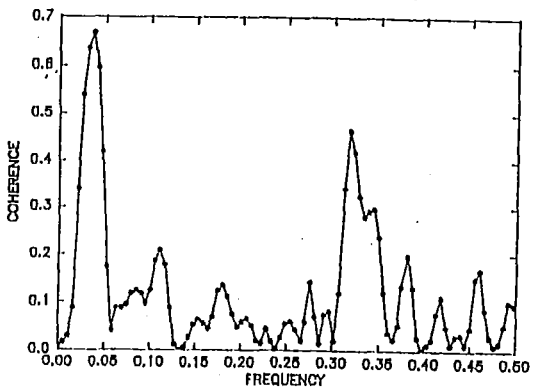

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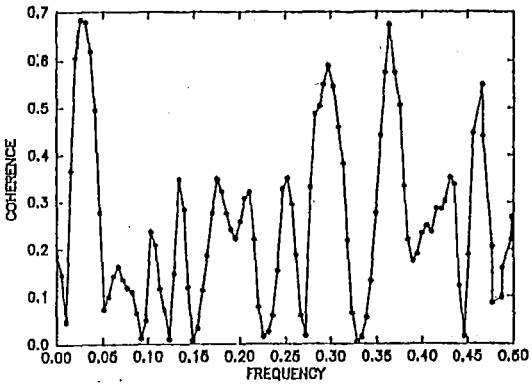

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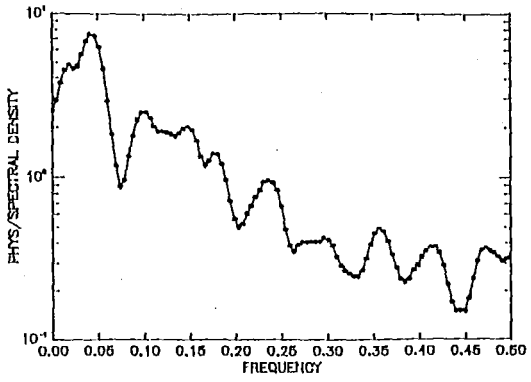
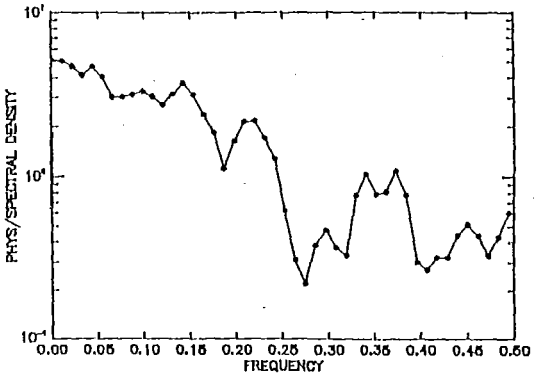
SUBJECT 7: PHYS/SPECTRAL DENSITY



SUBJECT 8: PHYS/SPECTRAL DENSITY



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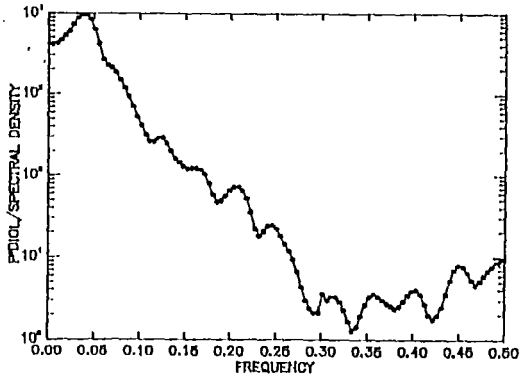

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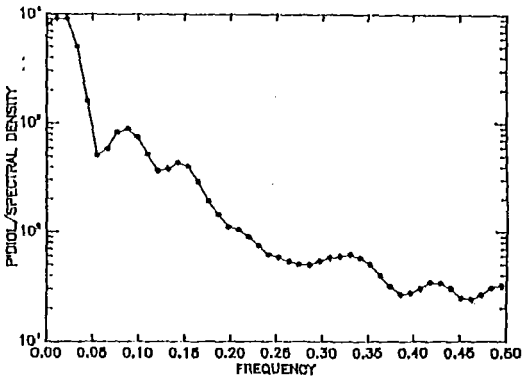

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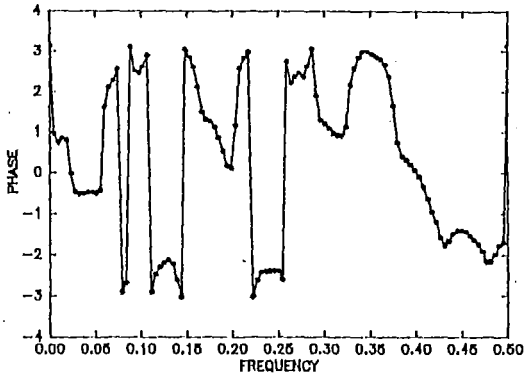

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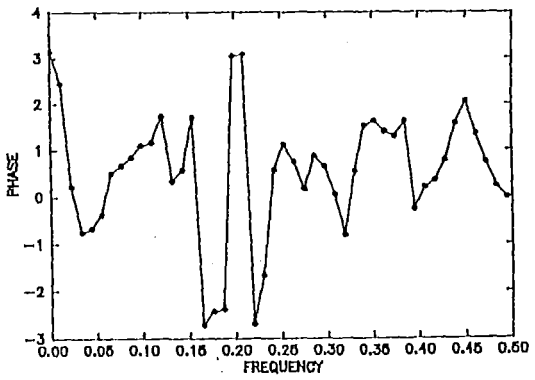

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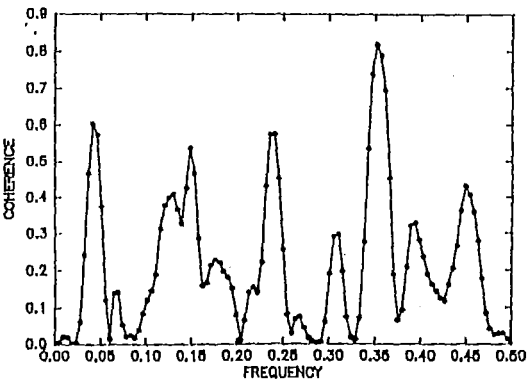

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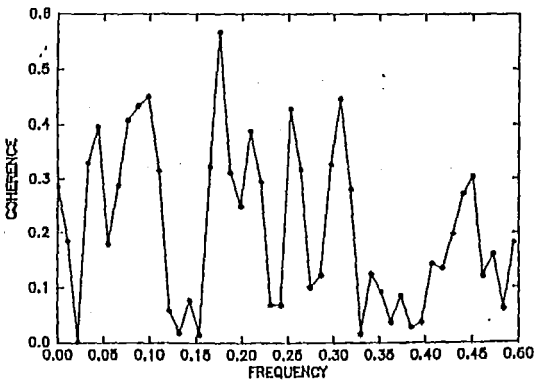

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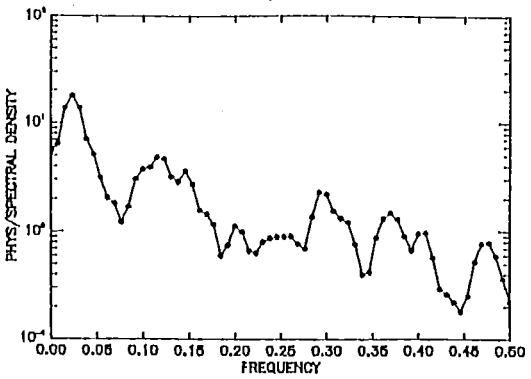
SUBJECT 9: PHYS/SPECTRAL DENSITY



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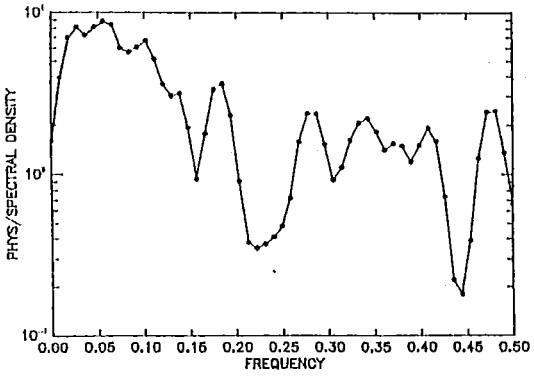
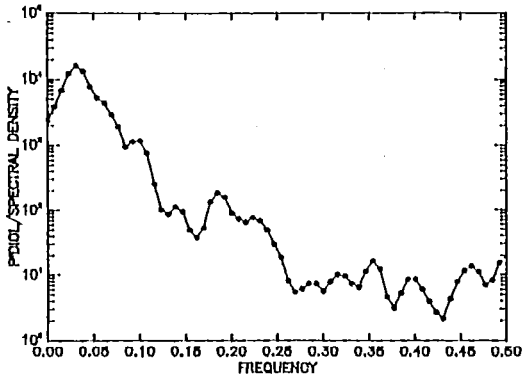


SUBJECT 9: P'DIOL/SPECTRAL DENSITY



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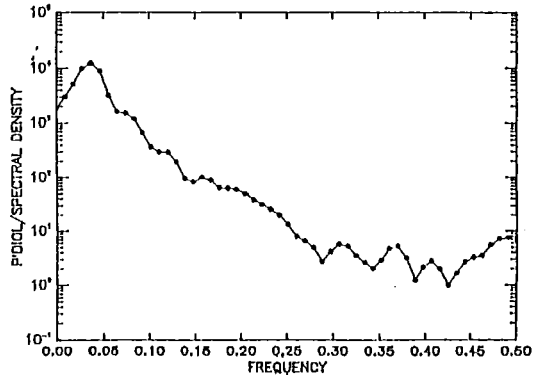

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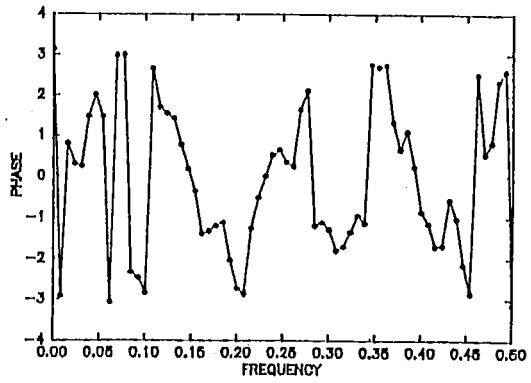

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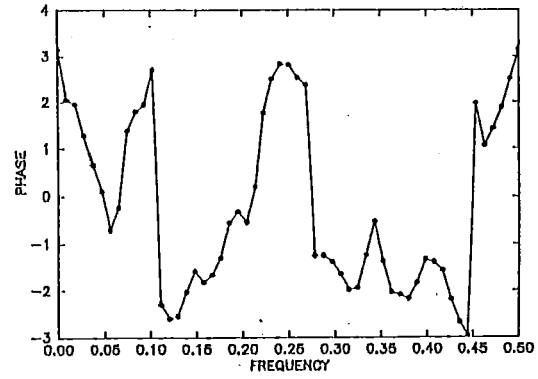

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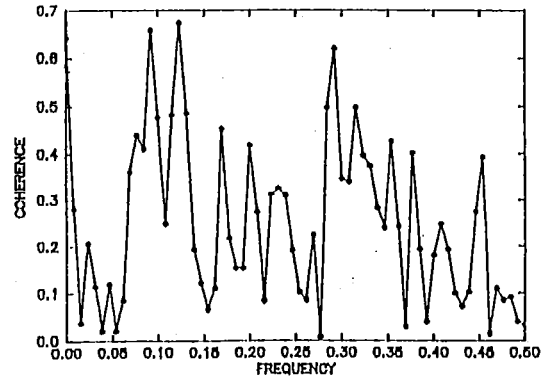

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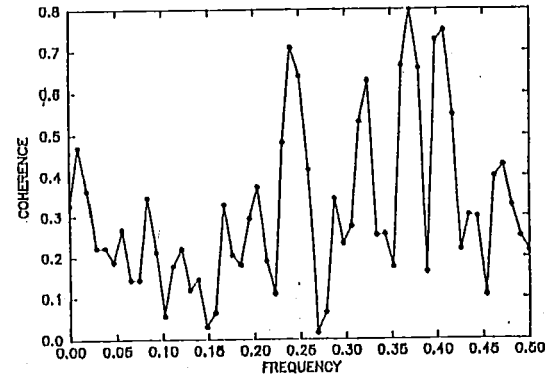

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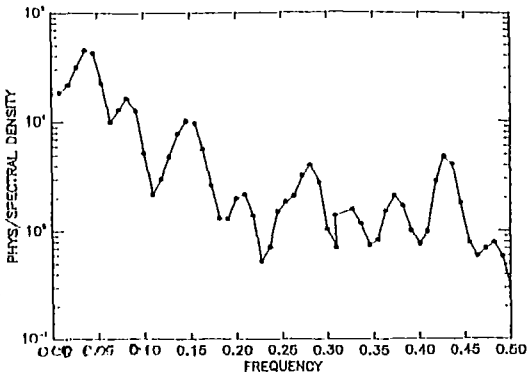
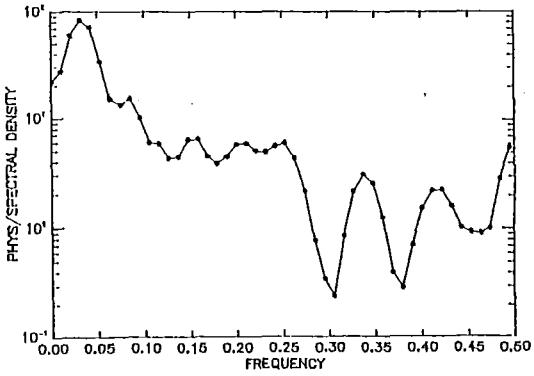
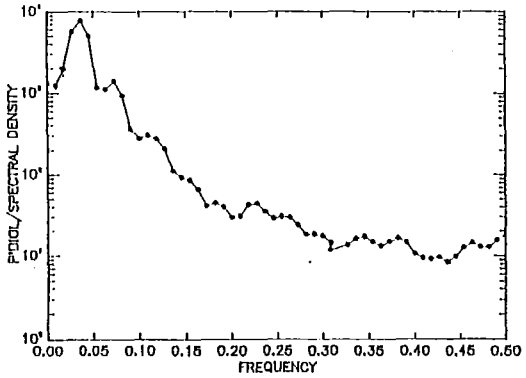
SUBJECT 11: PHYS/SPECTRAL DENSITY



SUBJECT 12: PHYS/SPECTRAL DENSITY



SUBJECT 11: P'DIOL/SPECTRAL DENSITY



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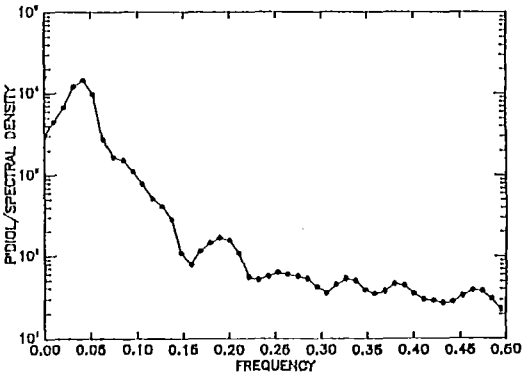

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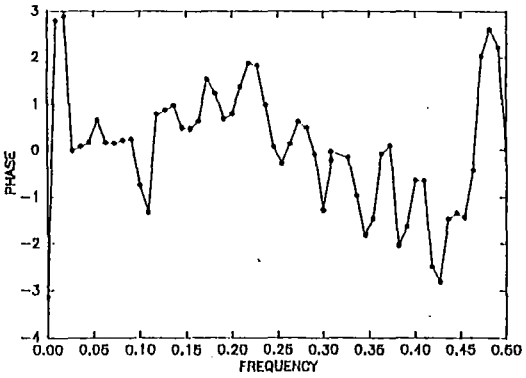

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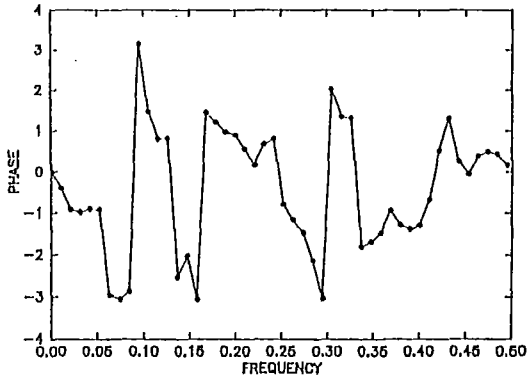

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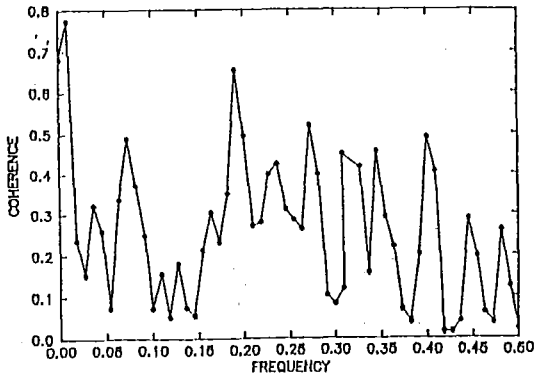

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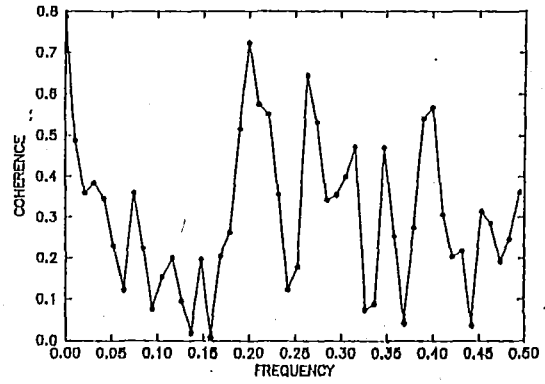

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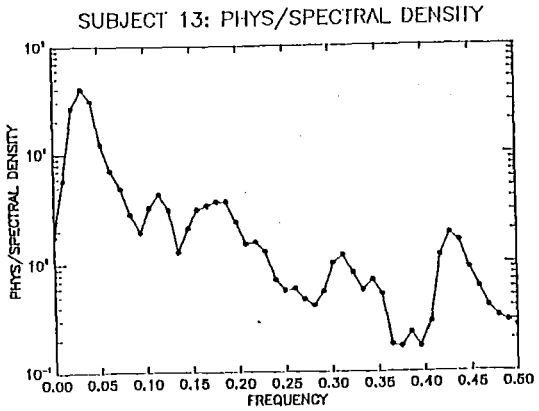
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PHYS/SPECTRAL DENSITY
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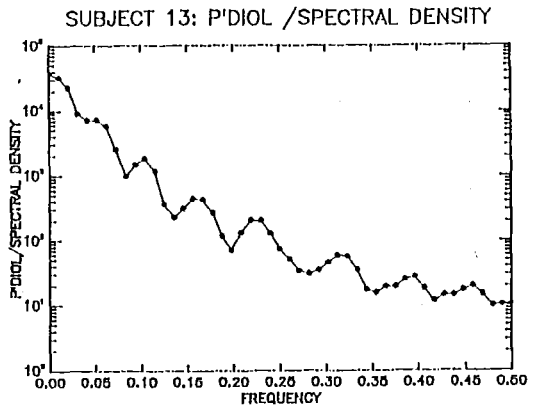
SUBJECT 13: P'DIOL /SPECTRAL DENSITY
P'DIOL/SPECTRAL DENSITY
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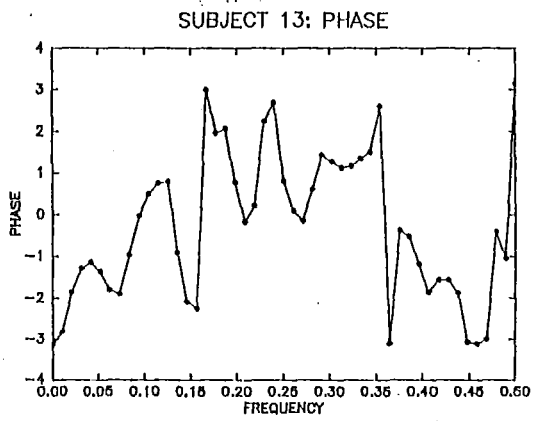
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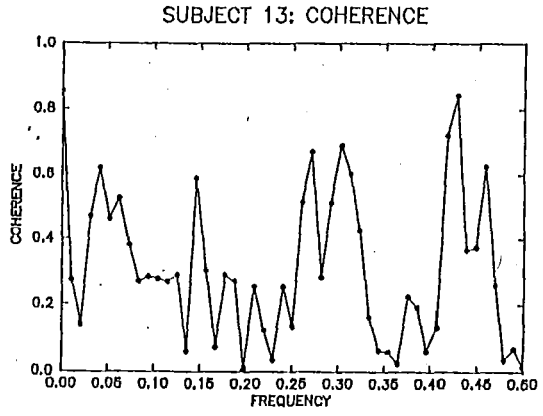
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