1980

Epilepsy and the Menstrual Cycle: The Contribution of Stressful Life Experiences and the Menstrual Cycle to Epileptic Seizures

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EPILEPSY AND THE MENSTRUAL CYCLE: THE CONTRIBUTION OF STRESSFUL LIFE EXPERIENCES AND THE MENSTRUAL CYCLE TO EPILEPTIC SEIZURES

by

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A Dissertation Submitted to the Faculty of the Graduate School of Loyola University of Chicago in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

July

1980

ACKNOWLEDGMENTS

The author wishes to thank Dr. Gilbert H. Glaser, Chairman of the Yale School of Medicine Department of Neurology, who provided the financial support for this dissertation research; and Dr. Richard H. Mattson, Chief of the Neurology Service at the West Haven V.A. Hospital, who provided generous access to his medical facilities as well as constant encouragement. Thanks are also due to Dr. Robert A. Novelly, Director of the Neuropsychology Department at the West Haven V.A. Hospital, who spent many hours with me in helpful discussion and criticism of this research. Ms. Susan Egelko, a fellow neuropsychology associate at the West Haven V.A., gave much appreciated help in transforming mountains of raw data into analyzable form. My appreciation and thanks are due to all of the women who consented to the long, arduous months of participation in this study. Without their willingness to cooperate with procedures which were often boring or uncomfortable, as well as very time-consuming, this study would never have been finished. I wish to thank Dr. Thomas Petzel, Dr. Frank Kobler, and Dr. Al DeWolfe for their willingness to serve as my dissertation committee after I had been away from Loyola for three years, and who endured with me the lengthy metamorphosis of this dissertation from prospectus to final product. Thanks are due to Mr. and Mrs. Harry D. Kamer, my parents, and Mr. Harry F. Kamer, my brother, who constantly encouraged me and believed in my ultimate success throughout the many years I have been in graduate school. My deepest gratitude goes to my husband, David R. Meador. Without his unfailing support and encouragement, and faith in me, this dissertation might never have been completed.

VITA

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CHAPTER 1

INTRODUCTION

Despite optimal anticonvulsant therapy, many epileptic patients continue to experience seizures. The reasons seizures occur on any given day or specific time of day often are not recognized or understood. However, missed medication, alcohol abuse, sleep loss, the menstrual period, and emotional upsets are among the factors that have been suspected as being important in modifying seizure threshold (Bennett, Mattson, Ziter, Calverley, Liske, & Pratt, 1964; Gastaut & Tassinari, 1966; Glass & Mattson, 1973; Gowers, 1885; Mattson, Heninger, Gallagher, & Glaser, 1970; Mattson, Lerner, & Dix, 1974; Mattson, Pratt, & Calverley, 1965; Pratt, Mattson, Weikers, & Williams, 1968; Servit, Dudas, Machek, Stercova, Kristof, & Cervenkova, 1962; Symonds, 1959). Infrequently, specific sensory stimuli such as light, sound, or touch may trigger attacks (Mattson et al., 1974; Servit et al., 1962).

Despite general agreement that these factors are important, little careful statistical data are available to support these clinical impressions, and it is not known whether certain precipitating and inhibiting factors are important for specific seizure types or electroencephalographic patterns. Information about precipitating and inhibiting factors of epileptic seizures is based largely on clinical impressions or anecdotal case reports (Daube, 1966; Gastaut & Tassinari, 1966; Gowers, 1885; Servit et al., 1962; Symonds, 1959).

For at least 100 years it has been recognized that seizures occur with menstruation (Gowers, 1885). Intensive studies of precipitating factors of epileptic seizures conducted at the Yale Epilepsy Center have indicated that 54% of a group of 100 epileptic women observed an association between seizure occurrence and the menstrual cycle, and 85% of these women noted an increase in seizures during the premenstrual and menstrual phases of their cycles. In addition, 58% of the same group of epileptic women observed an increase in their seizures when they were emotionally upset (Mattson et al., 1974; Glaser, Note 1). However, this data, like that from previous studies examining the relationship between seizures and the menstrual cycle, is based only on retrospective anecdotal reports. Nonetheless, many investigators have concluded that the increase in seizures near the time of the menstrual period has been related to emotional factors (Bandler, Kaufman, Dykens, Schleifer, & Shapiro, 1957; Gastaut & Tassinari, 1966; Laidlaw, 1956; Logothetis, Harner, Morell, & Torres, 1959).

Recently, however, reports have indicated that changes in seizure frequency near menstruation have been related to hormonal changes. Specifically, research has indicated that seizures tend to be more frequent and severe just prior to and during menstruation when estrogen and progesterone levels are low, and less frequent during the luteal phase when progesterone activity is maximal (Backstrom, 1976a, 1976b; Backstrom & Carstensen, 1974; Backstrom & Jorpes, 1979; Hall, 1977; Laidlaw, 1956; Logothetis, Harner, Morell, & Torres, 1959). The probable anticonvulsant action of progesterone and lowered seizure threshold due to estrogen which has been demonstrated in animal studies suggest a link between changes in hormone levels and epileptic seizures

(Sanchez & Saldana, 1966). Increased stressful life experiences appear to result in increased levels of extra-gonadal estrogen (Speroff, Glass, & Kase, 1973), so that a combined effect of stressful life experiences and fluctuating hormone levels due to phase of the menstrual cycle may interactively result in increased seizure frequency. Fluctuations in bioavailable antiepileptic drugs may also be a factor in seizure incidence (Fernandez & Zaninovich, 1975).

Werboff (1961) postulated that sex steroids may exert direct effects on brain excitability by altering threshold and convulsive patterns, thus causing changes in seizure frequency as levels of sex steroids change. Espir (1969) also suggested a second mechanism by which sex steroids may influence seizure frequency: estrogen and progesterone may compete for binding sites with anticonvulsant drugs, thus causing a changed binding of anticonvulsant drugs and consequently changed brain excitability.

Previous studies have not sufficiently controlled for hormonal and life stress correlates of seizures during the menstrual cycle. The purpose of the present study was to determine the hormonal and life stress correlates of increased seizure frequency in epileptic women with relationship to the menstrual cycle.

The principal hypotheses were:

H_1: Progesterone inhibits seizures and estrogen increases seizures; consequently, epileptic women should have the fewest seizures during the mid-luteal phase of their menstrual cycles when progesterone is high relative to estrogen; and conversely, seizure frequency should be greatest menstrually and premenstrually when progesterone levels are rapidly falling. A second seizure peak might be expected to occur during ovulation, when

estrogen is high relative to progesterone.

H_2: Stressful life experiences will be associated with increased seizure frequency independently of the phase of the menstrual cycle.

H_3: An interaction between low levels of progesterone and high levels of stress result in the highest seizure frequency.

The specific questions addressed by this study were: (a) Does progesterone inhibit seizures? (b) Does estrogen exacerbate seizures? (c) Does emotional stress result in increased seizure frequency? (d) Does an interactive effect occur between fluctuations in steroid hormone levels and high levels of life stress that results in increased seizure frequency?

CHAPTER II

REVIEW OF THE LITERATURE

Factors Facilitating Epileptic Seizures

The epileptologist is concerned with the questions "What determines the onset of the seizure?" and "Once a seizure has begun, why does it stop?" Symonds (1970) discusses a variety of patterns in the onset of seizures. Some epileptics experience seizures only at night; others only during the day. A large group experiences myoclonic jerks upon waking, and have learned that if they remain in bed for a half-hour after waking without engaging in any mental or bodily activity, they will not experience any seizures. Other groups of patients are particularly apt to have seizures after a short night's sleep; while dropping off to sleep; and during sustained and concentrated mental activity of any kind. Symonds (1970) hypothesizes that in the transition between sleeping and waking the brain's arousal mechanisms are in a greater state of functional activity than usual, and are thus more easily excited to a pathological level.

Various methods have been used to precipitate seizures for the purpose of diagnosis. One such method has been the combination of a maximal fluid intake with injections of pitressin. The physiological basis for this remains obscure but may be due to an excessive water intake and retention upsetting the electrolyte balance in the brain, favoring excitation and seizures.

Seizures are also commonly precipitated by overbreathing. A proposed mechanism involves gamma-amino-butyric acid (GABA) which has a powerful inhibitory effect at synaptic junctions and is formed in the brain from glutamic acid by the action of a decarboxylase and subsequently destroyed by a transaminase. Both enzymes are effective at the normal pH, but the decarboxylase becomes less effective and the transaminase more so with increasing alkalinity. Under normal conditions there is a steady state between the formation and decomposition of GABA so that its level in the brain remains constant. It is possible, therefore, that the alkalosis resulting from hyperventilation may facilitate convulsive activity by removing the dampening effect of GABA.

Photic stimulation is another widely used method to evoke epileptic seizures on EEG recording, and is recognized as a precipitating cause of petit mal seizures. Precipitation by visual stimuli of a more elaborate kind is less common, but includes staring at patterns of fabric or clothing (Bickford, 1956), staring at small objects (Mitchell, Falconer, & Hill, 1954), and looking at lines converging to a point and rotating wheels. Seizures may also occur after prolonged reading.

Auditory stimuli as precipitants of seizures vary from the most simple to the very complex, and sometimes the stimulation has to be prolonged. Examples include unexpected loud noises, prolonged musical sounds, repetitive monotonous sounds, and the noise of machinery (Critchley, 1937; Symonds, 1959).

The precipitation of attacks by tactile stimuli applied to the area primarily involved in focal seizures has been recorded, and it is generally observed that the stimulus has to be unexpected (Symonds, 1959). Painful stimulation of the part involved in the seizure is also

a well-recognized precipitant. Passive stretch of the muscle or tendon is known to provoke seizures especially of the myoclonic type; sudden voluntary movements can also precipitate seizures. Other precipitants of seizures include visceral stimulation, coughing, intestinal contraction, distention of the urinary bladder, and sexual orgasm (Symonds, 1959, 1970).

Investigating the phenomenon of the facilitation of seizures by psychological factors is one of the main purposes of the present study. Of the long-lasting emotional states, pent-up anger appears to be more effective than any other emotion in facilitating seizures (Symonds, 1970). Some patients with temporal lobe seizures state that a particular thought will start an attack, but some researchers have theorized that more probably the thought is the first symptom of the attack (Symonds, 1970). However, among those patients whose seizures begin with particular thoughts, many are able to arrest their attacks by a deliberate switching of attention; or by some form of activity or stimulation related to the mode of onset of the attack and therefore presumably to the cortical cells in which the discharge arose (Symonds, 1970). For example, a patient whose attacks began with a forced movement of the eyes to the left, might be able to stop his seizures by forcing his eyes back to the midline. In cases of this type, the promptness of the corrective action taken is a condition of success in stopping the seizure. A hypothesized mechanism is that the stimulus employed sets up an inhibitory process in the cortex which determines the cessation of excitatory discharges (Efron, 1956, 1957). Therefore, seizures can be suppressed by means of a training procedure, resulting in changes in patterned neural activity which would otherwise be outside voluntary control (Efron, 1956, 1957; Kugelberg & Hagbarth, 1958).

Another example of the mechanism of a training procedure in the inhibition of seizures is provided by Efron (1956, 1957). Efron's patient suffered from seizures arising in the left temporal lobe which included a transitory olfactory aura. He found that olfactory stimulation by essence of jasmine during the phase in which his patient was expecting her olfactory aura would arrest the attack. Subsequently a conditioned reflex was established between the smell of jasmine and the sight of a particular bracelet, and then between the smell of jasmine and the thought of the bracelet, until eventually the thought of the bracelet alone inhibited the seizure. In this case, repeated alteration of the sensory pattern eventually resulted in a reduction of epileptic activity, and the alteration was such that it might be expected to have an effect upon cortex in the immediate vicinity of the discharging focus. In the case of Efron's patient who had an olfactory element in her aura, an olfactory stimulus was employed. However, no one has ever successfully repeated Efron's training procedure.

Symonds' (1970) interpretation of these phenomena is that what happens to an afferent impulse once it has entered the central nervous system depends not only upon its own intensity and quality, but upon the quality and intensity of all other afferent impulses entering at the same time as well as upon what has previously happened. Epileptic seizures which appear to occur spontaneously are determined by a coincidence of many factors, among which afferent impulses are important. Symonds (1970) hypothesizes that most afferent impulses are outside the field of perception. Therefore, if certain stimuli are observed to precipitate attacks in some cases (olfactory, touch, pain, photic stimulation, and so on) it is reasonable to assume that many more seizures

are precipitated by afferent impulses of which we may not be currently aware.

The contribution of emotional factors to epileptic seizures. A major hypothesis of this study is that epileptic seizures are precipitated by psychological stress, as reported by the patients themselves, when such stress causes a high degree of excitation or change from everyday, usual levels of emotional functioning. Pruyser (1953) proposed that studies of psychological precipitants of epileptic seizures should take into account the following:

1. A longitudinal approach to the psychological correlates of seizures is appropriate, in which the patient is studied from day to day, or from hour to hour, and the focus of the study is on the changes that take place in the important psychological variables. The patient should be his own control subject.

2. Post-seizure states are just as important to consider as pre-seizure states, and a more or less normal baseline has to be established from observations in the inter-seizure period.

3. The assessment of facts at any point on the time axis should be comparable, based on identical techniques and cast in an identical conceptual system.

4. Inferences from data thus obtained do not imply a causal relationship between psychological and somatic events, but rather at best a synchronous relationship. Only when a definitely synchronous relationship has been established can one begin to think in terms of causality.

However, not all studies of psychological variables associated with epileptic seizures have employed Pruyser's (1953) recommendations,

which may be one of the reasons for the equivocal findings of different studies.

Allen (1956) studied two large groups of epileptic patients to determine the precipitating causes of their seizures. In the first group of 622 cases he determined through history and clinical examination that emotional factors influenced the occurrence of epileptic symptoms in 20.8 percent of the cases. In a second series of 182 cases he found emotional precipitants of seizures in 27.5 percent. Detailed examination of these cases revealed the following factors occurring in some of the instances: (a) Some patients manifested a steady increase of emotional tension for periods which varied in duration from two or three days up to three months before the epileptic seizure or a series of seizures occurred; and relief from this increase of emotional tension for an appreciable time after the seizure or the end of the series of seizures. (b) Another pattern was a rapid increase of emotional tension, sometimes with the appearance of manifest emotion, for a short time and at most for a few hours before the onset of the attack or series of attacks, followed by relative relief after the attack or series of attacks had ended. (c) In some cases the patient manifested anxiety in the form of hyperventilation, which resulted in alkalosis and other biochemical changes and then the appearance of an epileptic seizure. (d) Cases were seen in middle-aged individuals in which a rise in systolic blood pressure, sometimes accompanied by a rise in diastolic pressure and pulse rate, appear on a background of anxiety and tension. The patient becomes more likely to develop seizures during periods of tension compared to other times.

Allen (1956) reports that in almost all the cases in which the emotional factor was related in some way to the occurrence of the epileptic attack or a series of such attacks, the emotional tension with its accompanying symptoms appeared to be of a general character and not of a type associated with and due to the occurrence and site of the epileptic discharge. In some patients a background of a lifelong accumulation of emotional tension existed, epileptic seizures occurred, anxiety relating to the seizures developed, and eventually a vicious circle was set up with rapid aggravation of the patient's epileptic symptoms.

These data naturally suggest a central hypothesis of the present study, namely, that patients with higher life stress scores (as measured by the Schedule of Recent Experiences and the Life Events Diary) have more seizures than do patients with lower life stress scores. Patients who have more seizures might also be expected to have higher life stress scores on a yearly, as well as on a weekly basis.

In 1937, Critchley observed that in musicogenic epilepsy, fear or other negative emotions or physiological accompaniments of emotion intervened between the appropriate stimulus and the epileptic discharge. Allen's (1945) observations on reflex epilepsy showed that cases in which there was some manifest emotion or symptoms usually associated with emotion after the stimulus and before the seizure were characterized by a delay between the stimulus and the seizure. Allen (1948) also found that the onset of myoclonic seizures was often precipitated by an emotional crisis or the development of a state of anxiety tension. Attacks accompanied or followed by automatisms (Allen, 1951) occurred in all but two of 35 patients who showed clear evidence of emotional stress; in some patients automatisms occurred in conjunction with their seizures

only during periods of strong emotional tension.

Fremont-Smith (1934) showed that in 31 of a series of 42 patients some emotional situation related to the occurrence of the convulsion, and also showed that alleviating the emotional tension lessened the frequency of seizures in his cases. Cobb (1936) stated categorically: "Emotional stress often precipitates a convulsion in a patient who has a tendency to such a seizure. This does not mean that 'epilepsy' is 'psychogenic', but it does mean that psychological factors act physically on the organism and produce symptoms."

Bridge (1947) reviewed 22 cases of epilepsy in children and examined the influence of emotional factors. Bridge found that commonly the first seizure followed some emotional episode; recurrence of attacks could often be related to placement of the child in foster homes or adoption; and many children improved with psychotherapy alone and remained free from seizures. Richardson (1952) surveyed cases of epileptic seizures with predominantly psychic symptoms and described the emotional precipitation of attacks in some cases of reflex epilepsy. Parland (1953) illustrated the influence of emotional factors by describing the occurrence of seizures following emotional experiences accompanied by inner conflicts and guilt; and pointed out that the preliminary emotional tension might arise from fear, resentment, or guilt. Other writers who described cases in which epileptic seizures occurred subsequently to stressful emotional experiences are Barker (1948), Edelston (1949), and Gottschalk (1953, 1955).

Liberson (1954) proposed several mechanisms to explain emotionally-induced seizure activity. Emotional stimuli may induce a convulsion through the creation of a general excitatory state with an excessive

formation of either acetylcholine or insulin. Acetylcholine is a powerful convulsant; and excessive insulin can lead to hypoglycemia, which can also precipitate seizures in susceptible individuals. Another general mechanism may be through the influence of stress and emotion upon cortico-adrenal activity which is known to participate in the control of electrolytic balance and water metabolism. A disruption of this balance may contribute to the triggering of a seizure.

Another mechanism as discussed by Liberson (1954) is that brain structures which mediate emotional experiences, such as the rhinencephalon (olfactory brain), may be sensitized because of some local pathological process. If this occurred, then these areas could be induced into an epileptic discharge by stimuli having an emotional significance for the individual. The stimulus may be highly individualized and constitute a conditioned stimulus of certain types of affective states, which produces epileptic seizures coming from those areas of the brain which participate in the control of emotional processes.

Caveness (1955) differentiates between emotional problems that arise as a reaction to seizures; emotional problems that act as a precipitant to seizures; and emotional problems that contribute to the pattern of seizures, which in order to be interpreted correctly must be made with full appreciation of the anatomical and physiological substrata. Caveness (1955) reports on two cases in which emotional factors precipitated seizures, and in which personality changes later occurred as a reaction to the stress of recurrent seizures.

Friis and Lund (1974) studied 1,250 patients with convulsive disorders over a 13-year period, and identified 37 patients who had convulsive attacks preceded by severe stress. The method of identifying

these patients and their seizures was by clinical interview and review of case records. In this group, stress convulsions were twice as frequent in men as in women; no explanation for this phenomenon was given. Friss and Lund (1974) found that lack of sleep was the commonest stress factor precipitating seizures, followed by emotional strain and somatic over-exertion. However, the authors failed to further define "emotional strain." One or more of these three stress factors was reported prior to all convulsive attacks in this group of patients. The authors suggested avoidance of the provoking factors as prophylaxis; therapeutic doses of anticonvulsants did not prevent recurrence of stress-provoked seizures. Barker and Barker (1950, pp. 90-113) and Stevens (1959) have shown that mental stress may cause EEG changes in patients suffering from epilepsy.

Williams (1975) observed that in surveying his own neurological practice over a period of twenty years, only about two percent of his patients had neurosurgical causes for convulsions or advancing gross structural disease. This being the case, Williams (1975) considered what might be the precipitants of seizures in any particular instance for the vast majority of epileptics, and advanced the hypothesis that most seizures are the result of an accumulation of physical and emotional stress factors: "Either a set of predisposing events will anticipate immediate serial misfortunes in a predisposed person to culminate in a fit; or the wrath of God in the form of fatigue, fevers, furies, frustrations or fates will together make a fit equally inevitable." From Williams' (1975) observations of the patients in his own practice, he further asserts that controlled, obsessional epileptics who do not ventilate their emotions but keep them inside where their feelings build up,

are especially prone to seizures when stressful life experiences intervene. A difficulty in assessing Williams' observations occurs, however, because he presents no experimental measures of stress, or of the relationship of stress to seizures. His statements are limited to clinical observations.

Glass and Mattson (Note 2) compared temporal lobe epileptics, focal non-temporal-lobe epileptics and centrencephalic epileptics on a variety of measures. They found that the Wechsler Memory Quotients of the temporal lobe epileptic (TLE) group were significantly below those of the generalized group, while the focal group did not differ significantly from the others. Comparisons between pairs of groups showed no significant differences on any of the validity and clinical MMPI scales, although the TLE group generally showed the most elevated scores, and the generalized group the least elevated.

In the Glass and Mattson study (Note 2) all groups were asked to make self-reports on the extent to which they believed nine different emotional states caused an increase in seizure frequency. Roughly equivalent percentages of subjects in the Temporal Lobe Epilepsy group (75%), the Focal Non-Temporal-Lobe Epilepsy group (65%), and the Generalized group (75%) reported that some emotional states caused an increase in seizure frequency. Although none of the individual category differences reached significance, the Temporal Lobe Epilepsy group reported a mean of 2.5 of the 9 possible states as resulting in increased seizure frequency, as compared to the mean of 1.6 for the Generalized group and 1.9 for the Focal group. The results suggest that temporal lobe epilepsy, and to a lesser degree other focal epilepsy, are related to both heightened MMPI psychopathology and sensitivity of seizures to emotional precipitation. In the analysis of the effects of emotional

states on seizure frequency, the inter-group differences found here indicate that range of sensitivity across a spectrum of emotional states, rather than simply presence versus absence of such effects, may be intrinsically related to seizure type.

Mazurowa and Popielarska (1976) studied the effect of parental attitudes on the occurrence of psychological problems in epileptic children. In studying the case reports of 272 patients (146 boys and 126 girls) treated in the psychiatric department and out-patient clinic at the Institute of Paediatrics of the Medical Academy in Warsaw for at least three years, three main patterns of parental attitudes towards the epileptic child were recognized: (a) an overprotective attitude (58%); (b) an inconsistent attitude (32%); and (c) a rejecting attitude (8%). The authors assert that certain psychological disturbances occurred as a function of these parental attitudes, in the form of abnormal development of emotions and cognitive functions as well as abnormal social adaptation. Mazurowa and Popielarska (1976) stress the widespread occurrence of incorrect parental attitudes and the necessity of psychotherapeutic influence on the parents.

Mood disorders present in epileptics may be qualitatively or quantitatively different from mood disorders in non-epileptics. Taylor (1977) notes that the consensus of current literature is that there is an increased risk for schizophrenia in people with temporal lobe epilepsy. Cazzullo (1959) discussed the alterations in consciousness that occur in epileptics as a direct consequence of their seizures.

Scott (1977) discusses the interrelatedness of psychiatric problems and seizures in epileptic children and adolescents. He observes that seizures and psychiatric problems can combine to produce

both genuine epileptic attacks and functional attacks in the same patient. Scott (1977) emphasizes that children who are incapacitated for whatever cause have an increased psychiatric morbidity, and epilepsy is one of the disorders of the brain which leads to psychiatric problems. However, these psychiatric problems are not of a particular type and there is no evidence of what has been called the epileptic personality. The cause of psychiatric disturbance is the same in both epileptic and non-epileptic children, including such factors as maternal psychiatric illness and broken homes. Points of importance in the genesis of psychiatric morbidity appear to be early onset of epilepsy, chronicity, and brain damage. Seizures with EEG evidence of temporal lobe dysfunction are particularly likely to be associated with psychiatric disorder.

Semenov and Kamenskaya (1973) studied the effects of mental and emotional stress on the convulsive susceptibility of 100 epileptics with various types of seizures. Emotional stress was induced by stimulating recall of mental images of situations associated by the patient with positive or negative emotions; an EEG recording was made during the stimulation of emotional stress. Semenov and Kamenskaya (1973) noted no constant specific factors which may cause seizures; any afferent stimuli, mental activity, or emotional stress, depending on the degree of the changes in the state of brain function and reactivity and the localization of the pathological focus, can enhance convulsive susceptibility and provoke paroxysms. However, the authors did find that emotional factors may provoke and increase the frequency of paroxysmal activity in patients with multiple foci, and also in patients with subcortical and temporal foci. The mental recall of negative emotions induces responses with increased paroxysmal activity more frequently than the recall of

positive emotions. This result suggests that not only the strength of emotional stress, but also the quality of emotional reactions is important.

The general relationship between epileptic seizures and menstruation. Gastaut and Tassinari (1966) discuss various triggering mechanisms they have found in epilepsy by reviewing their own cases and by reviewing the literature. They found that all types of seizures have been reported to increase in frequency and intensity as menstruation approaches. These authors also found that puberty plays an important role in the genesis of seizures, especially in females, often coinciding with the appearance of generalized tonic-clonic seizures or, less commonly, of partial seizures. On the other hand, puberty often marks the disappearance of generalized non-convulsive absence seizures which can sometimes be replaced by generalized tonic-clonic seizures. Menopause can lead to the reappearance of seizures which had disappeared long ago. Pregnancy may reduce or entirely repress seizures, which appear again after delivery (Klessens, 1948). Gastaut and Tassinari (1966) conclude that cyclic seizures depend on factors modifying generalized biologic constants, especially a global modification of the threshold of cerebral excitability, which are extrinsic to the epileptogenic focus.

Gastaut and Tassinari (1966) also cite episodes of rest following sleep deprivation, or physical or intellectual fatigue as precipitating the appearance of epileptic seizures. Emotions may also trigger seizures, but Gastaut and Tassinari (1966) note that in none of their own cases were they able to collect objective proof of the relationship between the emotion and the seizure. Their observations of the relationship between emotions and seizures were based exclusively on the subjective

report of the patients or their families. They also noted that they have been able to collect only ten patients whose seizures were regularly provoked by emotions.

Dickerson (1941) followed 269 female epileptics for one year, and found that only 10% showed a relationship between menstruation and seizure incidence. During this calendar year, Dickerson noted an average of only four periods per patient, indicating marked menstrual irregularity.

Sutter and D'Eshougues (1949) discussed the relationship of menstruation to epileptic seizures, and stated that the slighter the local, nervous system predisposition to seizures, the more pronounced will the general disturbance have to be, such as hormonal changes during menstruation, before general disturbances can produce an attack.

Aird and Gordan (1951) obtained an anticonvulsant effect in eleven patients with refractory epilepsy using desoxycorticosterone acetate in the form of oral tablets in a double blind study using placebos. While desoxycorticosterone acetate was shown to be a good anticonvulsant by its increasing of the threshold of electroshock, cortisone and cortisol were found to be convulsant using the same method. In vitro studies by Michaelis and Quastel (1941) showed an anesthetic effect of steroids which was dependent upon the inhibition of the utilization of glucose and oxygen by brain tissue. Brain cells respiring in a glucose substrate take up oxygen at a fairly constant rate and the addition of steroids produces a prompt inhibition of the rate of oxygen uptake by these cells. The most potent steroids producing the effect were desoxycorticosterone and progesterone. The site of inhibition was shown to be probably at the dehydrogenase level rather than the cytochromes where other anesthetic agents exert this effect.

If steroids can inhibit the oxygen uptake of the brain, the hypothesis seems reasonable that steroids can act as brakes on cerebral metabolism (Sanchez Longo & Gonzalez Saldana, 1966). Since progesterone is one of the steroids that lowers oxygen uptake and reduces cerebral metabolism, increased progesterone should tend to raise the convulsive threshold and produce an inhibiting or protective effect against seizures.

Tsung-Yi, Greenblatt, and Solomon (1952) report on one case of petit mal epilepsy, and found that petit mal EEG discharges were the most irregular when their patient was menstruating, even more irregular than when she missed her medication.

Laidlaw (1956) surveyed fifty women who had 33,468 seizures over 939 patient years, and concluded that 72% of these patients had an increased incidence of seizures immediately before, during, and after menstruation, with a markedly reduced incidence of seizures during ovulation and the mid-luteal phases of the cycle. Unfortunately, Laidlaw (1956) did not take blood samples from his subjects to analyze their estrogen and progesterone levels, so he could not prove that the women had ovulated. The present study indicates that epileptic women have a high incidence of anovulatory cycles, so hypotheses about changes in seizure frequency due to or correlated with changes in hormone levels need to be substantiated by measurement of hormonal levels at different stages of the cycle.

Ansell and Clarke (1956) investigated the role of water retention and sodium metabolism in epileptic seizures during the menstrual cycle. Of the 148 female epileptics they studied, 63% reported more seizures during menstrual bleeding or during the twenty-four hours immediately preceding it; in fact, in some cases the seizures occurred more commonly

with the periods than before them. This relationship seemed to be equally common in both idiopathic and symptomatic groups. The premenstrual syndrome was no more common in epileptics than in healthy women, and it seemed to be as common in those with as in those without a menstrual aggravation of seizures.

In investigating water retention, Ansell and Clarke (1956) found no differences in changes in water retention between epileptics and non-epileptics, and there was no difference between those with and those without a menstrual exacerbation of seizures. When body weight and seizures were charted, there was no correlation between the greatest increase in weight and increased incidence of seizures; nor was there a correlation between the degree of premenstrual stress and the edema. Ansell and Clarke (1956) conclude that premenstrual edema does not play a primary role in the pathogenesis of menstrual epilepsy. The authors also found that alteration of sodium metabolism, with consequent retention of water before and during the menstrual period, was also not a prime factor in the pathogenesis of menstrual epilepsy. If water retention is not directly responsible for the premenstrual and menstrual exacerbation of epileptic seizures, Ansell and Clarke (1956) suggest that the complex hormonal changes that produce water retention may play a prominent role.

Bandler, Kaufman, Dykens, Schleifer, and Shapiro (1957) reviewed the literature relating epileptic seizures to menstruation, and noted that in most instances up to the time of their report the relatedness is a clinical impression rather than a statistical conclusion. Bandler et al. (1957) also noted that up to the time of their report, no studies were available which offered data about the normality of the menstrual

cycle in epileptic women with respect to length and ovulation; thus, no knowledge was available as to whether epileptic women as a group ovulate or not. Bandler et al. (1957) defined each menstrual cycle by means of daily vaginal smears and basal temperature records into five phases: ovulation, progestation, premenstruation, menstruation, and proliferation. They found that 23 of the 29 subjects studied over a period of three years ovulated every cycle, and the remaining six ovulated in at least half the cycles; they conclude that epileptic women have normal ovulatory menstrual cycles. The present study will demonstrate that the group of women that were followed do not have normal ovulatory menstrual cycles. Bandler et al. (1957) also examined the relationship between phases of the menstrual cycle and seizures by applying the chi square method to a comparison of the percent time represented by each phase and the percentage of all seizures occurring in that phase for each woman. By using this method, they found no significant increase of seizures during any phase. For Bandler's sample, seizures occurred at random throughout the menstrual cycle.

Bandler et al. (1957) also raise the issue of why their sample of women have a tendency to relate seizures to the menstrual cycle, when statistical analysis shows no relationship. They believe the answer lies in the psychological significance of menstruation and the dynamic meaning of a particular phase of the cycle to the patient at that particular time; for example, a patient with a strong unconscious wish for a child may suddenly have many seizures at the time of ovulation. These hypotheses, however, remain speculative.

Zaichkina (1963) studied sixty patients suffering from menstrual epileptic seizures. In twenty-five cases the connection between the

menstrual cycle and epilepsy was apparent only at a definite period, namely at puberty, in pregnancy or during the puerperium. During the pre-menstrual period 40 of the patients had severe vegetative disorders and 30 suffered from nervous tension. Many were found to have endocrine disorders and low blood pressure. Serial evaluation of sex hormones in the urine at various stages of the menstrual cycle revealed two types of deviation from normal excretion according to which the patients could be divided into two groups: one with hyperfolliculinuria (200 to 250 mg. of estrogens excreted) and the other with hypofolliculinuria (70 to 130 mg. of estrogens excreted). In the first group the excretion of pregnanediol was decreased, especially during the premenstrual period, while in the second group pregnanediol was excreted in excess. It was noted, however, that over a number of cycles the hormonal activity varied in one and the same patient. Zaichkina (1963) concludes that the deterioration of the patients' condition during the premenstrual and menstrual periods is not due to an increase or decrease in one or the other hormone, but to a disturbance of their balance. Zaichkina (1963) postulates that because of the role of hormonal disturbances in catamenial epilepsy, a combination of cortical temporal and diencephalic factors operate in these cases. Treatment should therefore consist of both anticonvulsants and hormonal preparations.

Sanchez Longo and Gonzalez Saldana (1966) report on three epileptic women who had seizures which occurred during menses or just prior to the onset of menses. In one of their patients, administration of the oral contraceptive Enovid, which contains both estrogen and progesterone, resulted in complete control of all her seizures.

Enovid contains 65 times more progesterone than estrogen in the mixture.

Sanchez Longo and Gonzalez Saldana (1966) also report on their overall clinical experience with epileptic women and observe that ovariectomy reduces epileptic seizures in patients; seizures often begin, or preexisting attacks recur or worsen at the menarche; seizure incidence is significantly depressed at the menopause in some instances; and estrogens appear to aggravate the epileptic condition.

Sallusto and Pozzi (1964) reported the case of a female patient who suffered convulsive seizures before puberty and later at menopause, but not at all during her reproductive years. The authors attributed the occurrence of the seizures at these times to the absence of progesterone activity, and hypothesized that during the fertility years the balance of estrogen-progesterone prevented the occurrence of seizures.

Backstrom (1976) made comparisons between the number and severity of seizures in epileptic women and their estrogen/progesterone ratios across different phases of their menstrual cycles. A comparison between 10 days with high estrogen/progesterone ratios during the follicular phase, and low estrogen/progesterone ratios during the luteal phase showed that both the number and severity of seizures was significantly higher during the follicular phase than during the luteal phase. This is in agreement with Laidlaw's (1956) demonstration that seizures are mildest during the luteal phase, and Logothetis et al.'s (1959) induction of grand mal seizures by treatment of epileptic patients with estrogen.

Rosciszewska, Dudkiewicz, and Blacharz (1976) carried out cytohormonal investigations during the menstrual cycle in 16 epileptic women aged 18 to 38. Estrogen and progesterone levels were calculated, and the authors found that in all but two cases the hormonal fluctuations

were abnormal. In 13 patients hypoestrogenic cycles were observed without adequate progesterone activity in the luteal phase; and in one patient estrogen levels were abnormally high. The authors hypothesized that very long anticonvulsant treatment as well as lower efficiency of the hypothalamo-hypophyseal system may reduce the level of steroid hormones produced by the ovaries.

Backstrom and Jorpes (1979) studied the relationship of serum anti-epileptic drug levels to the plasma concentrations of estrogen and progesterone. Six ovulatory and three anovulatory cycles were studied in seven patients with epilepsy, all of whom had been maintained on a constant dosage of anticonvulsant medication for at least one month prior to the investigation. Blood samples were taken every day. No correlations were obtained between the plasma hormone concentrations and the serum levels of the anti-epileptic drugs. Backstrom and Jorpes (1979) conclude that there is no evidence that the relationship between the seizure frequency and plasma hormone concentrations shown in a previous study (Backstrom, 1976) was related to a change in serum levels of the anti-epileptic drugs.

Summarizing the material presented in this section, the majority of authors have observed more seizures to occur just prior to and during menstruation in epileptic women. These authors have also observed that progesterone tends to inhibit seizures, while estrogen tends to exacerbate seizures. However, none of the studies presented above are carefully controlled statistical studies in which hormone levels and seizure frequency are systematically recorded. Most of the studies done to date relating epileptic seizures to the menstrual cycle are clinical case reports, rather than studies following a large number of women over an extended time.

The hormonal organization of the menstrual cycle, and its relationship to stress and epileptic seizures. The organization of the human menstrual cycle occurs through the interplay of hormones produced in the hypothalamus, the pituitary, the ovaries, and the placenta. During menstruation, the hypothalamus responds to the low levels of estradiol with the production of the follicle-stimulating hormone (FSH) secreted by the anterior pituitary. The single egg discharged each month from one or the other ovary matures in a follicle. This follicle grows in size and in number of cells during the early part of the menstrual cycle under the influence of FSH. As the follicle grows, its cells secrete the estrogenic hormones, chief among them estradiol, that act on both the pituitary and the uterus. The feedback to the pituitary reduces the output of FSH; the effect on the uterus is to stimulate the growth of the uterine wall and its glands.

As the follicle approaches full size, FSH output decreases while levels of estradiol increase, finally reaching a critical level at which a positive feedback on the hypothalamus results in the midcycle luteinizing hormone (LH) surge necessary for ovulation and the formation of the corpus luteum. LH completes the maturation of the egg and triggers the rupture of the follicle, discharging the egg into the oviduct. It also causes the residual follicle cells to be transformed into the corpus luteum, which secretes a second ovarian hormone, progesterone, that acts on the uterine wall to sensitize the uterus to contact with the blastocyst cells if fertilization occurs. If pregnancy does not occur, a new set of ovarian follicles begin to grow, and the corpus luteum derived from the ovulated follicle begins to decline. The demise of the corpus luteum results in a fall in progesterone levels, which produces

degenerative changes in the uterine wall, and menstruation begins. The low levels of progesterone and estradiol cause the hypothalamus to begin producing FSH again, and a new cycle is initiated (Grobstein, 1979).

This recycling mechanism is regulated in large part by estradiol. The negative feedback relationship of estradiol with follicle-stimulating hormone (FSH) results in the critical initial rise in that gonadotropin during menses, and the positive feedback relationship of estradiol with luteinizing hormone (LH) is the ovulatory trigger. Estradiol may therefore be viewed as the signal for appropriate hypothalamic-pituitary responses in this system. Two possible types of signal failure may occur: (a) levels of estradiol may be inadequate to produce the positive stimulatory effects necessary to induce the ovulatory surge of LH; and (b) estradiol levels may not fall low enough to allow sufficient FSH responses for follicular stimulation.

In this second instance, the necessary decline in blood estradiol requires cessation of secretion, appropriate clearance and metabolism, and the absence of a significant contribution of estradiol to the circulation by extragonadal sources.

Extragonadal contribution to the blood estrogen level has assumed recent and significant importance (Speroff, Glass, & Kase, 1973). While the adrenal gland does not secrete appreciable amounts of estrogen into the circulation, its normal function contributes to the total circulating levels of estrogen. This is accomplished by the extragonadal peripheral conversion of C-19 androgenic precursors, such as androstenedione, to estrogens. In this manner, psychological or physical stress may increase the adrenal contribution of estrogenic precursor, and subsequent conversion to estrogen may sustain the blood level of estrogen

at a time when a decline is necessary for successful recycling of the menstrual system. Anovulatory cycles will result.

From the above, the author suggests that greater reported stress would be associated with a larger number of anovulatory cycles for the epileptic women in the current study. Also, since high estrogen levels are associated with an increased frequency of seizures among epileptic women, one could expect a higher incidence of seizures during anovulatory cycles than during ovulatory cycles, when the protective effect of progesterone is present. Then, if stress produces anovulatory cycles which are characterized by high levels of estrogen, and if high levels of estrogen produce seizures, then high levels of stress should be associated with a high frequency of seizures, even when only the hormonal mechanisms are taken into consideration.

Beta-blockers and their proposed relationship to stress and epileptic seizures. Beta-blockers are substances which competitively and reversibly block beta-adrenergic receptors in the sympathetic nervous system, therefore acting as antagonists of noradrenaline and adrenaline (Brunner, 1977). As such, beta-blockers have anxiolytic (anti-anxiety) effects, since increased adrenaline and noradrenaline release is specifically associated with anxious emotional states (Carruthers, 1977). Beta-blockers have been proven to be useful in combating clinical anxiety and phobias (Gosling, 1977; Lader, 1977). The effectiveness of small doses of oxprenolol (Trasicor) in reducing anxiety symptoms could be accounted for by postulating that this treatment interrupts a self-perpetuating spiral in which anxiety leads to adrenaline secretion and learned peripheral sympathomimetic symptoms increase the anxiety still further (Breggen, 1964). Hypothetically, then, the author suggests

that beta-blockers such as oxprenolol (Trasicor) might be used by epileptics who are experiencing high degrees of stress, as a way of reducing seizures precipitated by stress. A possible side effect, which should occur only rarely if at all (Pichot, Olivier-Martin, & Poggioli, 1977), is drowsiness. However, Krishnan (1975) administered oxprenolol to nervous students studying for an examination, and concluded that the oxprenolol did not interfere with the students' critical faculties and therefore may be of value in treating people who have to face stressful situations calling for unimpaired cerebral function.

Since increased stress in epileptics should lead to increased adrenal production, and since increased adrenal production causes extra-gonadal production of estrogen, which leads to a higher seizure frequency and anovulatory cycles as already discussed, administration of beta-blockers to epileptics may result in a positive feedback loop in which seizures due to both increased stress and increased estrogen production, and to the cause-and-effect relationship between stress and increased estrogen production, are controlled.

Beta-blockers have already been given a trial in the prevention of the occasional tachycardia provoked by driving in busy traffic, the correction of cardiovascular and metabolic changes caused by public speaking, the treatment of catecholamine-induced symptoms in professional musicians, and the relieving of examination nerves in students (Siitonen & Janne, 1977). Beta-blockers can be used with success in cases of anxiety and tension, especially since they seldom produce unwanted side effects and do not give rise to drowsiness. Beta-blockers have been used in sports medicine in order to prevent the cardiovascular effects of intense emotional stress, such as that associated with car racing or

ski jumping. From most of the studies published it appears that small doses of beta-blockers do not impair either mental or physical performance; on the contrary, they may even improve it (Siitonen & Janne, 1977).

Theories explaining catamenial epilepsy. Thiry, Heusgem, and Legentil (1954) found one-third of a group of 58 women with catamenial epilepsy (seizures aggravated during menstruation) to suffer from hyperestrogenuria, further evidence for the disruptive role of estrogen in causing increased seizure frequency. Thiry et al. (1954) also raised the question of whether the endocrine disturbances observed are the consequence of disturbance or dysfunction of the diencephalic centers reacting on the hypothalamohypophyseal system. Their results suggested some degree of depression of the hypothalamohypophyseal system from the barbiturate treatment which the majority of these patients received for their seizures.

Logothetis, Harner, Morell, and Torres (1959) reviewed the main theories to explain the increased incidence of seizures shortly before or during menstruation in about 50% of epileptic women: (a) Premenstrual psychic disturbances and emotional instability have been thought to be of primary importance in the precipitation of seizures. Against the exclusively psychogenic theory is the fact that, although psychic premenstrual disturbances usually disappear with the onset of menses, exacerbation of seizures usually continues during the menstrual flow. (b) Water retention has been thought to be partly responsible for the symptoms of the premenstrual syndrome. (c) Progesterone is suggested to have anticonvulsant properties, since seizures are fewest when progesterone levels are greatest. (d) Estrogens appear to aggravate seizure frequency; when they are given to epileptic women premenstrually, seizures increase.

Logothetis et al. (1959) injected Premarin, an estrogen, into 16 epileptic women, and observed clear activation of electroencephalographic abnormalities in eleven of these women within 20 minutes of injection. Thirteen patients were given 20 mg. of Premarin, resulting in clinical seizures 12 to 24 hours after injection in one patient. Three patients were given 40 mg. of Premarin; all three had seizures fifteen minutes to a few hours after injection. The occurrence of seizures hours after injection of Premarin suggests a convulsive effect of estrogenic substances. If naturally occurring estrogen does precipitate seizures, one would expect seizure frequency to be greatest shortly before ovulation, when estrogen levels are highest. If, on the other hand, high levels of estrogen increase seizures while at the same time progesterone acts as a seizure inhibitor so that rapidly falling levels of progesterone increase seizures, two peaks of seizure activity during the menstrual cycle might be noted: (a) the first, shortly before ovulation when estrogen is at its peak; and (b) the second, immediately pre-menstrually and menstrually when progesterone levels are lowest.

Logothetis et al. (1959) note that if seizures are precipitated by increased estrogenic activity, administration of hormones having antagonistic properties to estrogen, such as testosterone and progesterone, may help prevent attacks. Logothetis et al. (1959) observed improvement in 3 out of 5 patients placed on 10 mg. of progesterone three times a day for 4 to 6 days before menstruation, after following these patients for six months. Costa and Bonnycastle (1952) had earlier found that progesterone prevented the appearance of convulsions following administration of a convulsant agent. Spiegel and Wycis (1945) also found that progesterone has an anticonvulsant effect.

Sanchez Longo and Gonzales Saldana (1966) reported the relationship between frequency of epileptic seizures and the menstrual cycle in three patients. Control with therapeutic levels of anticonvulsant drugs in these patients was poor, but striking improvement occurred after an oral contraceptive containing mestranol (an estrogen) and norethynodrel (a progesterone) was given. Seizures recurred on withdrawing this contraceptive and ceased when the contraceptive was resumed. Sanchez Longo and Gonzales Saldana (1966) reviewed the literature on the effects of hormones on brain activity, and concluded that, in general, estrogens, ACTH, and cortisone lower the threshold for seizures, while testosterone, progesterone, and desoxycortone acetate raise the seizure threshold.

Here is a case in which a combination estrogen-progesterone contraceptive reduced seizure frequency, which is in contrast to most of the literature in which combination drugs either have no effect on seizures or increase seizure frequency.

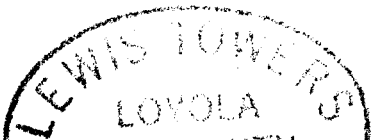
Stitt and Kinnard (1968) found that estrogen, administered in the form of estradiol benzoate, lowered the electroshock threshold in rats. Administration of progesterone had little effect on electroshock threshold. Werboff and Corcoran (1961) found that estradiol administration to castrated male rats resulted in an increase of audiogenic seizures, while in female rats testosterone administration and ovariectomy resulted in a decrease in seizure responses.

Wieczorek, Bock, and Kluge (1969) studied the effect of the ovulation inhibitor Ovosiston on 31 female epileptics. Ovosiston is a combination contraceptive that contains both estrogen and progesterone, in the forms of mestranol and pregnanediol, respectively. In the large majority of the cases reported by Wieczorek et al. (1969), the epileptic

women failed to show either a decrease or increase in the frequency of their seizures following a drug regimen of both ovosiston and their usual therapeutic dosage of anticonvulsant drug. In some individual cases an increased susceptibility to seizures occurred following the administration of Ovosiston. This study lends support to the thesis that combination estrogen and progesterone preparations have no effect or increase susceptibility to seizures in epileptic women.

Knight and Rhind (1975) investigated the relationship of epilepsy and pregnancy in 153 pregnancies of 59 epileptic patients. Six patients showed a tendency to have more frequent convulsions in relation to menstruation. Rosciszewska and Grudzinska (1975) found the relationship between increased seizure frequency and menstruation to be particularly marked in those patients who experienced their first convulsions during pregnancy. Over one-third of the weight gained in pregnancy is due to fluid retention; Dimsdale (1959) showed that rapid and excessive weight gains preceded more frequent seizures. The same mechanism may underlie seizures that occur predominantly at the time of menstruation, but such patients do not necessarily experience more frequent attacks when pregnant. A mechanism of increased seizure frequency during pregnancy may be as follows: increased secretion of estrogens, glucocorticoids, and aldosterone may be found during pregnancy, and all would tend to cause water and sodium retention which might dehydrate brain cells and cause seizures. However, a clear relationship between hormonal levels and clinical events has not yet been found (Knight & Rhind, 1975).

Hall (1977) reports a patient who suffered from an increased frequency of seizures before and during menstruation (catamenial epilepsy), associated with severe dysmenorrhea. Total control of seizures was



achieved by continuous administration of a low dose of progesterone, namely 0.35 mg. daily of Norethisterone, while she continued on her original dose of 90 mg. daily of phenobarbital. Norethisterone is a progesterone-only preparation. The patient was completely seizure-free for the seven months she had taken Norethisterone, and in addition had only mild dysmenorrhea.

Menstrual exacerbation of epilepsy occurred in 72% of the patients studied by Laidlaw (1956). Laidlaw suggested that the reduction of seizures in the luteal phase of the cycle is due to an anticonvulsant action of progesterone; the increase of seizure frequency before and during menstruation would then be explained by the diminished secretion of progesterone at that time.

Bickerstaff (1975, pp. 87-90) reported complete control of seizures using estrogen-progesterone combinations in some epileptics, but also noted that certain groups of epileptics are liable to an exacerbation of their seizures when using combined oral contraceptives. Zimmerman et al. (1973) reported complete control of seizures using injectable medroxy-progesterone acetate (Depo-Provera). Hall (1977) is the first report of complete seizure control with an oral progesterone-only preparation. The literature suggests that a trial of progesterone-only preparations may be warranted for control of catamenial epilepsy.

Backstrom (1977) studied nine periods in seven female epileptics. Six menstrual cycles were ovulatory and consequently accompanied by a rise in plasma progesterone after ovulation, and three cycles were anovulatory. Two periods of increased generalized seizure frequency were observed in the ovulatory cycles: one shortly after the rapid decrease of progesterone menstrually; and the second during the preovula-

tory elevation of estrogen. Partial seizures were observed to occur more evenly throughout the cycle, but with a trend towards peaks in increased seizure frequency at the same points as the generalized seizures. During times of high progesterone the number of generalized seizures was very low. A comparison between the follicular and luteal phases showed the greater number of generalized seizures occurring during the follicular phase, and fewer days were completely free from generalized seizures during the follicular phase. The three anovulatory cycles all showed an increased number of seizures during estrogen peaks. Backstrom (1977) notes that his findings are compatible with Laidlaw's (1956) hypothesis that progesterone inhibits seizures while falling levels of progesterone result in increased seizure frequency; and Logothetis et al. (1959) who found that estrogen activates seizures. Backstrom (1977) also suggests that further studies are needed to exclude a possible effect of hormones on changed serum concentration or binding of antiepileptic drugs.

In addition to the adverse effect estrogen seems to have on seizure frequency in epileptics, Backstrom (1977) believes that it also has an effect on premenstrual tension in non-epileptic women. Backstrom and Carstensen (1974) compared women who suffered from a pre-menstrual tension syndrome with a control group, and found that during the 2 to 5 days before the first day of menstruation the pre-menstrual tension group had significantly higher plasma estrogen levels than the controls. The plasma progesterone levels in the pre-menstrual tension group were significantly lower than in the controls during the whole mid-luteal phase. The estrogen/progesterone ratios were also significantly higher on days 3-6 before menstruation. This difference in plasma estrogen levels

between the pre-menstrual tension group and the control group was not due to changes in the plasma binding activity of estrogen. Backstrom and Carstensen (1974) also found a correlation between symptoms of anxiety and irritability and the plasma estrogen level on the third day before menstruation, suggesting that estrogen may influence emotional states in women.

An interesting extension of Backstrom (1977) and Backstrom and Carstensen's (1974) work would be to compare estrogen and progesterone levels between epileptics who have the greatest seizure frequency and those who have the least seizure frequency. Do women with the greatest number of seizures have significantly higher plasma estrogen levels and lower plasma progesterone levels?

Stress

Stress contributes to menstrual dysfunction and seizures. The concept of stress, first put forward in definite form by Selye (1946), has undergone radical revision in recent years. The original concept, developed solely from observations in the experimental animal, foretold in general the results of the non-specific reactions to various forms of stress, particularly those concerned with endocrine and metabolic transformations. The essence of Selye's hypothesis was that all stimuli resulted in either mental or physical stress, the reaction to a stimulus being determined by the integrated sum of the stresses induced.

This basic concept was extended by Levi (1972) and his colleagues. They have proposed that the stress induced by psychic stimuli originating from environmental causes or society-related events is determined by the propensity of each individual to react in the light of his experience,

with "genetic factors" influencing this psychobiological response to stimuli. The stress engendered by this composite reaction may under certain circumstances increase the subject's susceptibility to disease and may even lead to disease itself. This sequence of events may be promoted or neutralized by a number of negative feedback interactions. In its usual connotation, "stress" is almost universally accepted as being an accompaniment of noxious stimuli. One of the crucial points in the chain of reasoning presented above, however, is that nearly all psychic changes, whether pleasant or unpleasant, can be expected to evoke a stress reaction. This is an aspect of the stress thesis that has been largely ignored in the past.

The studies of Rahe (1969) lend support to the concept that the relationship between stimulus and stress is U-shaped. Rahe found that the relationship between life change (sum of pleasant plus distressing changes) and morbidity is unipolar, i.e., the higher the sum of stimuli the greater the morbidity risk. However, no one has subjected the evidence linking the many and complexly interrelated factors involved in such proposed mechanisms to critical analysis; extreme caution is necessary before such arguments are accepted as fact and before unwarranted cause-effect relationships are extrapolated.

Considerable difficulties exist in attempting to differentiate the primary effects of physical stimuli, or the physical reactions induced by stress, from the secondary or tertiary effects elicited by psychological reactions to these stimuli (Mason, 1977). Every factor stands in a cause-effect relationship to others; and, since it is rarely possible to define and measure all of them, their interactions and resulting biological activity can only be guessed at. Moreover, if

disease is indeed produced by psychic stress, then the disease itself can be expected to alter the response of the organism to the same stimulus. However, at a clinical therapeutic level the problem is more straightforward. Whatever may be the interplay of the primary, secondary, and other mechanisms concerned, and whatever may be the complex neuronal pathways followed by such stimuli in the central nervous system, the efferent effector pathways are clear; they predominantly involve the autonomic nervous system and, in particular, its sympathico-adrenal component. Selective interventions in the final common pathway of the physiological accompaniments of stress are thus possible and provide a useful therapeutic tool with which to analyze the link between psychic stress and its postulated disease potential (Taylor, 1977).

Various usages of the word "stress" have given rise to misunderstandings between the scientist working in animal-experimental research and the clinician. Both speak of "stress," but forget that, in the case of animals, cognitive factors can be disregarded under certain circumstances, with the result that the intensity of a stimulus may well correspond exactly to the intensity of the resultant "stress," whereas in man it is the cognitive factors associated with the stressful situation that have a decisive bearing on the strain involved, i.e., on the "stress." In clinico-experimental medicine an additional point to be considered is that the effect of stressful situations on the patients participating in a trial varies from one individual to another, the degree of variation being all the more pronounced the more closely these situations approximate to real life and thus resemble those occurring in genuine social interactions. The amount of strain imposed by such situations also depends on the patient's past history and on his ability to resist or

cope with strain.

Psychological stress can provoke symptoms, providing a setting for disease and sometimes even death. Engel (1968) collected 100 items from newspapers around the world, over a period of six years, reporting the occurrence of sudden death under unusual circumstances. One half of these deaths occurred in husbands or wives soon after the sudden death of their spouses. An additional ten died anticipating such a bereavement; 32 died suddenly during situations of danger; and 6 died on occasions of extraordinary joy. When psychological defenses crumble, neurally regulated, biological, emergency reactions take over; and in extreme cases these reactions may be catastrophic.

Cox (1978) reviewed the various approaches in the scientific literature to the study of stress and delineates three main approaches: (a) The first approach treats stress as a dependent variable for study, describing it in terms of a person's response to disturbing or noxious environments. (b) The second approach describes stress in terms of the stimulus characteristics of those disturbing or noxious environments, and thus usually treats it as an independent variable for study. (c) The third approach views stress as the reflection of a lack of fit between the person and his environment. Stress in this form is studied in terms of its antecedent factors and its effects. It is seen as an intervening variable between stimulus and response. Much of the physiological response to stress is not directly determined by the actual presence of the stressor agent but by its psychological impact on the person. This last approach to stress is the one favored by the present author.

In 1970, Weitz reviewed and classified the different types of situations which have been treated as stressful in current research.

He described eight: (a) speeded information processing, (b) noxious environmental stimuli, (c) perceived threat, (d) disrupted physiological function (as a result of disease, drugs, sleep loss, and so on), (e) isolation and confinement, (f) blocking, (g) group pressure, and (h) frustration. In addition, Lazarus (1966, 1974) sees perceived threat as the central characteristic of stressful situations and, in particular, threat to a person's most important values and goals, while Frankenhaeuser (1975a, 1975b) would add lack of control over events to Weitz's list.

Cox (1978) gives a working definition of stress which the present author views as a good framework for conceptualizing the present research results:

> Stress, it is argued, can only be sensibly defined as a perceptual phenomenon arising from a comparison between the demand on the person and his ability to cope. An imbalance in this mechanism, when coping is important, gives rise to the experience of stress, and to stress response. The latter represent attempts at coping with the source of stress. Coping is both psychological (involving cognitive and behavioral strategies) and physiological. If normal coping is ineffective, stress is prolonged and abnormal responses may occur. The occurrence of these, and prolonged exposure to stress per se, may give rise to functional and structural damage. The progress of these events is subject to great individual variation. (p. 25)

Viewed in this way the physiological response to stress is itself a form of coping mechanism. The physiological response is dominated by the major psychoendocrine systems, the sympathetic-adrenomedullary and pituitary-adrenocortical systems. Both are influenced by hypothalamic

and higher brain activity. Beginning with Cannon (1927) and repeatedly demonstrated by his successors, the sympathetic-adrenomedullary system has been shown to be responsive to environmental stimuli, both physical and psychological, and that its function should be discussed in relation to the individual person's behavior.

Qualitatively different stressors, but of the same potency, do not elicit exactly the same syndrome, and the same degree of stress induced by the same stressor may have different pathological effects in different individuals. Selye (1975) has addressed the issue of individual variations to stressors by observing, first, that different stressors may only differ in their specific effects and not in their non-specific stress effects. For example, cold produces shivering and heat produces sweating. These are specific effects. They both produce increases in adrenocortical activity, which is a non-specific stress effect. It has to be accepted that in some instances the specific effects may modify the non-specific effects. Individual differences in the pathogenic effects of the stress response Selye (1975) ascribes to conditioning factors, both endogenous (genetic predisposition, age, sex, personality) and exogenous (learning, drug and other physical treatments, diet). Such conditioning factors can selectively enhance or inhibit different aspects of the stress response.

Cox (1978) discusses the mechanism of physiological reaction to stress. The initial alarm reaction involves increases in sympathetic-adrenomedullary activity, while the stage of resistance is characterized by increased adrenocortical activity.

The activity of the adrenal cortex appears to be regulated to a large extent by the level of adrenocorticotropic hormone (ACTH) in the

blood. Adrenocorticotropic hormone is released by the anterior pituitary, its output being controlled by the secretion of corticotropin releasing factor (CRF) into the pituitary portal blood vessels by the hypothalamus. Overall, the anterior pituitary releases two hormones which act in their own right, growth hormone and prolactin, and four tropic hormones, including ACTH, which act by controlling the behavior of other glands. All have been related to the response to stress, and might appear to be involved in the stage of resistance. However, it is the anterior pituitary-adrenocortical system which appears to dominate.

The adrenal cortex through the action of ACTH produces glucocorticoids, which during stress are produced in high concentrations and have the effects of blocking the inflammatory response, interfering with the manufacture of proteins, causing the loss of calcium and phosphate from the kidneys, and raising blood sugar levels. The latter action may be necessary to fuel the activity of coping during the stage of resistance, while the other actions may account for part of the cost of the coping.

Urinary catecholamines represent estimates of sympathetic-adrenomedullary activity, when integrated over extended time periods, usually 1-3 hours. Using urinary catecholamines as a measure of the stress response, many laboratory experiments and field studies have been carried out in the investigation of the occurrence of the effects of stress (O'Connor-Miller, 1980). Enhanced sympathetic-adrenomedullary activity has been shown to occur in subjects exposed to a variety of stresses (Kagan & Levi, 1975). From his review of many studies, Levi (1972) concludes that there can be little doubt that psychosocial stimuli can effect changes in sympathetic-adrenomedullary activity and adrenaline secretion. Most importantly for studies of the response to stress, he

also concludes that, although intersubject variability is great, within the individual subject catecholamine excretion roughly parallels the degree of reported emotional arousal.

Cox (1978) organized a table in which he lists some of the many behavioral, physiological and health effects which have been variously suggested to be linked to the experience of stress:

1. Subjective Effects: Anxiety, aggression, apathy, boredom, depression, fatigue, frustration, guilt and shame, irritability and bad temper, moodiness, low self-esteem, threat and tension, nervousness, and loneliness.

2. Behavioural Effects: Accident proneness, drug taking, emotional outbursts, excessive eating or loss of appetite, excessive drinking and smoking, excitability, impulsive behaviour, impaired speech, nervous laughter, restlessness, and trembling.

3. Cognitive Effects: Inability to make decisions and concentrate, frequent forgetfulness, hypersensitivity to criticism, and mental blocks.

4. Physiological Effects: Increased blood and urine catecholamines and corticosteroids, increased blood glucose levels, increased heart rate and blood pressure, dryness of mouth, sweating, dilation of pupils, difficulty breathing, hot and cold spells, "a lump in the throat," numbness and tingling in parts of the limbs.

5. Health Effects: Asthma, amenorrhoea, chest and back pains, coronary heart disease, diarrhoea, faintness and dizziness, dyspepsia, frequent urination, headaches and migraine, neuroses, nightmares, insomnia, psychoses, psychosomatic disorder, diabetes mellitus, skin rash, ulcers, loss of sexual interest and weakness.

6. Organisational Effects: Absenteeism, poor industrial relations, and poor productivity, high accident and labour turnover rates, poor organisational climate, antagonism at work and job dissatisfaction. (p. 92)

The chain of events which lead up to pathological reactions to stress can be broken in several ways. First, the elements which contribute to the cognitive appraisal of demand and capability and of the consequences of coping can be altered. This may be achieved by restructuring the external environment, by changing the person's level of mental, physical and social skill, by supporting him in the use of those skills, or by altering his perceptual and cognitive processes. Second, if the occurrence and experience of stress cannot be avoided then its psychological and physiological effects may be modified, as may be the actual and perceived consequences of those effects. These prescriptions can be elaborated on by considering the specific points in the stressful event and its aftermath where an entry can be made to break the critical progression to pathology. These entries can be made by the person himself, or by another person, a therapist, or a group of people. Meichenbaum (1974) has developed a self-instructional approach to stress management, among other researchers.

Another approach to the treatment of stress is the psychopharmacological. Kielholz (1975) has argued that antidepressants can be usefully classified in terms of their effects on three different types of symptoms: inhibited drive, basic feelings of sadness, and anxiety. For example, clinical and experimental studies suggest that the effects of monoamine oxidase inhibitors (MAOIs), such as iproniazid and pargyline, are dominated by increased drive and by mood enhancement, the former

being the greater effect. Thus MAO increases with stress, while MAOI's inhibit the effects of stress by increasing drive and mood enhancement. The tricyclic compound, imipramine, has relatively little effect on drive, but has a powerful effect on mood. Neither of these two drugs produces much relief of anxiety; this can be achieved through the use of trimeprimine or chlorprothixene. The prescription of the wrong drug can have disastrous effects. in depressive states involving anxiety, the use of a drug which increases drive may aggravate the anxiety and by releasing inhibition may increase the risk of suicide.

In treating the different types of neurosis, the minor tranquilizers, in particular the benzodiazepines, and both tricyclic and monoamine oxidase inhibiting antidepressants are used. The benzodiazepines have a muscle-relaxant effect. Perhaps their major clinical effect is due to their relatively selective action on the limbic system and they are used extensively in combating anxiety and tension. Of the antidepressants, the tricyclic compounds appear to have fewer major side effects than the MAOI's, and are therefore the drugs of first choice. The MAOI's are more effective in reactive than in endogenous depression.

The use of drugs in the treatment of neuroses is usually seen as a short-term crutch to allow patients to deal more effectively with the demands they are experiencing. The anxiety experienced by a person as a result of stressful demands may exaggerate the problem by reducing capability. Without benzodiazepine treatment the patient may not cope; with the drugs he might cope effectively.

No specific hormonal pattern is uniquely characteristic of menstrual disorders arising from psychogenic factors. Indeed, the literature indicates a variety of hormonal patterns, and presumably a

number of different mechanisms by which psychogenic factors may cause menstrual dysfunction. Rakoff (1968) summarizes the clinical observations suggesting a relationship between psychogenic factors and disorders of menstruation:

1. Amenorrhea or dysfunctional bleeding occurs in previously normally menstruating women immediately following an acute psychic trauma. The spontaneous return of normal cycles follows alleviation of the trauma.

2. An increased frequency of menstrual disorders occurs in psychotic and psychoneurotic women.

3. A high incidence of amenorrhea is present in the female population during periods of prolonged psychic stress, such as during wars.

4. Amenorrhea occurs with concomitant symptoms of pregnancy in situations in which there is a great desire for or fear of pregnancy.

On the basis of clinical observations and hormonal studies, Rakoff (1968) also suggests several pathways by which psychogenic factors may influence menstruation. These include:

1. Stimuli operating by way of the hypothalamus to influence the gonadotropic-releasing factors (Martini, Fraschini, & Motta, 1968).

2. A direct influence on the ovary by way of the sympathetic nervous system or by some other route (Richter, 1968).

3. A direct action on the endometrium (Richter, 1968).

4. The hypothalamic-pituitary-ovarian mechanism may be indirectly disturbed by extra-gonadal endocrine dysfunction of psychogenic origin involving particularly the adrenal cortex and possibly the thyroid (Gibbons, 1968; Eayrs, 1968; Levi, 1968).

Selye (1947) suggested that stress increases ACTH in the pituitary at the sacrifice of gonadotropin secretion. The mechanism may be that emotional stress or trauma induces hypersecretion of corticotropin-releasing factor at the sacrifice of secretion of FSH- and LH-releasing factor at the hypothalamic level, resulting in hypersecretion of ACTH and hyposecretion of FSH and LH at the pituitary level, which could result in anovulatory cycles.

Several other investigators suggest that one common denominator of the stress response is the increased release of adrenocorticotropic hormone (ACTH) from the pituitary, initiated by the corticotropin-releasing factor of the hypothalamus (Harris, 1948; Pincus & Elmadjian, 1954; Vernikos-Danellis, 1964). Adrenaline and noradrenaline secretion also have been taken as an index of the same response (Elmadjian, Hope, & Lamson, 1958; Euler, 1960; Swan, 1958, pp. 142-162).

Sympatho-adrenomedullary and related biochemical reactions during experimentally induced emotional stress. Homeostatic neuroendocrine regulation in man is affected by psychic stimuli (Roessler & Greenfield, 1962; Selye, 1950; Simon, Herbert, & Straus, 1961; Tanner, 1960). Man reacts not only to the actual existence of danger, but to threats and symbols of danger experienced in the past. Man wants to be prepared to meet a new situation the moment it occurs. This creates a situation in which homeostasis is adjusted not only to the needs of the organism in the prevailing conditions, but to the anticipated needs as well. Irrespective of whether this preparedness is adequate or not, it affects the adaptive-protective mechanisms of the living organism (Levi, 1967, pp. 78-105). The organism's pattern of response involves physiological as well as psychic processes (Bajusz, 1967).

In most of the psychosomatically-oriented medical literature various disorders have been related to a number of stressors to which the patients state that they were exposed prior to and/or in conjunction with the onset of the particular disease (Levi, 1967). The constellations of stressors inherent in everyday life are, however, very complex as a rule and it is, therefore, difficult from clinical data alone to distinguish between cause and effect in the medical chain of events.

The assessment of causal connections has been made easier by the use of psychophysiological experiments, in which various emotional reactions are first induced and then studied together with the accompanying physiological phenomenon (Levi, 1967). The results of Levi's series of experiments have proved a valuable complement to clinical observations.

The use of different kinds of functional and provocation tests has long been practiced in physiology and clinical medicine, the patient being exposed to such stimuli as physical work, ACTH, insulin, cold, allergens, and so on. The psychophysiological experiments make use of mental stimuli in a corresponding way. These stimuli include induced failure and induced disturbance in a task, stimuli that elicit anxiety and physical discomfort, working aginst time, isolation and sensory deprivation, and fatigue arising from prolonged work. A number of investigations in this field have been performed by Levi at the Laboratory for Clinical Stress Research in Stockholm. The experiments conducted include investigations of sympatho-adrenomedullary responses during pleasant and unpleasant emotional states; central nervous function and sympatho-adrenomedullary response; emotional stress; plasma lipids and catecholamine excretion; specific stressor effects of sympatho-adrenomedullary function; and long-term stress.

In all of these experiments, simultaneous recordings were made of a number of psychological as well as physiological and biochemical variables. The design usually involved a stress period, flanked by two control periods of equal duration or, alternatively, consecutive periods characterized by different degrees of intensity or quality of stimulus. The experiments suggested the following conclusions:

1. Psychic stimuli are capable of evoking an increased catecholamine excretion.

2. The between-subject variability in catecholamine secretion is very considerable, but intra-individually the catecholamine excretion very approximately parallels the degree of reported emotional arousal.

3. The catecholamine excretion rates of each individual during corresponding periods of different experiments are positively correlated.

4. Experimental stimuli evoking responses of calmness and equanimity lower the catecholamine excretion significantly below control levels.

5. Pleasant stimuli evoking amusement are nearly as potent as the unpleasant ones in provoking an increased catecholamine excretion rate.

6. Stressors of short duration and moderate intensity are potent in increasing free fatty acids and triglycerides of arterial plasma. This response is significantly blocked by treatment with large doses of nicotinic acid.

7. Stressors of longer duration (three days or more) are potent in inducing a number of bodily reactions including changes in erythrocyte sedimentation rate (ESR), protein-bound iodine and serum iron, as well as electrocardiograms (EKG) during work.

8. Some support has been found for the hypothesis that the experimentally-induced reactions reflect functional changes in the organism which, if they persist for a long time, may be of pathogenic significance in disposed individuals.

Thus, Levi's (1967) results suggest that emotional changes produce physiological changes in levels of catecholamines, fatty acids, triglycerides, erythrocyte sedimentation rate, electrocardiograms, protein-bound iodine and serum iron. The psychically produced emotions appear to be causes, and the physiological changes are the effects.

Levi (1968) conducted another series of experiments in which he demonstrated that (a) stimuli lowering the degree of emotional arousal below a control level decreased urinary catecholamine output; and (b) pleasant emotional stimuli were as effective as unpleasant emotional stimuli in evoking an increased sympatho-adrenomedullary response. Thus, mental stressors can elicit an increased release of adrenal hormones.

Gibbons (1968) found that a modest but significant increase in adrenocortical activity was a common accompaniment of all sorts of emotional disturbances, whether this was in response to the normal vicissitudes of life or to artificial situations in the experimental laboratory. Similar increases in adrenocortical activity were found in patients whose emotional disturbance was part of a psychiatric disorder. Gibbons (1968) also showed a modest increase in adrenocortical activity when a group of normal subjects encountered various novel experiences.

The results of these studies suggest that the intensity and duration of psychological stress may be accounted for on the physiological level by disturbances in (a) hormonal regulatory mechanisms, (b) vascular homeostasis, (c) permeability of histohematic barriers of the internal

organs, (d) blood-brain barriers, (e) tropic processes in the cells, (f) efferent and afferent neural transmissions, or (g) interrelationships between neocortex and subcortex centers.

Physiology of the Menstrual Cycle

The ovary. The ovary is anatomically divided into three separate compartments: (a) the follicles where germ cell maturation and estrogen synthesis occur during the first half of the ovarian cycle; (b) the corpus luteum, which is derived from the ruptured ovarian follicle and is responsible for progesterone and estrogen secretion during the latter half of the cycle; and (c) the interstitium which surrounds the follicles and corpus luteum and is responsible for androgen synthesis. Ovarian function is coordinated in a cyclic manner by the central nervous system, through the secretion of pituitary FSH and LH. During an ovarian cycle a group of follicles are developed, a single ovum is ovulated, and a corpus luteum develops and is maintained for a fixed period of time. As corpus luteum function decreases a new set of follicles begins to develop and a new ovarian cycle begins. During the ovarian cycle the endometrium proliferates under the influence of ovarian estrogen and progestins. With regression of the corpus luteum, the endometrium is sloughed and a menstrual period occurs. The period of time between the beginning of one menstrual period and the beginning of the next is termed the menstrual cycle (Bardin, 1973, pp. 7-95 to 7-111).

Although in the strict sense the ovarian cycle and the menstrual cycle refer to cyclic changes in the ovary and endometrium, respectively, these terms are often used synonymously with "reproductive cycle" which implies the cyclic morphologic and hormonal changes which occur in the central nervous system, anterior pituitary, ovary, and uterus.

Reproductive hormones.

1. Follicle-stimulating hormone (FSH). The function of FSH is to stimulate growth of the ovarian follicle. FSH promotes mitosis of the granulosa cells and conversion of the surrounding stroma into a layer of theca cells. Administration of pure FSH stimulates follicular growth but ovulation does not occur (McCracken, Uno, Goding, Ichkawa, & Baird, 1969). Furthermore, ovarian follicles do not reach mature size and secrete significant quantities of estrogen until LH is administered with FSH (Gemzell & Roos, 1966, pp. 492-517).

2. Luteinizing hormone (LH). In contrast to FSH, LH has a much more varied action. It is synergistic with FSH in bringing about follicular maturation and estrogen secretion. The midcycle peak of LH is believed to trigger ovulation in 16 to 24 hours. Furthermore, recent studies of hypophysectomized women have demonstrated that LH facilitates maintenance of the corpus luteum.

3. Estrogens. The most important estrogen secreted by the ovary is estradiol. The important biologic activities of estrogen include: (a) stimulation of growth of both the myometrium and endometrium; (b) maintenance of a thick vaginal mucosa and indirectly the acidic vaginal pH; (c) stimulation of cervical glands to secrete copious quantities of viscous mucous; (d) stimulation of breast growth and development; (e) deposition of subcutaneous fat which results in a characteristic feminine habitus; (f) sensitization of the ovaries to gonadotropins; and (g) retardation of linear body growth in association with facilitation of epiphyseal closure.

4. Progestins. Progestin was the name originally given to the crude extract of the corpus luteum which could prepare and maintain a

secretory endometrium during the latter half of the reproductive cycle and during pregnancy. The biologic actions of progesterone and other gestagens include: (a) antagonism of the growth promoting effect of estrogen on the endometrium and conversion of this rapidly proliferating organ into a secretory structure capable of maintaining an implanted blastocyst; (b) conversion of the cervical mucous from a very viscous to a nonviscous fluid; (c) stimulation of gland growth and development; and (d) inhibition of uterine motility.

During the reproductive cycle and in the first trimester of pregnancy, progesterone is secreted almost exclusively by the corpus luteum. During the latter two-thirds of pregnancy the placenta assumes this function. The adrenal also secretes a small quantity of progesterone.

Hormonal changes during the reproductive cycle. For descriptive purposes the reproductive cycle can be divided into a follicular phase, which can be subdivided into a first and second half; an ovulatory phase; and a luteal phase (Ross, Cargille, Lipsetti, Rayford, Marshall, Strott, & Rodbard, 1970; Vandewiele, Bogumil, Dyrenfurth, Ferin, Jewelewicz, Warren, Rizkallah, & Mikhail, 1970).

1. Follicular phase, first half. This period begins in the late luteal phase of the preceding cycle with a rise in the plasma levels of FSH and a concomitant initiation of follicular growth. LH levels also rise during this phase but the increase starts several days later than the increase in FSH. It is important to note that during the first half of the follicular phase there is no change in the blood levels of estrogens or progestins.

2. Follicular phase, second half. This portion of the follicular phase begins approximately 7 to 8 days before the preovulatory LH surge

and is characterized by an increase in plasma estrogen levels (estradiol and estrone). Estradiol increases slowly at first and then rapidly reaches a maximum on the day before the LH peak. The initial rise in estrone is not as great, but estrogen levels reach a peak concomitant with the peak of LH. While plasma estrogen levels are increasing, plasma FSH decreases and plasma LH slowly and steadily increases. Several days before ovulation there is a rise of 17-hydroxyprogesterone which reaches a maximum on the day of the LH surge. It is significant that plasma progesterone levels do not increase during this period.

3. Ovulatory phase. During this period there is a rapid rise in plasma LH levels which leads to the final maturation of the Graafian follicle and follicular rupture some 16 to 24 hours after the LH peak. Soon after the beginning of the LH surge and prior to ovulation, plasma estradiol levels drop precipitously and plasma progesterone increases slightly.

Both estrogen and 17-hydroxyprogesterone secretion decrease rapidly in the ovulatory period but both increase again in the luteal phase as the corpus luteum with both its theca interna cells and luteinized follicular cells becomes vascularized.

4. Luteal phase. As noted above, luteinization is initiated by LH. Recent studies also have indicated that ova exert an inhibitory influence on follicle luteinization. LH is required for normal corpus luteum survival and function. Furthermore, LH administered in high doses can luteinize follicular cells even without ovulation and can produce a luteinized follicle with a trapped ovum (Ludwig & Horowitz, 1969). These observations indicate that either LH or ovum removal can luteinize the ovarian follicle; however, during a normal reproductive

cycle both mechanisms are probably operative.

The sine qua non of the luteal phase is the marked increase in progesterone secretion which reaches a maximum about 8 days after the midcycle LH peak.

5. Control of FSH and LH secretion. Both FSH and LH are subject to negative feedback control as evidenced by the rise in both of these hormones following castration and from the decrease in their levels following estrogen administration. Examination of the hormonal events of the reproductive cycle indicates that control mechanisms in addition to negative feedback inhibition are operative. This is particularly true in the second half of the follicular phase when FSH decreases and LH increases concomitant with a rapid rise of blood estrogens. This paradox may be explained if one assumes that there are hypothalamic centers for positive and negative feedback control of gonadotropins in man as there are in the rodent (McCann & Porter, 1969). In addition to the negative feedback upon gonadotropin secretion, estrogens also exert a positive feedback on LH secretion but not upon FSH. The factors which determine whether LH will increase or decrease in response to estrogen administration are not completely understood at the present time. Suffice it to say that from the available data it would appear that both a positive and negative feedback control of LH are operative at different periods during the reproductive cycle.

In light of these observations the difference between the behavior of FSH and LH during the late follicular and luteal phases may be explained. In the second half of the follicular period as estrogens rise, FSH decreases due to the negative feedback effect. By contrast, the positive feedback control of estrogen is operative upon LH secretion

during this period as the level of this hormone increases. Both FSH and LH decline during the luteal phase under the negative feedback inhibition of estrogen and possibly progesterone.

A midcycle LH surge represents still another facet of the complex mechanisms which are operative in the control of gonadotropin secretion in women. The available studies support the hypothesis that the rise in estrogens during the later follicular phase triggers the preovulatory LH surge. Evidence in favor of this theory has been provided by several of the above-named investigators who demonstrated that estrogen administration can produce repeated bursts of LH, and in some instances, ovulation.

Sawyer (1975, pp. 401-408) summarizes some of the brain-pituitary-ovarian relationships discussed above. Luteinizing hormone-releasing hormone is produced by neurons in the arcuate nucleus of the hypophysiotropic area and secreted into the proximal capillary plexus of the pituitary portal system in the median eminence. Ovarian steroids feed back directly to the pituitary and to several sites in the brain where they influence both pituitary-ovarian function and sexual behavior. Electrophysiological evidence has been presented for "ultrashort" feedback action of luteinizing hormone-releasing hormone on arcuate neurons as well as the "short" feedback loop of LH. Evidence has been presented that adrenergic mechanisms influence luteinizing hormone-releasing hormone release with norepinephrine facilitatory and dopamine inhibitory to the process. Rapid strides are now being made in these areas of research with the use of immunological methods such as radioimmunoassay and immunohistochemistry.

Chan and O'Malley (1976) state that the regulation of protein synthesis in the target tissue is the principal action of steroid hormones.

The steroid molecule must be transported to the target tissue via the bloodstream and tissue fluids. It then penetrates the cell by simple or facilitated diffusion. On entry of the hormone into the cell, it is bound to a specific hormone receptor. This hormone-receptor complex is then transferred to the nucleus, in an "activated" form, where it is bound to the target-cell genome. Then the target cell responds by increased RNA synthesis followed by increased protein synthesis. This sequence of events is probably the primary mechanism by which the sex steroids regulate target-tissue metabolism (Chan & O'Malley, 1976).

The specific sex steroid progesterone is an estrogen antagonist. The simultaneous administration of these two hormones results in inhibition or modification of estrogen-induced growth and differentiation of target organs. Progesterone does not compete for the estrogen-receptor binding site, and it does not interfere with the cytoplasmic estrogen-receptor complex to translocate the nucleus (Anderson, Clark, & Peck, 1972). One possible effect of progesterone would be the interference with the replenishment of cytoplasmic estrogen receptors. That such an effect can indeed occur was demonstrated by Hsueh, Peck, and Clark (1975). The reduction of cytoplasmic estrogen receptor rendered the uterus much less responsive to additional estrogen.

The Psychoendocrinology of the Menstrual Cycle

While there is little evidence for serious cyclical deficits in motor or intellectual performance during the menstrual cycle (Pierson & Lockhart, 1963; Somner, 1972; Wickham, 1958), many women clearly suffer from some premenstrual symptoms which may range from mild tiredness and depression to extreme irritability and fatigue (Dalton, 1964; Lamb, 1953; Moos, 1968; Redgrove, 1971). Among the physiological explanations for

these symptoms have been Wineman (1971) who postulated increased sympathetic nervous system activity; MacKinnon (1954) who found higher postovulatory heart rate with less sweat gland production; and Lyons (1969) who reported a higher respiration rate during the luteal phase of the menstrual cycle. Wiener and Elmadjian (1962) found a significant increase in the urinary excretion of norepinephrine during the premenstrual period as compared with the preovulatory period, which was accompanied by irritability and depression. However, Patkai, Johannson, and Post (1974) failed to find significant cyclical differences in the excretion of either norepinephrine or epinephrine.

Lamprecht, Matta, Little, and Zahn (1974) assessed changes in peripheral sympathetic nervous system activity during the menstrual cycle as reflected in the activity of plasma dopamine-beta-hydroxylase (DBH) and compared these changes with peripheral indicators of autonomic functioning, such as skin conductance and heart rate. Lamprecht et al. (1974) found that the activity of this enzyme does not parallel levels of estrogen, progesterone, skin conductance, or heart rate; but that the mood "Surgency," as measured by the Nowlis Adjective Check List (Nowlis, 1965, pp. 353-398), showed comparable changes over the cycle. Both DBH activity and Surgency increased during the follicular phase, peaked soon after ovulation, and decreased to a minimum during the premenstrual phase.

Ito (1964), Suwa, Yamashita, Ito, Yoshimura, and Moroji (1966), and Yoshimura (1964) studied the interrelation between emotional changes and gonadal hormone secretion, and found some abnormal patterns in the urinary output of estrogens, pregnanediol and gonadotropins during periods of emotional distress. Yamashita (1964) also reported several

cases with abnormal endocrine findings, particularly the decrease of pregnanediol levels. It is now generally accepted that the steroidal hormones produced by the gonads act upon the brain to control the secretion of pituitary gonadotrophic hormones and to promote sexual behavior (Donovan, 1968; Martini, Fraschini, & Motta, 1968; Swyer, 1968).

Smith and Sauder (1969) surveyed 300 nurses and found an association between the occurrence of cravings for food and sweets on the one hand, and premenstrual feelings of tension or depression on the other. They also found an association between cravings for food and premenstrual fluid retention. The authors hypothesized that the basis for the food cravings might be hypoglycemia, and suggested that this possibility be investigated.

Patkai, Johannson, and Post (1974) found no significant differences in adrenaline and noradrenaline excretion between the menstrual, ovulatory, post ovulatory, and premenstrual phases of the cycle in six free-cycling women. Restlessness and disturbed night sleep were greater and more significant during the premenstrual phase of the cycle than during other phases.

Rose (1978) notes that an unfortunate tradition in research on sexual behavior during the menstrual cycle has been the almost complete isolation of psychological and endocrinological studies, with the work of Benedek and Rubenstein published in 1939 and 1942 being an outstanding exception. Psychologists have focused on changes in moods and sexual behavior without using appropriate endocrinological markers, and conversely many papers document daily endocrine changes during the cycle but without psychological assessment. Because variability of the menstrual cycle is well established, levels of estrogen and progesterone are difficult to

infer from estimated cycle day alone. Psychological research without endocrine data consistently makes these assumptions.

An important aspect of the present study is that both psychological data and endocrinological data are collected on all subjects, making possible the endocrinological validation of the stage of the menstrual cycle at which data are obtained.

Rose (1978) also points out that the absence of appropriate endocrinological data has made it difficult to validate or invalidate some commonly held beliefs, among them the belief that women are substantially and uniformly incapacitated by premenstrual distress because of changing hormone levels. When one examines the literature, the paucity of relevant psychoendocrine data is clearly evident (Parlee, 1973).

Adams, Gold, and Burt (1978) found a thirty percent increase in the average rate of female initiated and mutually initiated sexual behavior during the periovulatory phase of the menstrual cycle. Rose (1978) believes that Adams et al. (1978) might have found even more substantial differences between female initiated sexual behavior at the periovulatory phase of the cycle versus other phases of the cycle, if they had been able to measure the peak of estradiol or the initiation of the rise in progesterone and thus to define more clearly the time of ovulation. Rose (1978) found that estimating the time of ovulation from counting backwards 14 days from the beginning of the next menstrual bleeding is correct only 70 to 75 percent of the time.

Examination of Adams et al. (1978) data suggests another peak of sexual behavior in the early follicular stage of the menstrual cycle, when estrogen levels are low. This finding raises the issue of mediating mechanisms. Rose (1972, pp. 251-293) presents data suggesting that

adrenal androgens may be more important in influencing human female sexuality than estrogens.

Progesterone metabolism in the menstrual cycle. Estimates of the prevalence of psychic disturbances in the premenstrual phase of the menstrual cycle vary considerably, from about 5% (McCance, Luff, & Widdowson, 1937) to 95% (Pennington, 1957), with a mean perhaps around 50%, if all the many studies are considered (Ladisich, 1977). These large differences might be due to differences in methodology or to different sociocultural attitudes in the investigated population.

There is an interesting common feature of the premenstrual and postpartum disorders: they occur at a time of withdrawal of progesterone from the system. While this withdrawal is most abrupt at the time of partuition, a similar though less dramatic change occurs at the end of each menstrual cycle. Data on fluctuation of progesterone levels during the normal menstrual cycle are considerably less reliable than those of pregnancy; smaller amounts of hormones are involved. Nevertheless, investigations by Short and Levett (1962) and by Woolever (1963) utilizing recently devised assay procedures, indicate the occurrence of a premenstrual fall in circulatory progesterone levels, as would be predicted on the assumption that most of this steroid occurs in the corpus luteum. Pre-ovulatory plasma progesterone levels are very low -- about 1 μg. percent. Progesterone concentration is higher in the second half of the cycle -- about 2-3 μg. percent. There is often an abrupt rise beginning about mid-cycle, and a rapid fall starting several days before the onset of menstruation. The latter point is strengthened by measurement of progesterone in human ovarian vein blood (Mikhail, Zander, & Allen, 1963). More recent results are consistent with this pattern of cyclic variation

(Van Der Molen & Groen, 1965). By the first day of menstruation, there is often no detectable progesterone. In their comprehensive review of the existing data, Dorfman and Unger (1965) give the following figures for progesterone secretion: in the follicular phase, 4-5 mg. per day; in the luteal phase, 30 mg. per day. Thus, there is approximately a 7-fold increase in secretion of progesterone, as compared to a 2-3 fold increase in blood levels. One line of inquiry in this area involves the concomitant measurement of progesterone and behavioral variables through the menstrual cycle, centering attention particularly on the final week of the cycle, and utilizing comparisons of women who do and do not have severe premenstrual distress (Hamburg, Moos, & Yalom, 1968). These investigators have not found differential progesterone levels between women who do and do not have severe premenstrual distress.

Ladisich (1977) investigated whether there were differences in physiological reactions to experimental stress at a time in the menstrual cycle when progesterone production is high compared with a time when it is low. Half the subjects received 10 mg. a day of Provera and the other half did not. The experimental stress was administered as follows: the subject sat in a darkened room and was instructed to memorize a list of words she heard from a tape, and during the six minutes she was given to do this she received four mildly to moderately painful electric shocks administered to one hand. Afterwards, she was asked to recall the words she had heard. Pulse and respiratory rates were recorded before, during, and after the stress period. The hypothesis that larger differences in progesterone levels might go along with higher fluctuations in mood was tested by correlating the differences in a mood scale, the Scale of Well-Being, with progesterone concentrations, but no correlations

could be found. There was a significantly higher reaction to stress one day before menstruation than eight days before menstruation for the drug group only. Thus, the subjects who received Provera appeared to be more sensitive to emotional stress than the subjects on placebo. This result is contradictory to the reported beneficial effect of medroxyprogesterone on premenstrual tension (Soule, 1960), but there were large individual differences between subjects, which colors the interpretation. No correlations were found between mood ratings, stress reaction, and progesterone levels.

Creutzfeldt, Arnold, Becker, Langenstein, Tirsch, Wilhelm, and Wuttke (1976) found that an acceleration of the EEG alpha rhythm during the luteal phase of the menstrual cycle was paralleled by an acceleration and improvement of performance in psychometric tests such as reaction time, simple arithmetic, and spatial orientation. Creutzfeldt et al. (1976) hypothesized that the common denominator of these changes during the luteal phase was probably concentration and speed of performance. The significant correlation between the psychometric changes and the changes of alpha rhythm suggest a common cause.

Creutzfeldt et al. (1976) also found that of all the hormonal changes observed during the menstrual cycle, the increase of progesterone during the luteal phase appears to be most closely related to the alpha acceleration and the psychological performance acceleration. The temporal correlation shows, however, a delay of the functional acceleration by 1-2 days as compared with the hormonal data. Furthermore, comparison of individual values of progesterone increase and alpha acceleration did not reveal a direct correlation. Therefore, if the speeding up of cerebral functions is caused by the progesterone increase, an intermediary link

should be assumed.

The speeding up of mean alpha frequency and psychometric performance, especially during the second half of the luteal phase, might be the physiological basis of the premenstrual psychological syndrome. The physiological changes may produce different objective and subjective psychological effects in different persons, however, since basic brain mechanisms, identical in principle, may find variable expression in different personalities.

Monoamine oxidase and mechanisms of action of behavioral changes in the menstrual cycle. A mechanism which can hypothetically explain behavioral changes during the menstrual cycle is monoamine alteration by increased levels of monoamine oxidase.

Schildkraut's (1965) "catecholamine hypothesis" holds that mental depression reflects a deficiency of catecholamines at adrenergic receptor sites in the brain. Monoamine oxidase, found intracellularly in the mitochondria, is one enzyme believed to regulate catecholamine action in the brain, and drugs which inhibit high MAO activity are found to transiently relieve psychological depression and have been also used to treat ovarian-hormone-linked menstrual depressions (Dalton, 1964; Slitton & Gershon, 1966).

The success of such treatment with MAO inhibitors led several researchers to investigate the levels of MAO over the normal menstrual cycle and in oral contraceptive users. Endometrial MAO was found to fluctuate throughout the human menstrual cycle in accordance with hormonal changes in estrogen and progesterone (Cohen, Belensky, & Chaym, 1965; Southgate, Grant, Pollard, Pryse-Davies, & Sandler, 1968). Southgate et al. (1968) found that in normal cycling women, MAO activity

is highest premenstrually. In oral contraceptive users, endometrial MAO activity was increasing from day 12 of the cycle for women taking pills high in progesterone. For strongly estrogen pill users, MAO levels remained low throughout the cycle. Grant and Pryse-Davies (1968), Klaiber, Broverman, Vogel, Kobayashi, and Moriarity (1972), and Youdim, Holzbauer, and Woods (1974) found that progesterone acts to increase MAO levels and conversely that estrogen has an inhibitory effect on MAO activity.

Because estrogen appears to inhibit MAO activity, and since MAO inhibitors appear to relieve psychological depression, estrogen therapy has been utilized and reported to alleviate menopausal depression and involutional depression. Klaiber et al. (1972) has observed that free-cycling depressed women have higher plasma MAO levels than nondepressed women, as measured by the Hamilton Rating Scale of Depression and clinical psychologists' evaluations of depression.

Plasma and platelet MAO activities in humans and in the rhesus monkey have been shown to vary during the menstrual cycle (Belmaker, Murphy, Wyatt, & Loriaux, 1974; Redmond, Murphy, Baulu, Ziegler, & Lake, 1975). Belmaker et al. (1974) found a preovulatory increase in platelet MAO that peaks during the ovulatory interval and then decreases sharply and reaches a nadir 5 to 11 days later. This roughly parallels the menstrual changes in progesterone levels. However, no statistically significant relationship was observed between platelet MAO activity and a global scale of menstrual mood variation.

Carruthers (1977) found that monoamine oxidase inhibitors increase brain noradrenaline and can alleviate depression.

Emotional Aspects of Menstrual Dysfunction

The menstrual and premenstrual phases of a woman's cycle are a time of increased stress and susceptibility to injury. Suicides and accidents are at a peak during the luteal phase of the cycle, as are the number of attempted suicides, admissions to psychiatric hospitals for depression, and acute outbreaks of schizophrenia (Dalton, 1959; MacKinnon & MacKinnon, 1956; Mall, 1958, p. 96). During the menstrual and pre-menstrual phases the tendency to commit violent crimes is greater (Dalton, 1961) and symptoms of emotional stress such as anxiety are at their maximum 2 to 4 days before the onset of menstruation (Moos, Kopell, Melges, Yalom, Lundh, Clayton, & Hamburg, 1969; O'Connor-Miller, 1980).

It is clinically well known that fluctuations of mood frequently occur in correlation with the menstrual cycle. Typically, the premenstruum can be a phase of increased irritability and depression. The phenomena has attracted considerable clinical attention. Thus, Dalton (1959) studied the emergency admissions of 276 female psychiatric patients to a London hospital and found that the overall rate of admissions during the 4-day premenstruum and during the 4-day period of menstruation was nearly twice as high as at the other times in the cycle. More than half (53%) of all attempted suicides in her sample took place during the premenstruum or menstruation. Coppen and Kessell (1963) note that the premenstrual syndrome occurs in about one-fourth of all women.

Moos (1968) undertook a large scale questionnaire study to determine the incidence and severity of different symptoms in the menstrual, premenstrual and intermenstrual phases of the menstrual cycle in a sample of young married women. Each woman was asked to describe her experience of 47 symptoms during four different time periods: (a) during her most

recent menstrual flow; (b) during the one week before her most recent menstrual flow; (c) during the remainder of her most recent menstrual cycle; and (d) during her worst menstrual cycle.

Results showed that only about 20% of the women in the sample complained of moderate, strong, or severe symptoms of irritability, mood swings, depression, and tension in the menstrual and premenstrual phases of their most recent menstrual cycle. This is clinically significant when compared to the sample's intermenstrual scores, but by no means an indication of hormonal determinism. Less than 10% of the sample reported behavioral changes such as lowered performance, naps in bed, or decreased efficiency, menstrually and premenstrually.

The questionnaire devised by Moos (1968) was also used to examine the characteristics of the menstrual cycle in women taking steroid contraceptives. Four hundred and twenty women currently taking oral contraceptives were compared with a matched group of 298 women currently not taking steroid contraceptives but utilizing other means of contraception.

Results showed that women not on oral contraceptives complained of greater severity of symptoms in both the menstrual phase and the premenstrual phase of their cycles, as compared to women taking oral contraceptives. These symptoms were mainly in the areas of pain (cramps, general aches and pains), concentration (lowered judgment, distractibility), negative affect (restlessness, tension, depression, and irritability), and behavior change (lowered school or work performance, decreased efficiency). For example, 36% of the non-oral contraceptive group complained of moderate, severe, or disabling irritability in the premenstrual phase whereas only 24% of the oral contraceptive group showed similar complaints. The fact that there were no control symptoms which significantly

differentiated the groups, and that there were no significant differences between the two groups in symptoms during the intermenstrual phase, and only three significant differences in worst menstrual cycle symptom reports, indicates that the women not on oral contraceptives are not merely prone to excessive, generalized complaints.

Kane, Daly, Ewing, and Keeler (1967) reported adverse psychological effects from progestational agents used for contraception. However, the present author suggests that progesterone compounds such as oral Provera might have positive psychological effects, so that women taking them might complain of fewer menstrual and premenstrual symptoms, including decreased seizure frequency.

Glass, Heninger, Lansky, and Talan (1971) assessed the differential effect of the menstrual cycle on psychiatric emergencies by completing a quantified clinical evaluation intermittently over a one year period on a representative female sample of emergency room psychiatric patients. The actively menstruating patients not on oral contraceptives entered the emergency room twice as frequently as expected during the premenstrual week and as frequently as expected during the menstrual week. Suicide attempts occurred at three times the expected frequency during the premenstrual week and the premenstrual patients were rated higher on hostility and suicidal ideation and had a more severe past medical history than the patients seen during the intermenstrual phase of the cycle. Glass et al. (1971) suggest that their data indicate that the menstrual cycle does have a differential effect on the psychiatric admissions of women, specifically, non-psychotic menstruating women with more severe past medical and gynecological histories who have more sexual and marital problems appear to be more susceptible to a premenstrual psychiatric

emergency characterized by hostility, suicidal ideation, and actual suicide attempts.

Kramer (1977) reports on psychotic episodes lasting four to seven days that occurred in an adolescent epileptic girl only at the time of her period. Unfortunately, in this case the patient was not consistently compliant on her anticonvulsant regimen of Dilantin; and when therapeutic blood levels of Dilantin were maintained, the psychotic episodes were eliminated. Nonetheless, this is another example of how the onset of the menstrual period implicates hormonal or metabolic changes occurring around the time of the menses in the expression of underlying psychopathological processes.

Kramer (1977) also suggests that various hormonal therapies might be efficacious in controlling the postulated underlying endocrinological disturbance. Livingston (1966, pp. 99-119) achieved seizure control in menstrual epilepsy by means of conventional oral contraceptives, and Zimmerman, Holden, Reiter, and Dekaban (1973) reported successful treatment of menstrual epilepsy in an 8-year-old precocious girl with medroxyprogesterone acetate (Provera).

Check (1978) asserts that psychological factors are the most common cause of menstrual dysfunction. He cites instances in which couples who have been trying unsuccessfully to conceive for years, do so after they have adopted a child and quit worrying about pregnancy. In most of these cases, the mental pressures of failing to conceive induced such anxiety that ovulation ceased; when anxiety ended, spontaneous ovulation and pregnancy followed.

Mild anxieties may lead to changes in the menstrual cycle, infertility, or habitual abortion by causing an inadequate development of the

corpus luteum. This is due to insufficient secretion of progesterone. The main function of progesterone is to cause secretory changes in the endometrium in preparation for implantation of the fertilized egg. With inadequate progesterone, the endometrial lining is insufficient to support implantation, and abortion or infertility occurs.

The same emotional factors causing an inadequate corpus luteum may result in anovulation, irregular periods due to breakthrough bleeding (oligomenorrhea), or no period at all (amenorrhea). Some of the common environmental factors leading to these problems that Check (1978) has documented include loss of a loved one, moving to a new environment, fear of pregnancy, marital strife, and change of jobs.

The mechanism of how emotional problems can lead to irregular cycles, dysfunctional uterine bleeding, or amenorrhea can be examined at the hypothalamic level. The basic control of the menstrual cycle is dependent on a very exact and delicate relationship between the hypothalamus, pituitary, and ovary (Check, 1978). The dominant relationship during the preovulatory phase of the menstrual cycle (the follicular phase) is a positive feedback to the cyclic center of the anterior hypothalamus, resulting in pulsatile release of gonadotropin-releasing hormone, and thus causing pulsatile release of luteinizing hormone (LH) and to a lesser degree follicle-stimulating hormone (FSH). This eventually results in the mid-cycle surge of LH required for ovulation.

Mild dysfunction in the hypothalamic-pituitary-ovarian axis may involve production of either slightly less estrogen than needed to cause the positive stimulation necessary for the mid-cycle LH surge or slightly too much estrogen, which exerts a negative feedback for FSH, thus preventing proper follicular maturation.

The hypothalamus is not the highest center of control, however; the cerebral cortex and limbic system both influence hypothalamic control by means of biogenic amines, and it is through this mechanism that emotions alter ovulatory function. The main CNS biogenic amines are dopamine, norepinephrine, and serotonin. They influence all hypothalamic-releasing hormones. At present, there is evidence that dopamine suppresses LH (Lachelin, LeBlanc, & Yen, 1977; LeBlanc, Lachelin, Abu-Fadil, & Yen, 1976).

Another hormone involved in control of the menstrual cycle is prolactin. Elevation of serum prolactin causes reciprocal lowering of the gonadotropins, especially FSH, resulting in amenorrhea and sometimes galactorrhea (Bohnet, Dahlen, Wuttke, & Schneider, 1975). Malarkey, Jacobs, and Daughaday (1971) found that dopamine is the prolactin-inhibiting factor that normally keeps the prolactin-producing cells in a suppressed state. Psychological stress can result in an increase in prolactin, which in itself can alter the menstrual cycle by the inhibitory effect that it has on LH (Miyabo, Hisada, Asato, Mizushima, & Ueno, 1976).

Stress may alter ovulatory function through its effect on still another pituitary hormone, ACTH (Check, 1978). ACTH stimulates secretions of glucocorticoids from the zona fasciculata and androgens from the zona reticularis of the adrenal gland. There seems to be two areas of the hypothalamus producing the corticotropin-releasing factor (CRF), which is responsible for ACTH secretion. The lower area is considered the center responsible for the daily normal diurnal type of secretion of cortisol; the higher hypothalamic center causes greater increases of ACTH under stress conditions, resulting in greater cortisol secretion necessary

during fight or flight. An increase in either cortisol or androgens can inhibit the gonadotropins. This adrenal stress syndrome can result in anovulatory cycles, among other problems.

Psychological disturbances can thus cause certain somatic manifestations that are difficult to discern from organically caused disease. However, in most instances the psychological disturbance interfers only with ovulation, and the ovary continues to produce estrogen, allowing the endometrial lining to build up. Depression can occasionally cause dysfunctional uterine bleeding that is extremely resistant to hormonal therapy. Thus, the psyche appears also to have a direct effect in some instances on the endometrial lining. This endometrial factor can also be responsible for amenorrhea, which can be very resistant to hormonal therapy even with high doses of estrogen and progesterone (Goldzieher & Goldzieher, 1952). For some reason, this condition occurs frequently following automobile accidents. Its etiology has not yet been explained.

Psychological factors also may influence the ovary directly. Check (1978) reports several cases of women who developed amenorrhea, hot flashes, elevated gonadotropins, and other symptoms of menopause shortly after their husbands died. When these women began dating, their symptoms frequently abated, with return of menstrual function and normal levels of LH and FSH.

These findings suggest the hypothesis that high emotional distress should manifest itself in anovulatory cycles and cycles with inadequate luteal production (ILP), in the specific group of epileptic women seen in this current study. Even more strongly, one may postulate that high levels of emotional distress cause anovulatory and ILP cycles. High ratings on the SRE Weekly Schedule of Recent Experiences should be

highly correlated with anovulatory and ILP cycles. Since anovulatory cycles are by definition deficient in the production of progesterone, anovulatory cycles should also be highly correlated with increased seizure frequency, if one accepts that seizures are inhibited by high levels of progesterone. By this mechanism, increased seizure frequency should be highly correlated with emotional distress.

Schematically, the author proposes that the following relationships hold:

1. Emotional distress leads to anovulatory cycles, via the hypothalamic-pituitary-ovarian pathways outlined above.

2. Anovulatory cycles are deficient in progesterone.

3. Seizures increase when progesterone is low.

4. Anovulatory cycles should therefore be associated with increased seizure frequency, particularly in the last two weeks (normal luteal phase) of the cycle as compared to a normal ovulatory cycle.

5. Therefore, by this mechanism increased seizure frequency should be highly correlated with emotional distress.

Mood changes during the menstrual cycle. Ivey and Bardwick (1968) tested 26 female college students for differences in anxiety level during the menstrual cycle. The subjects were asked to talk for five minutes on any memorable life experience, during their ovulatory phase and also during their premenstrual phase, for two menstrual cycles. Ovulation was determined from basal body temperature records and by history from the length of previous menstrual cycles. The verbal samples were scored according to Gottschalk's (1966) Verbal Anxiety Scale and were examined for thematic variations. The Verbal Anxiety Scale showed that anxiety premenstrually was significantly higher than at ovulation for all subjects.

Consistent themes of hostility, depression, and noncoping appeared premenstrually, as opposed to themes of self-satisfaction, adequacy, and coping at ovulation. Ivey and Bardwick (1968) conclude that their findings support significant affective fluctuations during the menstrual cycle which correlate with presumed endocrine changes.

Schell, Roca, McMahan, Bearup, and Pederson (1974) found only very mild effects of cycle day on mood and symptom variables in a group of nine free-cycling women, with subjects experiencing slightly more negative affect or lack of activation and water retention during the premenstrual and menstrual period. Reaction time increased but performance on the Miller Analogies test improved slightly premenstrually. Heart rate and skin conductance were unaffected. These findings suggest that changes in mood and ANS system activity are not an inevitable consequence of the normal menstrual cycle in young, healthy, free-cycling women.

Golub (1976) studied the magnitude of premenstrual and intermenstrual mood changes in 50 parous adult women, using the State-Trait Anxiety Inventory and the Depression Adjective Check List. Golub notes that none of the studies done previously to his 1976 study assessed the magnitude of mood changes with respect to the menstrual cycle in a way that would permit comparison with normative data; or evaluated premenstrual anxiety as a transitory or state phenomenon, as opposed to a manifestation of trait anxiety, which is a relatively stable personality characteristic.

Golub (1976) found that premenstrual state anxiety and depression mean scores were significantly higher than those obtained midcycle, but were much lower than those of a normative group of patients with psychiatric disorders. The state anxiety scores of Golub's sample were close to normative values for freshmen college women taking an examination.

Trait anxiety scores were low and were not significantly correlated with premenstrual depression and anxiety scores.

The Moos Menstrual Distress Questionnaire. Clinically, it is well known that the premenstrual phase of the menstrual cycle is a time of increased irritability and depression. However, few studies have taken systematic account of the role of biochemical factors in the premenstrual syndrome. Hamburg, Moos, and Yalom (1968) report on the Moos Menstrual Distress Questionnaire and observe that the differentiated menstrual cycle symptom profile analysis suggested by the eight scales of Pain, Concentration, Behavioral Change, Dizziness, Water Retention, Negative Affect, Positive Arousal, and Control Symptoms would allow for investigation of differential treatment effects of drugs or hormones on different types of menstrual symptoms and investigation of the biochemical correlates of each type. Hamburg, Moos and Yalom (1968) found that anxiety is high during the menstrual flow, decreases sharply, and then slowly increases up to the 90-93rd percentile of the cycle. A sharp and puzzling decrease occurs in the 94th to 97th percentile of the cycle, and then anxiety goes up again just before the menstrual flow begins. Sexual arousal is lowest during the menstrual flow, gradually increases up to mid-cycle, and then decreases and levels off for the remainder of the cycle. The pattern of anxiety described above suggests that progesterone may inhibit or at least be related to anxiety; while sexual arousal may be influenced by the amount of estrogen present.

The Moos Menstrual Distress Questionnaire was designed to assess changes in several symptom clusters across the various stages of women's menstrual cycles. Form A and Form T of the Questionnaire appears in Appendix A. Form T of the Questionnaire was designed to be suitable for

repeated assessments of symptoms from the same subjects. Subjects note their experience of each of 47 symptoms on a 6-point scale, ranging from no experience of the symptom to an acute experience of the symptom. Since the questionnaire is repeatable, women can differentiate between their experience of different symptoms in terms of the phases during the cycle in which they occur. The intercorrelations among the eight scales are all positive (Moos, 1977), indicating that women who score high on one scale also tend to score high on the others. The control scale is positively related to each of the other scales, indicating that women who tend to complain of relatively frequently occurring menstrual cycle symptoms also tend to complain about non-menstrually related symptoms. High inter-cycle symptom correlations suggest women tend to complain of generally consistent symptomatology from one menstrual cycle to another.

The Moos Menstrual Distress Questionnaire, Form T, is sensitive to menstrual cycle phase effects: women do complain of more symptoms in the menstrual and premenstrual than in the intermenstrual phase of their most recent cycle. Voda (1976) used Form T to study 20 ovulating women every other day for one menstrual cycle. She factor analyzed the Menstrual Distress Questionnaire (MDQ) and generated four symptom categories (positive affect, negative affect, concentration, and physical complaints). Negative affect, concentration, and physical complaints showed significant phase effects. Other researchers who found significant phase effects for various scales on Form T have been O'Connor-Miller (1980), Silbergeld, Brast, and Noble (1971), Stultz (1971), and Wilcoxon, Schrader and Sherif (1976). Since normal subjects do show phase effects on the different scales of the MDQ, an important question to ask regarding epileptic women is whether they also show these phase effects and if

they do, whether heightened menstrual distress occurs in conjunction with increased seizure frequency. However, reported relationships between cycle phase and mood may be independent of underlying physiological changes and more a consequence of women's expectations. Ruble, Brooks, and Clarke (1976) found that women who believed they were premenstrual reported a significantly higher degree of menstrual distress than women who believed they were intermenstrual, regardless of whether the women were actually premenstrual or intermenstrual. Possibly epileptic women may expect more seizures premenstrually and menstrually if they believe they are in these phases, and the tension caused by this expectation may actually produce more seizures. However, Markum (1976) found that expectations about phase of the menstrual cycle that a woman thought she was in, did not affect responses to the MDQ. Markum argues that this casts doubt on the hypothesis that the MDQ measures stereotypic beliefs about menstruation.

Wilcoxon, Schrader, and Sherif (1976) found no substantial evidence of MDQ deterioration over the course of longitudinal studies.

Several of the MDQ scales are related to complaints of physical symptoms and of negative affect. Paige (1973) found that women who complained of physical discomfort and psychological stress during menstruation tended to report such symptoms in other situations as well. A related question that can be raised with regard to the epileptic population is, do women who complain the most of physical discomfort and psychological stress during menstruation also tend to report more seizures and have more seizures. Silbergeld, Brast, and Noble (1971) found high correlations between MDQ anxiety and Mood Adjective Checklist (MACL) anxiety, and between MDQ irritability and MACL aggression.

The MDQ appears to be an adequate instrument to measure psychological stress in the form of anxiety, at least as anxiety is defined by these constructs. In terms of the present study, the MDQ has construct validity as a measure of anxiety and psychological stress. Symptom scores on the MDQ are positively related to scores on other questionnaires measuring physical symptoms, general health, and negative affect.

Several studies investigated the relationships between menstrual cycle symptomatology as measured by the MDQ, and attitudes regarding menstruation, sex, and femininity. Ruble, Brooks, and Clarke (1976) concluded that a woman's attitudes about menstruation may be related to her expectations regarding her menstrual cycle symptoms, and that these expectations may, in turn, influence the actual symptoms she experiences. However, an alternative explanation is that these attitudes are directly related to a woman's actual symptoms, since women who experience more symptoms probably expect more symptoms in subsequent menstrual cycles.

Di Nardo (1974) suggested that women with fewer MDQ symptom complaints have more positive attitudes about their bodies, whereas those with more symptom complaints are less likely to accept certain aspects of their sexual role (Berry & McGuire, 1972). According to other studies, however, other important variables are operative. For example, Gough (1975) found that women with higher MDQ total distress scores tended to have higher scores on femininity, but lower scores on well-being, tolerance, good impression, achievement via conformity, intellectual efficiency, and self-control. Paige (1973) also found that those who believed that a woman's place was in the home, and who had no personal career ambitions, were the most likely to have severe menstrual symptoms. Paige concluded that, contrary to popular stereotypes,

the traditionally feminine woman, rather than ambitious career types, are most likely to complain the most about menstrual and premenstrual distress.

The foregoing results indicate that any relationship between menstrual distress and various aspects of femininity may be moderated by such factors as religious orientation, somatic concern, social competence, and self-esteem. Investigations which have attempted to relate MDQ scale scores to various general personality characteristics and psychiatric diagnostic categories have met with little success, since there are important moderating variables (Gough, 1975; Gruba, 1973).

Gruba and Rohrbaugh (1975) found that the MMPI subscales of Hypochondriasis (Hs), Psychasthenia (Pt), Hysteria (Hy), and Schizophrenia (Sc) were significantly related to the MDQ scales of Behavior Change and Autonomic Reactions in the menstrual phase; and Pain, Negative Affect, and Autonomic Reactions in the premenstrual phase. They interpret their results as supportive of the hypothesis that premenstrual tension, irritability, and depression are related to neuroticism. It should be pointed out that correlation does not speak to the nature or direction of causality, but does suggest areas in which causal relationships may be investigated. Personality variables may influence mood, pain perception, and hormonal changes; but physiological processes may also influence personality variables; or both directions of causality may operate simultaneously. However, Moos points out that these findings may simply indicate that women who complain of menstrual and premenstrual symptoms also tend to complain of other physical symptoms and of general negative affect.

Most studies indicate that women's cognitive and perceptual-motor

performance is not affected by menstrual cycle phase (Dalton, 1969; Favreau, 1974; Golub, 1976(a); Golub, 1976(b); Niesz, 1976; Olasov, 1972). However, Sommer (1973) found that women who complain of more symptoms in the menstrual phase of their cycles tend to perform more poorly on perceptual-motor tasks. Baisden and Gibson (1975) found some relationships between performance on complex perceptual-psychomotor tasks and the Menstrual Distress Questionnaire subscales. They point out that the symptoms measured by the MDQ are common reactions to stress for both men and women, and speculate that people who have a general tendency to complain and a low tolerance to stress and discomfort may experience performance decrements as a reaction to any type of environmental or physical stress. In regard to the present investigation, then, one might hypothesize that women epileptics who have a lower tolerance to stress, as perhaps manifested in increased seizure frequency, may experience performance decrements. An alternative possibility is that when women epileptics have seizures, a reaction to their seizures may be performance decrements. Extrapolating from the literature, one might speculate that women who have an increased seizure frequency menstrually and premenstrually, will also complain of a greater severity of other menstrual and premenstrual symptoms. Women epileptics might be expected to show more menstrual and premenstrual complaints as measured by the Moos MDQ scales, compared to the intermenstrual phase of their cycles; just as non-epileptic women have been shown in the literature to have more complaints menstrually and premenstrually, as compared to intermenstrually. Epileptic women whose seizures cluster menstrually and premenstrually might also be expected to have more menstrual and premenstrual distress than epileptic women whose seizures do not cluster menstrually

and premenstrually.

Moos (1977), in his review of the literature on the Moos Menstrual Distress Questionnaire, has concluded that subtypes of women exist who are differentiated in terms of the particular areas in which they complain of symptoms. Moos then raises the issue of whether women who are having only one set of symptoms are experiencing the same syndrome as the women who have another set of symptoms; for example, are the women who have only pain symptoms experiencing the same syndrome as the women who have only autonomic reaction symptoms? Moos (1977) relates that some women appear to have dysmenorrhea but little or no premenstrual tension, whereas others have premenstrual tension but little or no menstrual pain, and still others complain of both dysmenorrhea and premenstrual tension. Certain clusters of symptoms may be more highly related to cyclical physiological fluctuations than others (Cullberg, 1972) and the present author hypothesizes that this may be true for epileptic women as well as non-epileptic women. Possibly only a small subgroup of epileptic women exist in which premenstrual complaints are clearly hormone dependent.

Stressful life events questionnaires. Growing numbers of investigators are using lists of stressful life events, in an attempt to delineate the relationship between these events and physical and psychological disorders. The hope is that through careful detailing of events antecedent to physical and psychiatric distress, predictions can be made about the type and amount of stress that might precipitate illness in individuals experiencing such stress. An important function of behavioral assessment can be to establish the relationship between changes in psychological events and changes in a physiological response, as many

psychiatric and medical disorders involve physiological changes to specific environmental stimuli. In the present study, an important issue that has been addressed is the nature of the precipitants of increased seizure frequency in epileptic women. The author postulates that an important correlate, if not cause of seizure episodes, is an increase in the experiencing of stressful life events prior to seizure onset. A well-designed life events questionnaire administered to an epileptic population could be of great value in delineating the relationships between stressful life events and seizure frequency. It is from this perspective and interest that the present review and critique of life stress literature is presented, with suggestions for improving the sampling and recording of stressful life events for individual subjects. An experimental self-monitoring diary is also included, and is meant to be an improved way of recording and analyzing daily stressful life events that might precipitate seizures in epileptic women.

Research on life events originated with Adolph Meyer's work in psychobiology. His invention of the "life chart" (Lief, 1948) organized medical data as a dynamic biography, and provided a method for demonstrating his schema of the relationship of biological, psychological, and sociological phenomena to the processes of health and disease in man. Beginning in 1949, the Social Readjustment Rating Scale, developed by Holmes and Rahe (Holmes & Masuda, 1973) and arising out of the theorizing of Adolph Meyer, has been used systematically with more than 5,000 subjects to study the quality and quantity of life events that were empirically observed to cluster at the time of disease onset. The Social Readjustment Rating Scale remains the most widely used of all rating scales. The life events on the scale were derived from both ordinary

and extraordinary social and interpersonal transactions, and pertain to major areas of dynamic significance, including family constellation, marriage, occupation, economics, residence, group and peer relationships, education, religion, recreation, and health. A criteria for inclusion on the scale were those life events that usually evoked, or were associated with, some adaptive or coping behavior on the part of the involved individual. Each item was constructed to contain life events whose advent either is indicative of, or requires a significant change in, the ongoing life pattern of an individual. The emphasis was on change from the existing steady state and not on psychological meaning, emotion, or social desirability.

Scaling of the Social Readjustment Rating Questionnaire (SRRQ) was described by Holmes and Rahe (1967). In order to provide an estimate of the magnitude of life events, a sample of convenience of 394 subjects was asked to rate a series of life events according to their relative degrees of necessary readjustment. The event of Marriage was given an arbitrary value of 500. The subjects were instructed:

> As you complete each of the remaining events think to yourself, "Is this event indicative of more or less readjustment than marriage?" "Would the readjustment take longer or shorter to accomplish?" If you decide that the readjustment is more intense and protracted, then choose a proportionately larger number and place it in the blank directly opposite the event in the column marked "Value." If you decide that the event represents less and shorter readjustment than marriage, then indicate how much less by placing a proportionately smaller number in the opposite blank. (Holmes & Masuda, 1973, p. 166)

Thus, the magnitude of each life event was derived by calculating the mean score of each event for the entire sample. Guilford (1965) documented high correlation coefficients demonstrating that consensus was high concerning the relative order and magnitude of the means of items between the discrete groups contained in the sample. Replication and validation of the scaling method was made on two American samples (Pasley, 1969; Ruch & Holmes, 1971). Appendix A shows the items in the Holmes and Rahe Social Readjustment Rating Questionnaire, and their relative weights.

The Holmes and Rahe (1967) Social Readjustment Rating Questionnaire has generated a great deal of research, including methods for assigning magnitudes to each of the life events (Holmes & Rahe, 1967; Masuda & Holmes, 1967); the prediction of near future health changes from subjects' preceding life changes (Rahe, Mahan, & Arthur, 1970); and changes in health as a consequence of long-term life changes (Casey, Masuda, & Holmes, 1967). Long-term stress up to ten years prior to the onset of illness, and frequency of disease occurrence have been studied in groups exposed to the same conditions, one of which comes down with the disease and the other of which does not (Rahe, Meyer, Smith, Kjaer, & Holmes, 1964). Validation of the Social Readjustment Rating Scale across different populations has been done in a variety of cross-cultural studies (Harmon, Masuda, & Holmes, 1970). Pesznecker and McNeil (1975), using a linear correlation and multiple regression design, studied the relationship among health habits, social assets, psychological well-being, life change, and alterations in health status. Garrity, Somes, and Marx (1977) found that social conformity, liberal intellectualism and emotional sensitivity are independently and significantly predictive of health

change; these relationships hold even when recent life experience is introduced as a significant predictor of health change. Ruch (1977), performing a multi-dimensional analysis of the concept of life change, found that life change has three dimensions: the degree of change evoked, the desirability of the change, and the life area in which the event occurs. Ruch's analysis also indicated that while the life change data are multidimensional, the quantitative dimension (degree of life change) is more primary than the qualitative dimension (desirability of life change and area of life change). Holmes and Masuda (1973) have written a review of the Social Readjustment Rating Scale (SRRS), and have concluded that across a wide variety of studies, the magnitude of life change was observed to be highly significantly related to time of disease onset. The greater the magnitude of life change, the greater the probability that the life change would be associated with disease onset, and the greater the probability that the population at risk would experience the disease. A strong positive correlation also exists between magnitude of life change and seriousness of the chronic illness experienced. The major health changes observed covered a wide range of psychiatric, medical, and surgical diseases.

One obvious problem with the Holmes and Rahe (1967) method of scaling their Social Readjustment Rating Scale is that the magnitudes assigned to each of the life change items represent magnitudes for a group, not for an individual. A common sense observation might be that a particular event could be very stressful for a given individual, but not for another individual. For example, some people who have lived in the same house, which they owned for 25 years, might find that the

adjustment to a residential move is enormous, while students who move from college dorm rooms to off-campus apartments every summer and back again may feel that very little life adjustment is required to move. A form currently in use by psychiatrists in the United States Navy, called the Recent Life Changes Questionnaire (Rahe & Arthur, 1978), recognizes this point and asks respondents to both indicate what life changes they have experienced during different time periods and to assign their own ratings, from 1 to 100, for each of the life changes they experienced. Knowledge of the precipitants of physical and psychiatric illness in a given individual is far more useful to a physician in the treatment of that individual, than general knowledge of precipitants of physical illness in a group.

The Navy Recent Life Changes Questionnaire (Rahe & Arthur, 1978) illustrates another problem with the popularly used Holmes and Rahe (1967) Social Readjustment Rating Questionnaire: the SRRQ samples too limited a population of stressful life events. Holmes and Rahe (1967), in devising the SRRQ, argued on a priori grounds that their particular list was a good one: they appealed to "common sense" by making the assumption that most people would agree that the events chosen were stressful. However, what can be considered as stressful might be much better arrived at by asking subjects to indicate these events solely on the basis of their own introspective experience, without recourse to any prearranged lists, as well as by indicating the magnitude of the life change experiences for themselves individually. The Navy Recent Life Changes Questionnaire contains more items than the standard SRRQ, including events that are specific and meaningful to military populations, such as demotions and transfers.

Holmes and Rahe (1967) also sample events that occur too infrequently to make meaningful correlations between daily changes of life events and daily changes in specific types of physical illness, for example seizure frequency in an epileptic population. In fact, such rarely occurring events as death or divorce, or even a major change in the number of arguments with a spouse, can be far separated in time from such relatively frequently occurring physical disabilities as seizure frequency. Seizure frequency could have far more mundane immediate antecedents, for example a particularly bad single argument with a spouse; although seizure frequency may conceivably be correlated with, say, death of a family member six months previously. A far more useful strategy would be to look at life changes that occur on a monthly, weekly, or even daily basis as they are related to changes in physical illness and psychiatric disorder, rather than life changes that occur in the distant past.

Holmes and Rahe (1967) do not sample the day to day, stressful life events that people might experience, such as arguments with spouse, problems with children, in-laws coming to visit, failures of household equipment, and overly-hectic days at the office. Very conceivably, these daily and relatively minor occurrences, or a certain magnitude of them, may be most responsible for physical ailments such as headaches, stomach aches, accidents of various kinds, and seizure frequency. Knowledge of the particular stressful occurrences that precipitate illness in a given individual is extremely important for treatment and management of that individual.

Holmes and Rahe (1967) have not published the only life change questionnaire; nor is their questionnaire the only one with major

theoretical and methodological problems. Other investigators who have published their own lists of stressful life events include Antonovsky and Kats (1967), Brown and Birley (1968), Dohrenwend (1973a), and Murphy, Robins, Kuhn, and Christensen (1962). Although the events lists compiled by different investigators always overlap to some extent, the lists are by no means identical. They vary in number of items: from 27 on the list used by Murphy, Robins, Kuhn, and Christensen (1962) to 62 on the list used by Myers and his co-workers (1972). They also vary in content: for example, court martial is specific to lists used to investigate military personnel (Rahe et al., 1967); experience in Nazi concentration camps is included in research done in Israel (Antonovsky & Kats, 1967). The dictates of common sense definitions vary with the subjects being studied, the setting in which the research takes place, and the type of illness or disorder being investigated.

Other differences between the various lists of life change events reflect theoretical divergencies among the investigators. For example, differences exist between investigators over how important it is to distinguish between objective events and subjective events (Thurlow, 1971), gain events and loss events (Dohrenwend, 1973a), and between events the individual is responsible for bringing about and events over which he has no control (Brown, Sklair, Harris, & Birley, 1973; Dohrenwend, 1973b).

A difficulty in all of the life change questionnaires is the failure to separate the relationship of psychopathology to physical illness from the relationship of other life events to physical illness, as well as the converse: the relationship of physical illness to psychopathology. In such research, physical illness is one type of event among many, as is psychopathology one type of event among many; the contribution of physical

illness to psychopathology is obscured in reductions of the life events reported to total Life Change Unit scores (Masuda & Holmes, 1967; Rahe & Arthur, 1968), total events, or summary qualitative distinctions such as "gain" versus "loss" (Dohrenwend, 1973a) or "desirable" versus "undesirable" (Myers et al., 1972). Likewise, the contribution of psychopathology to physical illness is obscured. Individuals may bring about many of their own life changes and physical illnesses because of emotional instability which leads them to behave in bizarre ways, provoking individuals close to them and disrupting their environment (Fontana, 1976).

We have already mentioned that the defense of the event lists used by different investigators has been based on appeals to common sense and reference to retrospective reports of the types of event or crisis included by patients under treatment for various disorders or illnesses. Only Dohrenwend (1974) reports on nominations of items for a life events list which are made independently of the researcher-constructed lists themselves, by samples of subjects drawn from the general population. Dohrenwend (1974) had leaders, a community sample, psychiatric outpatients, psychiatric hospital patients, and convicts nominate the last major event in their lives that, for better or worse, interrupted or changed their usual activities. Dohrenwend (1974) also had his sample complete a standard checklist. He found that very few of the events reported in response to the checklist were previously nominated by the respondents themselves as the last major events in their lives occurring in the preceding year. Most of the events on the standard checklist were not "major" by even a substantial minority of the respondents who experienced them.

A standard checklist, then, is apparently not a very good way to

elicit events that respondents consider to be major. However, in reference to the Dohrenwend (1974) study, the types of events that respondents nominate as major appears to be very much dependent on the personality structure and degree of success of the respondents. Community leaders tend to report as major events, objective gain events that they were likely to have some responsibility for bringing about. By contrast, patients and prisoners tend to report either subjective or objective loss events for which they were likely to be at least partly responsible. Community sample respondents who resemble leaders in reporting last major events involving gain also resemble them in showing low rates of psychiatric disorder. Unfortunately, Dohrenwend (1974) does not specify in any great detail the specific life events which his sample reported, that are different from the more usual checklist events.

Dohrenwend (1974) concludes from his analysis of the responses of his sample that examining stressful life events in terms of whether they represent gain or loss, the number involved, or the amount of change associated with them is not likely to tell us much about their role in the etiology of psychopathology. Some types of gain or loss events are too hopelessly confounded with superior functioning on the one hand and impairing psychopathology on the other to be helpful in investigating the causation of either. Rather, what appears to be crucial to the differences in psychopathology among those reporting different types of objective loss event is whether the events involve physical illness or injury to the respondent and whether or not their occurrence is outside the subject's control.

What are some of the implications of Dohrenwend's (1974) findings for future research? If an investigator's interest is in the role of

stressful life events in the etiology of physical illness, then Dohrenwend's results imply that there are several different event populations: for example, objective and subjective events, gain and loss events, and events for which the individual may or may not be responsible. In addition, it is necessary to keep analytically distinct at least three different populations of events if the investigation is focused on problems of etiology: (a) a population of events that are confounded with the psychiatric condition of the subject; (b) a population of events consisting of physical illness and injury to the subject; and (c) a population of events whose occurrences are independent of either the subject's physical health or his psychiatric condition. The more the sample of items in a particular measure of stressful life events represents a mixture from these three event populations, the more difficult it will be to assess the implications of a relationship between such a measure and either various types of psychopathology or various types of physical illness. The key problem becomes how to sample these events in such a way that their interrelations with each other and their possible contribution to psychopathology can be evaluated.

A possible research design to solve this problem might consist of the following: (a) a probability sample of subjects unselected for psychopathology and preferably drawn from the general population; (b) baseline measures of their psychiatric condition, including measures of various types of psychopathology and related role functioning; (c) retrospective measures that sample and date the most significant events from each of the three event populations over the major developmental stages of the subject's life history; and (d) a short-term follow-up, at which time postmeasures of the psychiatric condition of the respondents

would be secured, as well as intervening measures of the most important events that occurred during the year from each of the three populations, with each event carefully dated with respect to every other in terms of time occurrence. In this design, the key variables whose etiological significance would be evaluated are events from the populations of physical illness and injury, and events outside the subject's control, that occur between the pre-measures and post-measures of psychiatric condition. The events from event population 1 that occurred between the pre-measures and post-measures would be used as control variables to test for possible early onset or exacerbation of psychopathology if they preceded the events from event populations 2 and 3 or as part of the post-measures of psychiatric condition if they followed the events from event populations 2 and 3. A similar strategy could be used to study the etiological significance of life events in physical illness rather than psychopathology.

Several reviews on the status of the life stress questionnaires and problems inherent in them have been written (Hull, 1976; Mason, 1975a; Mason, 1975b; Mechanic, 1975; Mechanic, 1976; Rahe, 1978; Singer, 1977). Many of the problems of the current life stress questionnaires and some ideas for improving them have been considered in this paper. Some further prospects for research on stressful life events will now be considered.

The process of measuring the stressfulness of life events involves making a decision on how the domain of possibly stressful life events is to be defined; how a sample of events is to be drawn from that domain; and how the actual stressfulness of events is to be reliably measured. The investigator needs additionally to ask himself what are the factors that mediate the impact of stressful life events on the

individual. This specifically translates to asking: (a) What are the physiological processes that mediate the individual's response to stressful life events? (b) What are the psychological processes that mediate the individual's response to stressful life events? (c) What are the social processes that mediate the impact on the individual of stressful life events? The problem for the investigator is to ask the right questions about life events and their effects under circumstances in which the answers will provide clear demonstrations of whether and to what extent they are causally implicated in the disorders in which he is interested. Reviewing the literature on and criticisms of life events questionnaires suggests a number of considerations for future research:

1. Prospective designs need to be used more frequently in the development of life events questionnaires. Procedures need to be developed to assess whether stressful life events are perceived as being within or outside the control of the individual and whether the events were anticipated or unanticipated.

2. Another issue for future research is specification of relevant populations of life events and systematic sampling of the events from each population. Events contemporaneous in the lives of the individuals being studied and events in their past both need to be sampled. Such sampling would permit us to seek answers to questions such as: (a) What are the roles of primacy, frequency, and recency for different types of events in the life of the individual? (b) What are the relationships among events from different event populations? (c) Are there combinations and sequences of events that fit a stress-strain model of stress and illness? (d) Do some types of events at different developmental stages

of the individual have inoculation effects for some types of disorders?

3. Research designs need to be expanded to include a larger number of possible outcome variables, involving both physical illnesses and psychopathology.

The Schedule of Daily Experiences (SDE) adapted to weekly visits of an epileptic population. Holmes and Rahe (1967) originally developed the Social Readjustment Rating Questionnaire (SRRQ) as a scaling instrument for the life changes empirically determined to precede major health changes. The Schedule of Recent Experiences (SRE), a self-administered paper and pencil survey (Hawkins, Davies, & Holmes, 1957; Rahe et al., 1964), lists these life changes by year of occurrence. By assigning to the life changes the empirically determined magnitudes of the SRRQ, it was found that the higher a person's life change score for a given year, the greater his chances of experiencing a major health change within the near future (Edwards, 1971; Holmes, 1970; Rahe, 1968; Rahe & Lind, 1971; Rahe & Paasikivi, 1971; Theorell & Rahe, 1971; Tollefson, 1972; Wold, 1968).

From the Schedule of Recent Experiences, Holmes and Holmes (1970) derived a Schedule of Daily Experiences (SDE). In the Schedule of Daily Experiences, the 42 life change items in the Schedule of Recent Experience and the Social Readjustment Rating Questionnaire were recorded on a daily basis. Using the SDE, Holmes & Holmes (1970) adduced data about the association of life change and minor health change. Minor health changes were defined as the signs and symptoms of everyday life, such as cuts, bruises, headaches, stomachaches, backaches, and colds, that do not cause time lost from work or require a visit to the doctor. The findings indicated that subjects were much more likely to experience the signs and symptoms of everyday life on days of greater-than-average life changes.

Life changes tended to cluster significantly around health changes. The opposite also was confirmed: subjects were much less likely to experience signs and symptoms on days of less-than-average life change; and low amounts of life change tended to cluster significantly around symptom-free days.

The Schedule of Daily Experiences can easily be modified to fit the needs of weekly monitoring the relationships between life changes and seizure frequency in epileptic women. The author hypothesizes that epileptic women are much more likely to experience seizures during weeks of greater-than-average life changes, independently of hormonal fluctuations during different stages of the menstrual cycle. Although the Schedule of Daily Experiences includes many items that occur only rarely in the average person's life and cannot be expected to fluctuate very much from week to week, and although the SDE does not sample the day to day, stressful life events that people might experience (such as minor arguments with spouse, problems with children) and that might reasonably be expected to correlate with minor physical ailments, yet it is the life stress questionnaire that has been most widely used and shown most reliably to be highly significantly related to occurrence, time, and magnitude of disease onset. Additionally, Holmes and Holmes (1970) have shown that the SDE can be used as it stands to show the relationship between life change and minor health changes.

The directions for the Schedule of Daily Experiences, as administered by Holmes and Holmes (1970) are as follows:

> Each of the following items has a space beside it for each day of the coming week. If, during the course of the week, any of the items applies to you, check the appropriate box. If one

should apply more than once in a single day, indicate by the appropriate number in that box. Begin the chart on the day you receive it, and indicate the day by circling it and writing in the date. Do not mark in any space which does not apply.

In the spaces below, record briefly the day to day health changes which you may experience. These might include minor accidents, injuries, cuts, bruises, eyestrain, backache, headache, toothache, earache, stomach ache, muscle strain, coughing, sneezing, running nose, bloody nose, allergic reactions, nausea, vomiting, diarrhea, shortness of breath, skin rash, acne, athlete's foot, hay fever, sunburn, and the like. If you can, try to give some brief reason for a symptom, such as "Sore eye due to irritation of contact lens" or "Sore muscles due to swimming yesterday."

Also try to give some indication of your general state of thought, feeling, and behavior, for example, nervousness, tension, elation, moodiness, irritability, anxiety, anger, fatigue, etc. In general, include the signs, symptoms, and inconveniences of everyday life which usually pass unnoticed. Try to be as complete as possible. (p. 121)

These directions were modified as follows to make them appropriate to the epileptic sample that was followed on a weekly basis in the present study:

For each life event listed below please do the following:

Think back on the event and decide if it happened to you within the past week, including today.

If, during the course of the last week, any of the items applies to you, place a check mark in the appropriate space to

the right. If one of the items should apply more than once during the week, indicate the number of times the event occurred to you within the past week.

If the event in question did not happen to you during the past week, check under "Does not apply."

Instead of recording briefly the day to day health changes which the subject might experience, in the Schedule of Weekly Experiences used for the present study the subject was asked to record the number and type of seizures which she may have had during the previous week.

Appendix A shows the Schedule of Recent Experiences (SRE), as devised by Holmes. Appendix A also shows the author's adaptation of the Schedule of Recent Experiences for use on a weekly basis.

The POMS Profile of Mood States. The POMS Profile of Mood States was developed to assess transient, fluctuating affective states, both positive and negative (McNair, Lorr, & Droppleman, 1971). The POMS has been factor analyzed to identify six separate mood or affective states: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. In their scoring manual, McNair et al. (1971) note that the POMS has been proven to be a sensitive measure of the effects of various experimental manipulations upon normal subjects, psychiatric outpatients, and various nonpsychiatric populations.

The original POMS was developed to assess a subject's mood within the week prior to the rating, including the day the rating is done. However, to meet the demands of a particular study, other time sets have been used with the POMS, including the one which has been used in the present study, POMS Today (Pillard, Atkinson, & Fisher, 1967). However,

most of the data reported in the manual are based on a one-week rating period; Pillard et al. (1967) have cautioned that it should not be considered applicable for longer or shorter rating periods. Norms are available for comparisons with psychiatric outpatients and with college students.

Six independent factor analytic studies have been conducted in the development and validation of the POMS (Lorr & McNair, 1964; Lorr, McNair, & Weinstein, 1964; Lorr, McNair, Weinstein, Michaux, & Raskin, 1961; McNair, Lorr, & Droppleman, 1971). These studies indicate the same six mood factors can be identified, measured reliably, and replicated in VA male psychiatric outpatients, in male college students, and in male and female outpatients at a private teaching institution. Further, the factors appear to be relatively invariant whether the rating period is the immediate present or spans a one-week period.

In the studies reported by McNair et al. (1971), t tests indicate sex differences at a high level of significance on most POMS factors; however, the authors of the POMS do present standardized T scores for each sex for their psychiatric outpatient norms. Separate norms for each sex are not given for the college student norms. McNair et al. (1971) therefore recommend that unless the researcher wants to remove treatment-by-sex interactions from consideration, POMS raw scores should be used in the analysis of research data.

For the purposes of the present study, the POMS was given to the entire sample of subjects on a weekly basis, with instructions to take the test keeping in mind how the subject had felt throughout the previous week. In this way, weekly changes in mood could be related to changing life events, blood hormone levels, more enduring and stable personality

traits, and of course seizure frequency. The POMS answer sheet and scoring norms appear in Appendix A.

The Spielberger State-Trait Anxiety Inventory. One of the goals of the present study was to establish the magnitude of the anxiety and depression associated with the various phases of the menstrual cycle in epileptic women, and to compare these mood changes with available normative data. Another goal was to determine the interrelationship between premenstrual mood changes and trait anxiety. If changes in mood during the premenstrual phase are a function of personal adjustment, one would expect the greatest mood disturbance among women high in trait anxiety. Conversely, if premenstrual depression and anxiety are hormonally determined, no significant correlation would be expected between depression and state anxiety on the one hand, and trait anxiety on the other.

The Spielberger State-Trait Anxiety Inventory (STAI), developed by Spielberger, Gorsuch, and Lushene (1968) is designed to measure state anxiety as well as trait anxiety and has good reliability and validity data. State anxiety refers to a transitory emotional state characterized by conscious feelings of tension and subjective awareness of heightened autonomic nervous system activity. Conversely, trait anxiety refers to anxiety proneness, which is a relatively stable, baseline personality characteristic. The STAI consists of two separate 20-item self-report rating scales for measuring state and trait anxiety. The A-State scale is given first, followed by the A-Trait. Instructions on the State scale require that the examinee report how she feels at the time of administration, whereas the Trait scale instructions ask that she indicate how she generally feels. Spielberger et al. (1968) have demonstrated in several studies that A-State scores increase in response to situational stress

and decrease under relaxed conditions, and that A-Trait scores reflect relatively stable individual differences that are unresponsive to situational stress.

Golub (1976) found that in a group of normal women studied menstrually and intermenstrually, their premenstrual mood changes were not a function of personal adjustment. The A-Trait scores of this group were low compared with normative data obtained from Spielberger's sample of college women, yet they showed a high incidence of premenstrual depression and anxiety. In addition, no significant correlation was found between trait anxiety and premenstrual state anxiety or depression. This means that within the sample studied those subjects who were high in trait anxiety were not necessarily those who were high in premenstrual depression and state anxiety. Consequently, trait anxiety should be a relatively stable measurement, regardless of the stage of the menstrual cycle in which the present group of subjects respond to this item. However, state anxiety might be expected to fluctuate according to rises and falls in progesterone levels (O'Connor-Miller, 1980).

Life Events Diary. Another method of assessing the relationship between environmental events and physiological processes is self-monitoring, which requires the subject to detect and record environmental events by keeping track of them herself on a daily basis, for instance in a small spiral notebook which has been arranged for the recording of necessary information. An advantage of self-monitoring for stressful life events is that the subject has the opportunity to indicate what life events are particularly emotion-provoking for her, rather than trying to respond in terms of the prearranged categories of an instrument like the Schedule of Daily Experiences which may have many categories of life events which

she herself does not experience as particularly stressful, or which pre-selected life changes may occur so infrequently that the predictive value of the Schedule for seizure frequency is minimal. Self-monitoring can thus be used to generate hypotheses about important controlling environmental events. From an analysis of self-monitored logs of daily stressful life changes, events that are reliably related to a disorder can be identified, operationally defined, and then again self-monitored to produce a fine-grained analysis of the relationship between specific events and the disorder.

The method used in this study for self-monitoring life events that may be associated with the occurrence of seizures in epileptic women is the Life Events Diary presented in Appendix A. The author hoped that tabulation of this data would help generate good hypotheses about important controlling environmental events in the onset of seizures in epileptic women.

The present study. The present study will assess both cyclical hormonal changes and various environmental stresses and frustrations, specifically the interaction between physiological and environmental stress in producing seizures in epileptic women.

The hypotheses are: (a) H_1: High levels of progesterone inhibit seizures; (b) H_2: High levels of stress, as measured by the Spielberger State-Trait Anxiety Inventory, the POMS Profile of Mood States, the Moos Menstrual Distress Questionnaire, the Holmes and Rahe Schedule of Recent Experiences, and the daily Life Event Diary result in increased seizure frequency; and (c) H_3: An interaction between H_1 and H_2 results in the highest seizure frequency. The epileptic subjects were expected to have the greatest number of seizures during the menstrual and the

premenstrual stages of their menstrual cycles when estrogen and progesterone levels were lowest, if life stress was held constant. The subjects were also expected to have a large number of seizures if life stress was great, independently of phase of the menstrual cycle. The highest seizure frequency would be expected to occur during maximal psychological stress, plus lowest estrogen and progesterone levels (which occurs during the menstrual and premenstrual stages of the cycle).

CHAPTER III

METHOD

Subjects

Subject selection criteria. The experimental group was composed of 15 female epileptic subjects. Criteria for including potential subjects in the experimental group were:

1. All women must be between the ages of 18 and 45.

2. All subjects should currently have a regular menstrual cycle (i.e., not amenorrheic, menopausal, or using oral contraceptives).

3. All subjects should be experiencing at least a moderate number of seizures per month by history (at least three or four seizures a month) with no upper limit of number of seizures per month.

4. All subjects should be aware of the occurrence of their seizures, and be capable of counting them and recording the count. Relatives whom the subjects were living with were enlisted in counting and verifying the number of each subject's seizures. All subjects except two were living with a relative who could verify the seizure count.

5. All subjects should have a measured I.Q. of at least 80.

6. Subjects should have a reasonable likelihood of complying with the experimental procedures, as based on previous clinical history and the opinion of their neurologists.

7. Subjects must have a history of compliance on their anticonvulsant medication, as indicated by previous clinical history. Compliance was monitored by measuring anticonvulsant blood levels on each visit for the

study. In addition to the author, all subjects were screened by Richard H. Mattson, M.D., Chief of the Neurology Service at the West Haven V.A. Hospital, for compliance with these criteria.

Criteria for excluding potential subjects from the experimental group were:

1. Women who were pregnant or wished to become pregnant during the time period covered by the study were excluded.

2. Subjects should have a non-psychotic MMPI profile (Dahlstrom & Welsh, 1960; Meehl & Dahlstrom, 1960).

Characteristics of subjects. The subjects comprising the experimental group were drawn from female epileptic patients followed at the Epilepsy Center of the West Haven V.A. Hospital, the Seizure Clinic of Yale-New Haven Hospital, and private patients referred from department neurologists. An extensive history data form concerning precipitating and inhibiting factors in epilepsy, seizure type, and seizure frequency prior to entering this study, was completed by every subject and reviewed by the present author. This history data form, entitled Epilepsy Background and History, appears in Appendix B. This information was supplemented and validated by detailed review of all medical records, including reports of observed seizures.

Seizure type or types were coded according to the International Classification System (Gastaut, 1970). In addition to extensive interviews with the patient, the classification was based on a description of a witnessed attack by a family member or other observer. In every case, this was checked independently with reports made by nurses, physicians, or other medical personnel. In some patients, videotape recording of the seizures added further validation. These videotape recordings can be

obtained at the West Haven Veterans Administration Hospital Seizure Clinic. Seizure frequency prior to entrance into the study was recorded in clinic and hospital written reports.

The purpose of the study was explained to each patient. Specific data relating to seizures was answered by the patient and family utilizing the Epilepsy Background and History questionnaire previously mentioned (Appendix B). This form was reviewed during detailed interviews with the research investigator. The form was returned by the patient and family after initial completion, at which time it was reviewed and amplified by extensive documentation and anecdotal support of positive responses.

Other forms made detailed inquiry into the timing of seizures within a twenty-four hour period and other observed cyclical patterns. These forms were the Epilepsy and the Menstrual Cycle Patient Information form; the Early Morning Temperature Record and Daily Seizure Record, Menstrual Cycle Study; the Seizure Record; the Epilepsy and the Menstrual Cycle Clinic Visit form; and the Checklist for Menstrual Cycle Study form (all in Appendix B). The subjects and/or family members were instructed to keep records of seizure occurrence by numbers, hour, and date. These written records were reviewed at each clinic visit, not only to record seizure frequency, but to note time of occurrence and percent of seizures occurring at any given time. Subjects were instructed to make a record of seizures occurring during the morning, the afternoon, and at night. These did not represent comparable segments of time but could be expressed as a percent of the twenty-four hour day.

The effect of selected emotional factors in precipitating seizures was a major issue addressed by this study. As a separate category, a

record was made of the emotional state of the subject antecedent and consequent to seizures. This record was kept by means of a Life Events Diary, in which the subject recorded daily life experiences on a scale ranging from 1 = Extremely Pleasurable through 6 = Extremely Upsetting (Appendix A). The frequency of seizure occurrence during emotional stress was later compared with the number of seizures occurring under non-stressful circumstances.

Potential risks and consent forms. At each testing session, approximately 27 cc of blood was drawn from each subject. The venipunctures and EEG recording required as part of a larger study presented no risk, but did involve minor discomfort. The nature of the potential discomfort was explained to the epileptic subjects in Consent For Participation In A Research Project, Part 1 (Appendix C).

Material inducements. Visits to the Epilepsy Laboratory/Clinic and blood tests for antiepileptic drug levels were free of charge for the duration of the study. Thus, routine clinic visits which the subjects normally would have to pay for during this time period were not charged.

Apparatus

Basal body temperature recording and seizure record. The time of ovulation for the epileptic subjects in this study was calculated primarily from two sources of information: knowledge of the women's usual menstrual cycle length and basal body temperature. Knowledge of a woman's usual menstrual cycle length was useful in pinpointing the time of ovulation because ovulation usually occurs fourteen days, plus or minus two days, prior to the onset of menses regardless of the length of the cycle (Shapiro, 1977, p. 116). Thus, a woman with a thirty-seven day cycle, measured from the first day before the next period, usually

ovulates between Days 21 and 25. It is a misconception that ovulation occurs on the fourteenth day of the cycle, unless the woman has the twenty-eight day cycle described in textbooks, which only 8% of all women of childbearing age do. Therefore, with the group of women used for this study, ovulation was assumed to occur 14 days prior to the onset of the next menstrual cycle, and this specific point was defined in relation to each woman's reports and the examiner's observations of usual menstrual cycle lengths. The only time when ovulation was not assumed to occur fourteen days prior to the onset of the next menstrual period was when information from basal body temperature records indicated that ovulation occurred at an earlier point in time.

Following ovulation, progesterone is produced by the corpus luteum and is responsible for an elevation of a woman's temperature for approximately fourteen days until the onset of menstruation. The basal body temperature (the temperature taken immediately upon rising in the morning before getting out of bed), will rise between .4° and .8° F. during those fourteen days. By charting an accurate daily record of temperature using Tempa-Dot oral thermometers (Organon, Inc.), the women in the study had an aid in determining the time of ovulation. Daily temperatures were recorded on the Early Morning Temperature Record and Daily Seizure Record (Appendix B). A pamphlet was also given to the women to explain in more detail the technique of recording the basal body temperature (Planned Parenthood Federation of America, Inc., 1977).

The temperature rise usually takes place within twenty-four hours after ovulation, although there may be variations in the temperature record. Occasionally the temperature may rise gradually each day by less than .4°, and at other times it may have a step-like appearance, with a .2° rise

every two or three days. This may lead to inaccuracies in pinpointing the time of ovulation if only the basal body temperature method is used. Statistically, only 8 percent of women of childbearing age have perfectly regular cycles each month (Shapiro, 1977, p. 121). The burden of charting temperatures in the early morning when the subject is only half awake may lead to inaccuracies both in faking the temperature and in recording it. A source of confusion may be a temperature elevation in the presence of an unrecognized infection or of tension, or following a sleepless night. Smoking a cigarette prior to taking the basal temperature may falsely elevate it, while drinking large amounts of alcohol may falsely lower it.

Since the women in this study showed many variations in the temperature record, the main technique relied upon in pinpointing the time of ovulation was counting backward 14 days from the next menstrual bleeding, based on the women's usual menstrual cycle length. Two of the women in the study reported experiencing a short, sharp pain at ovulation, known as Mittelschmerz (Shapiro, 1977, p. 128); they were encouraged to report this pain and the information was used to schedule their ovulatory testing sessions.

For the epileptic subjects, seizures were recorded on the Early Morning Temperature Record and Daily Seizure Record (Appendix B). For subjects who had more than one type of seizure, space was provided for indicating the different types. Also, subjects were instructed to describe in detail any atypical seizures on a chart provided, called the Seizure Record (Appendix B). By recording seizures on the same chart as the basal body temperature, a direct visual comparison could be made between seizure frequency and stage of the menstrual cycle. Historical information on each epileptic subject with regard to menstrual cycle

and seizures was obtained and recorded on the Epilepsy and the Menstrual Cycle Patient Information Form (Appendix B), and on the Epilepsy Background and History form (Appendix B).

A Checklist for Menstrual Cycle Study (Appendix B) was used to make sure that all necessary information was collected on each clinic visit by every subject. An Epilepsy and the Menstrual Cycle Clinic Visit form (Appendix B) was used to review current anticonvulsant drug dosage and levels, seizure frequency, stage of the menstrual cycle, and use of adjunct medication with each subject at each clinic visit.

Mood measures. On the initial visit, each subject filled out the Moos Menstrual Distress Questionnaire, Form A (Appendix A); the Holmes and Rahe Schedule of Recent Experiences (Appendix A); the Spielberger State-Trait Anxiety Inventory, Form X-2 (Appendix A); and the POMS Profile of Mood States (Appendix A).

On all clinic visits, including the initial visit, each subject filled out the following questionnaires: the Moos Menstrual Distress Questionnaire, Form T (Appendix A); the Holmes and Rahe Schedule of Recent Experiences, modified to reflect life changes occurring on a weekly basis (Appendix A); the Spielberger State-Trait Anxiety Inventory, STAI Form X-1 (Appendix A); and the POMS Profile of Mood States (Appendix A).

The questionnaires given on each clinic visit were for the purpose of measuring ongoing stressful life events and changes in mood since the previous clinic visit.

The questionnaires given on the initial visit only were for the purpose of comparing each subject's expectations and impressions of changes occurring during different phases of the menstrual cycle, with the actual changes that took place during different phases of the cycle

as reported in the questionnaires filled out at each clinic visit. The initial questionnaires were also given to establish baseline measures of trait anxiety and stressful life experiences for each subject.

Diary. Each epileptic subject recorded on a daily basis all stressful life events in a Life Events Diary. Instructions given with each Diary are shown in Appendix A. All subjects recorded, from their perspective, life events which they considered to cause a significant amount of upset or which gave them a significant amount of pleasure. Life events were rated according to the following scale:

1 = Extremely Pleasurable

2 = Moderately Pleasurable

3 = Mildly Pleasurable

4 = Mildly Upsetting

5 = Moderately Upsetting

6 = Extremely Upsetting

This scale appeared on each page of an otherwise blank diary, which subjects kept for the period of time they were followed in the study.

The purpose of this diary was to determine whether epileptic subjects have more seizures in conjunction with or following significant amounts of life stress, either positive or negative, as viewed from their personal perspective.

Biochemical analysis.

1. Anti-epileptic drug levels. At each testing session, approximately 27 cc of blood was drawn from each subject. Serum concentrations of anti-epileptic drugs taken by the subjects were obtained for each testing session. One 9 cc tube was drawn for this purpose. The reason for

obtaining the anti-epileptic blood levels was to guarantee that subjects were taking their medication, so that seizures occurring because of sub-therapeutic levels of anti-convulsant drugs could be ruled out. Serum concentrations were obtained on the following anticonvulsant drugs: diphenylhydantoin (Dilantin), phenobarbital, primidone (Mysoline), carbamazepine (Tegretol), ethosuximide (Zarontin), mephobarbital (Mebaral), and valproic acid (Depakene). Commonly accepted therapeutic ranges of the serum concentration of these drugs are as follows: diphenylhydantoin, 10 - 22 μg/ml; phenobarbital, 18 - 45 μg/ml; primidone, 5 - 12 μg/ml; carbamazepine, 5 - 12 μg/ml; ethosuximide, 40 - 100 μg/ml; mephobarbital, 18 - 45 μg/ml; and valproic acid, 40 - 85 μg/ml (American Society of Hospital Pharmacists, 1975).

Gas liquid chromatography (GLC) was the standard analytical method used in the laboratories of the West Haven V.A. Hospital for measuring the total serum concentration of anti-epileptic drugs in this study. A modified method of Kupferberg (1970) was used for GLC analysis.

2. Steroids. Estrogen and progesterone assays allowed positive delineation of each subject's menstrual cycle into menstrual, ovulatory, high progesterone, and premenstrual phases. Two 9 cc samples of blood were drawn for this purpose during each testing session. A progesterone level of at least 8.0 mg/ml was used as the indicator of an adequate luteal phase and the occurrence of ovulation. Burton Caldwell, M.D., an obstetrician/gynecologist at the Yale University School of Medicine, was the consultant who judged whether an adequate or inadequate luteal phase took place in each cycle. The subjects' menstrual cycles were separated for further study according to whether ovulation had or had not taken place.

The Endocrinology Laboratory at Yale-New Haven Hospital performed the tests to determine serum concentration of the steroid hormones estrogen (measured in pg/ml) and progesterone (measured in ng/ml). Determination of estradiol levels was accomplished by the method of Jiang and Ryan (1969) and Kley, Bartmann, and Kruskemper (1977). Progesterone determination took into account the serum protein binding affinity of progestins (Blanford, Wittman, Stroupe, & Westphal, 1978; Duax, Cody, Griffin, Rohred, & Weeks, 1978; Heyns, 1977; Westphal, Stroupe, Cheng, & Harding, 1978). Recent advances in radioimmunoassay (RIA) technology have resulted in sensitive, accurate, and reproducible procedures for the assay of steroid hormones in biologic fluids. The basic principle of RIA is the competition between radiolabeled and unlabeled antigen for a fixed number of antibody binding sites. If increasing amounts of unlabeled (standards on samples) and fixed amounts of labeled antigen are allowed to react with a constant and limiting amount of antibody, a decreasing quantity of labeled antigen is bound to the antibody. After separation of bound from free antigen, the radioactivity in one or both of these fractions is determined and the data is used to construct a dose-response curve (Note 1).

In the procedure used at the Yale-New Haven Endocrinology laboratory, the New England Nuclear procedure, specificity is achieved by chromatographic purification prior to RIA. The plasma extracts are chromatographed on columns of Sephadex LH-20 to minimize potential interference of other naturally occurring steroids. Since the antiserum is not monospecific, the step is considered essential for the accurate determination of each steroid hormone.

Charcoal is utilized to separate the bound antibody from free

antigen. The charcoal differentially adsorbs the free material, and the supernatant containing the antibody-antigen complex is counted. The concentration of the particular steroid hormone assayed is obtained by correcting the amount read on the dose-response curve with appropriate dilution and recovery factors.

The determination of estrogens in plasma was specific for estradiol using standards prepared by New England Nuclear. The tracer was tritium labeled Estradiol - 17B - H^3. Progesterone was determined in plasma using tritium labeled Progesterone [1, 2-H^3 (N)] (Note 1).

Electroencephalography. The present study was part of a larger grant, and consequently electroencephalograms (EEGs) were performed on each subject during each testing session, in addition to the monitoring that was done for the purposes of the present study. The electroencephalograms were performed using a Beckman R611 8-Channel Polygraph with a Beckman 702 Lead Selector Panel and a Beckman Type 944A Lead Terminal Box. The EEGs were simultaneously recorded on the Beckman polygraph yielding a paper printout, and on Scotch Brand #888 1/4 X 2300 PR Instrumentation Tape (audiotape) by means of a Hewlett-Packard 3968A Instrumentation Recorder. Recordings consisted of 20 minutes of eyes opened and ten minutes of eyes closed, using a parasaggital montage with a temporal bite, and measured according to the International Ten-Twenty System of electrode placement (Harner and Sannit, 1974). Thirteen needle electrodes were used for this placement (Grass Instrument Company E2B 48" Length Subdermal Electrodes).

Electroencephalograms were recorded for each testing session, so that ideally twelve EEGs were obtained from each subject: during the menstrual, ovulatory, high progesterone, and premenstrual phases of her

cycle over three consecutive menstrual cycles.

Procedures

Each subject was monitored for three to four months. The goal was three months of complete data for each subject in which the menstrual, ovulatory, high progesterone, and premenstrual phases of the cycle were correctly identified and sampled.

Initial laboratory visit. The timing of the initial laboratory visit was to coincide with the menstrual phase of the subject's cycle. Each subject was told that when she got her period, she was to call the examiner to make an appointment to come in sometime during the next two days.

Procedures for the first laboratory visit were as follows:

1. Subjects were instructed to record all seizures, including their number and severity, for the duration of the study.

2. Subjects were instructed to indicate the onset of menses on their seizure calendar.

3. Subjects were instructed to record their daily basal body temperature.

4. Subjects were informed they would visit the laboratory four times a month for three months (the dates would be adjusted to individual cycle variations). The dates would be as follows:

(a) Day 1 - 2, onset of menses, follicular phase.

(b) Approximately day 14, mid cycle, ovulatory phase.

(c) Approximately day 21, late cycle, luteal phase.

(d) Approximately day 25, premenstrual phase.

5. Subjects were told that during each visit to the laboratory, three small tubes of blood (approximately 27 cc) would be drawn,

including during the initial visit. The purpose of the blood tests was to analyze anticonvulsant blood levels, estrogen levels, and progesterone levels.

6. Subjects were instructed in keeping a daily Life Events Diary.

7. Certain psychological tests to measure stressful life events and changes in mood retrospectively were administered only during the first testing session. These tests were:

(a) Moos Menstrual Distress Questionnaire, Form A.

(b) The Holmes and Rahe Schedule of Recent Experiences.

(c) The Spielberger State-Trait Anxiety Inventory, Form X-2.

(d) The POMS Profile of Mood States.

8. Psychological tests to measure ongoing stressful life events and changes in mood were given both during the first laboratory visit and during each subsequent laboratory visit. These tests were:

(a) Moos Menstrual Distress Questionnaire, Form T.

(b) Holmes and Rahe Schedule of Recent Experiences, modified to reflect life changes occurring on a weekly basis.

(c) Spielberger State-Trait Anxiety Inventory, STAI Form X-1.

(d) POMS Profile of Mood States.

Succeeding laboratory visits. The phases of the menstrual cycle during which each subject was studied are as follows: menstrual, ovulatory, high progesterone, and premenstrual. These phases were defined in the following way:

1. Menstruation -- defined as the days of menstrual bleeding.

2. Ovulatory -- defined as the periovulatory period, i.e., the point in time fourteen days prior to the onset of the next menstrual period is found, and the periovulatory period extends from two days before this

point to two days after this point.

3. High Progesterone -- defined as the point in time ten days prior to the onset of the next menstrual period up until the point in time four days prior to the onset of the next menstrual period.

4. Pre-Menstrual -- defined as four days prior to the onset of the next menstrual period, until the onset of the next menstrual period.

At least three full menstrual cycles were recorded for each subject. For each menstrual cycle, a subject came for a laboratory visit during the menstrual, ovulatory, high progesterone, and pre-menstrual phase of her cycle. Thus, each subject had a total of at least twelve laboratory visits. Analysis of estrogen and progesterone levels during the course of each subject's laboratory visits indicated that some subjects experienced one or more anovulatory cycles. Those subjects who were identified as experiencing anovulatory cycles were invited to remain in the study for additional menstrual cycles. The goal was to record at least three full ovulatory cycles for each subject.

Procedures for each laboratory visit succeeding the initial visit were as follows:

1. The Early Morning Temperature Record and Daily Seizure Record, Menstrual Cycle Study was reviewed with each subject. In order to chart each subject's menstrual cycle for the purpose of determining the time of ovulation and for recognizing the premenstrual phases of each subject's cycle, each woman kept a Basal Body Temperature Record. Temperatures were to be taken immediately upon arising each morning, using Tempa-Dot single-use sterile thermometers (Organon, Inc.), and recorded on the Early Morning Temperature Record and Daily Seizure Record. This record and the instructions for using it are in Appendix B.

The subjects were impressed with the importance of taking their temperatures every morning immediately upon awakening, before arising. They were told not to take aspirin or diuretics, such as Midol or Diuril, because of the possibility of changing and rendering inaccurate the Basal Body Temperature record. If a subject did take any additional medications, or had any infections or illnesses, these were recorded on the Epilepsy and the Menstrual Cycle Clinic Visit form (Appendix B).

2. The Seizure Record was reviewed with the subject.

3. The examiner recorded the number of seizures since the last clinic visit on the Epilepsy and the Menstrual Cycle Clinic Visit form. The date, time of day, and type of each seizure was also recorded on this form. Additionally, the total daily dose of anticonvulsant medication and the number of hours since the last dose were recorded. The date that the last menstrual period started was recorded. The number of days since the first day of the last menstrual period was calculated to determine the phase of the cycle that the subject was experiencing at the time of a given clinic visit. Any medication besides the subject's regular anticonvulsant medication that she took since the last clinic visit was recorded, if relevant.

4. The subject was given a specific date for the next clinic visit, if this was appropriate.

5. Approximately 27 cc of blood were drawn for the analysis of anticonvulsant blood levels, estrogen levels, and progesterone levels.

6. The Life Events Diary was reviewed.

7. The following psychological tests were administered:

(a) Moos Menstrual Distress Questionnaire, Form T.

(b) Holmes and Rahe Schedule of Recent Experiences, modified to reflect life changes occurring on a weekly basis.

(c) Spielberger State-Trait Anxiety Inventory, STAI Form X-1.

(d) POMS Profile of Mood States.

8. The examiner reviewed the Checklist for Menstrual Cycle Study to make sure that all procedures had been completed.

Additional monitoring. This study was part of a larger research grant. For the purposes of the larger research grant, during each clinic visit subjects also experienced the following procedures:

1. Electroencephalogram recordings, 20 minutes eyes open and 10 minutes eyes closed. Thirteen needle electrodes were used to record a parasaggital montage with a temporal bite.

2. Neuropsychological tests were administered:

(a) Grip Strength

(b) Finger Tapping

(c) Lafayette Pegboard

(d) Color Naming (Rennick)

(e) Trunkal Ataxia

(f) Digit Span

(g) Digit Symbol

(h) Trails B

(i) Visual Search (Rennick)

CHAPTER IV

RESULTS AND DISCUSSION

The three main hypotheses investigated by this study are: (a) high levels of progesterone inhibit seizures, and consequently seizures will occur most frequently during premenses and menstruation when levels of progesterone are low, and least frequently during ovulation and high progesterone phases of the menstrual cycle; (b) high levels of stress, as measured by the STAI, POMS, Moos MDQ, Holmes and Rahe Schedule of Recent Experiences, and Daily Life Events Diaries will be associated with high seizure frequency; and (c) a combination of low levels of progesterone and high stress is associated with the highest seizure frequency. In order to address these hypotheses adequately, several steps of analysis need to be performed.

Since the stages of an ovulatory menstrual cycle are marked by distinct differences in the estrogen/progesterone ratio, the first step in the analysis is to examine these ratios. Ovulation was considered to have occurred in a given cycle if the progesterone level at the luteal peak reached at least 5 ng/ml, if the estrogen level at the luteal peak reached at least 100 pg/ml, and if the estrogen/progesterone ratio at the luteal peak was at least 4:1 (Caldwell, 1979; Speroff, Glass, & Kase, 1973). Using those criteria, 30% of all cycles studied were anovulatory. Sixty percent of the subjects had at least one anovulatory cycle. Given that the absolute hormonal levels and estrogen/progesterone ratios are vastly different in ovulatory and anovulatory cycles, and also given that an important physiological event -- ovulation

-- occurs in ovulatory cycles but not in anovulatory cycles, the two types of cycles will be examined separately in all the subsequent analyses reported here.

Hypothesis: Level of Progesterone Is Related to Seizure Frequency

To test the hypothesis that level of progesterone is associated with seizure frequency, seizure frequency at each of four stages of the menstrual cycle was examined for ovulatory cycles. The follicular phase of the cycle was defined as beginning at menstruation and continuing until two days before ovulation. Ovulation was defined as occurring fourteen days prior to the onset of the next menstrual cycle; the periovulatory period extended from two days before ovulation until two days after ovulation. The next seven days constituted the high progesterone phase of the cycle; and the last four days prior to the onset of the next menstruation constituted the premenstrual phase of the cycle. During the follicular phase estrogen and progesterone levels are both low and near ovulation they both begin to rise slowly. During the periovulatory phase estrogen levels peak and progesterone levels are low, so that the estrogen/progesterone ratio is highest. At the high progesterone phase progesterone levels peak and estrogen levels are at a midpoint, so that the progesterone/estrogen ratio is highest. Premenstrually both estrogen and progesterone are rapidly falling to low levels. Thus, the subjects were expected to have the fewest seizures during the high progesterone phase of their menstrual cycles when progesterone levels are highest, and seizure frequency was expected to be greatest menstrually and premenstrually when progesterone levels are low or rapidly falling.

To test this relationship, a one-way repeated measure factor analysis of variance was performed, in which the dependent measure was

total seizure frequency, and the repeated measure factor was stage of the menstrual cycle. The four levels of the factor were the follicular, periovulatory, high progesterone, and premenstrual stages. The unit of analysis was one complete menstrual cycle for one subject. Results of this analysis appear in Table 1. The analysis of variance indicated a significant stage of the menstrual cycle effect, F (3, 39) = 7.0517, $p < .001$. When the Tukey multiple-range test was performed on the $K(K - 1)/2$ paired contrasts representing the four stages of the menstrual cycle, a significant difference was found between seizures at menstruation ($\bar{X}$ = 10.0714) and seizures at ovulation ($\bar{X}$ = 1.9286), q (39) = 7.3617, $p < .01$. Significant differences were also found between seizures at menstruation ($\bar{X}$ = 10.0714) and seizures at high progesterone ($\bar{X}$ = 2.0), q (39) = 7.3617, $p < .01$; and between seizures at menstruation ($\bar{X}$ = 10.0714) and seizures premenstrually ($\bar{X}$ = 1.4286), q (39) = 7.3617, $p < .01$.

Therefore, the subjects had the highest number of seizures at menstruation. The number of seizures at menstruation was significantly greater than the number of seizures at ovulation, at high progesterone, and at premenses. The results of this group of analyses indicate that a simple relationship does not exist between progesterone levels and seizure frequency. A graphic illustration of the relationship between seizure frequency and hormone levels appears in Figure 1.

Seizure frequency during anovulatory cycles, when progesterone levels are consistently low and estrogen levels fluctuate, was also analyzed (Figure 2). A one-way repeated measure factor analysis of variance was performed, in which the dependent measure was seizure frequency, and the repeated measure factor was stage of the menstrual cycle

Table 1

Means and Analysis of Variance for Seizure Frequency Across Four Stages of the Menstrual Cycle, Ovulatory Cycles Only (N = 14)

	Stage of Cycle				
	Menstruation	Ovulation	High Progesterone	Premenses	Grand Mean
Mean	10.0714	1.9286	2.0000	1.4286	3.8571
SD	12.7065	4.1411	4.4202	2.4088	

Source of Variation	Sum of Squares	df	Mean Square	F-Test
Between Subjects (Error)	1317.3571	13	101.3352	
Within Subjects	2057.5000	42	48.9881	
Stage of the Menstrual Cycle	723.5714	3	241.1905	7.0517***
Stage of the Menstrual Cycle X Unit	1333.9286	39	34.2033	
Total	3374.8577	55	61.3610	

***$p < .001$.

Figure 1

SEIZURE FREQUENCY DURING OVULATORY CYCLES OF THE EPILEPTIC SAMPLE (N = 14)

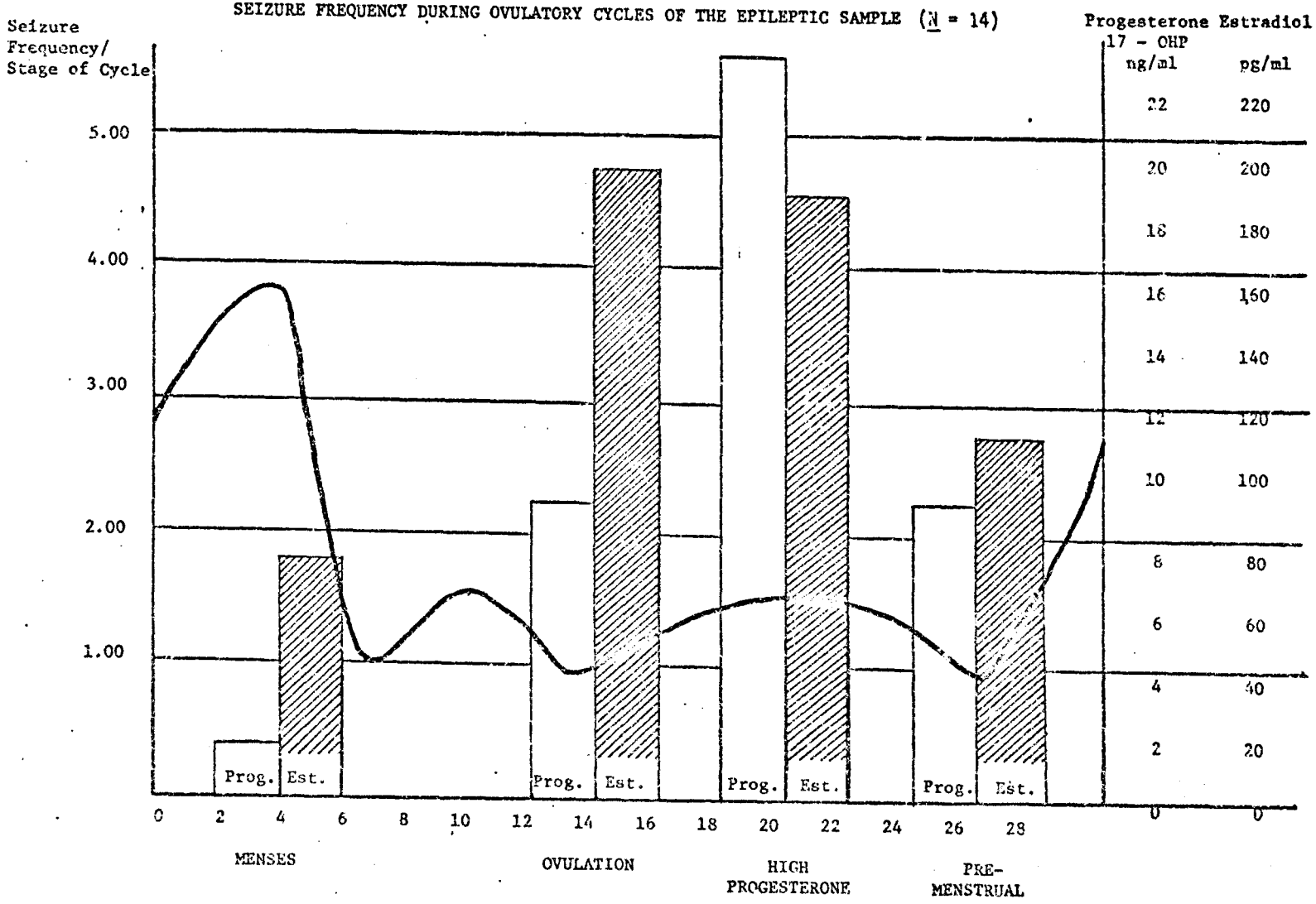
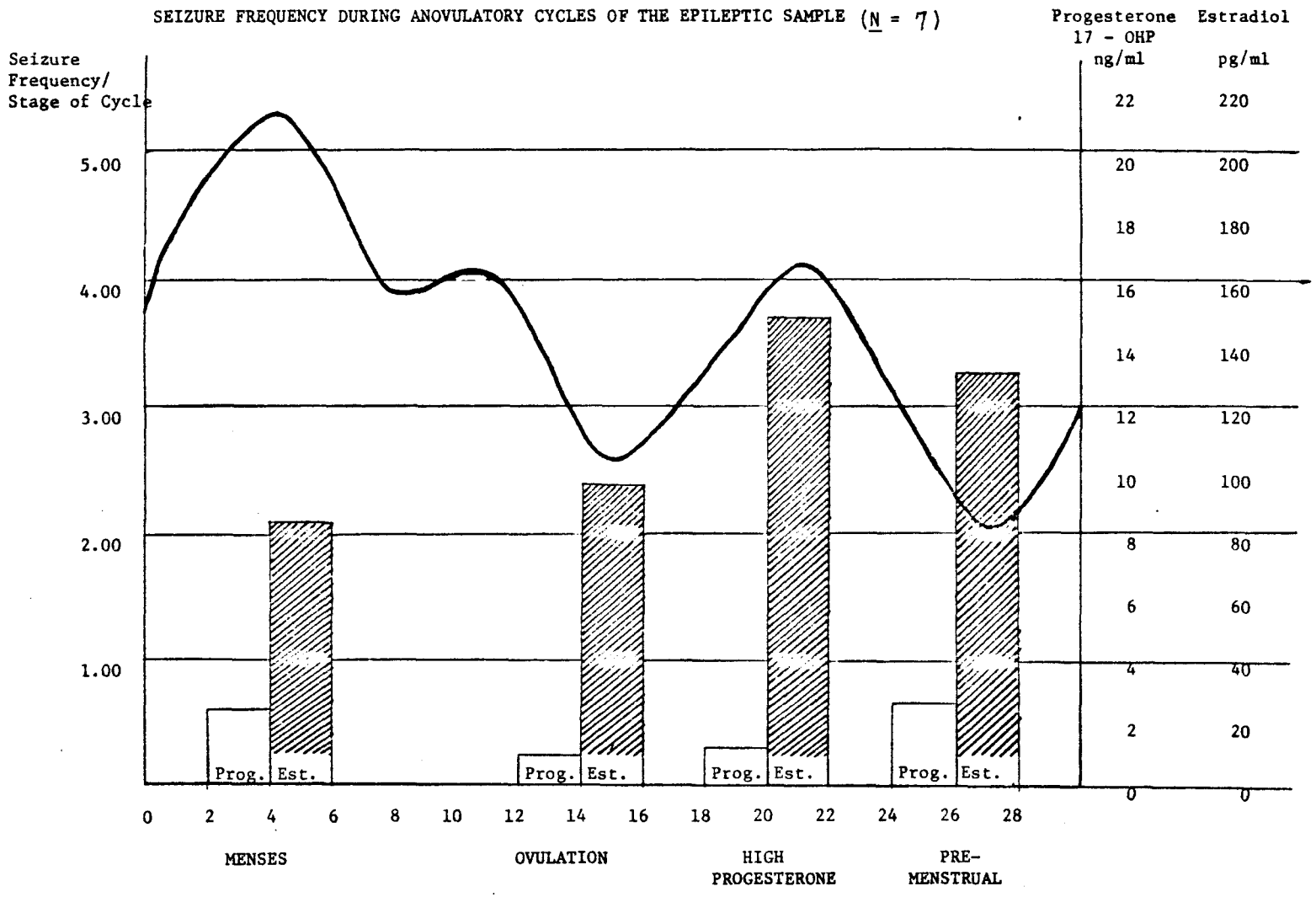


Figure 2


SEIZURE FREQUENCY DURING ANOVULATORY CYCLES OF THE EPILEPTIC SAMPLE (N = 7)
Seizure Frequency/ Stage of Cycle
5.00
4.00
3.00
2.00
1.00
Progesterone 17 - OHP ng/ml
Estradiol pg/ml
22 220
20 200
18 180
16 160
14 140
12 120
10 100
8 80
6 60
4 40
2 20
0 0
Prog. Est.
Prog. Est.
Prog. Est.
Prog. Est.
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
MENSES
OVULATION
HIGH PROGESTERONE
PRE-MENSTRUAL

for anovulatory cycles only. Of course, ovulation does not occur during anovulatory cycles by definition, so the four levels of the factor were equivalent time periods only to the follicular, periovulatory, high progesterone, and premenstrual stages of an ovulatory cycle. The unit of analysis was one complete anovulatory menstrual cycle for each subject. Results of this analysis appear in Table 2. The analysis of variance indicated a significant stage of the menstrual cycle effect, F (3, 18) = 3.4597, $p < .05$. When the Tukey multiple-range test was performed on the K(K - 1)/2 paired contrasts representing the four stages of the menstrual cycle, a significant difference was found between seizures at menstruation ($\bar{X}$ = 14.8571) and seizures premenstrually ($\bar{X}$ = 2.0), q (18) = 4.0, $p < .05$.

By comparing Figure 1 with Figure 2, one can see that: (a) almost twice as many seizures occur during anovulatory cycles, $\bar{X}$ = 25.5714 per cycle, as occur during ovulatory cycles, $\bar{X}$ = 15.4286 per cycle; (b) seizure frequency peaks during menstruation for both ovulatory and anovulatory cycles; and (c) the seizure frequency curves are very similar for ovulatory and anovulatory cycles, with the exception that the curve for anovulatory cycles is much higher. Although Table 3 shows that the mean of 15.4286 seizures for all ovulatory cycles was not significantly different from the mean of 25.5714 seizures for all anovulatory cycles, inspection of Table 3 also shows that for both ovulatory and anovulatory cycles, seizure frequency is highest at menstruation.

Even though a simple relationship between level of progesterone and seizure frequency was not found in this data, when progesterone is nearly eliminated seizure frequency doubled since a major difference between ovulatory and anovulatory cycles is the virtual absence of

progesterone in anovulatory cycles. Of course, changes in mood states may also account for differences in seizure frequency at different stages of the cycle for this sample of subjects, either independently of hormonal variables or interactively with hormonal variables. The contribution of mood states to changes in seizure frequency will be examined later in this Chapter.

All subjects were seen for three to six successive menstrual cycles, with measurements being taken at the four stages of the cycle each month. A two-repeated measure factor ANOVA, with the first repeated measure factor being month of observation and the second repeated measure factor being stage of the cycle showed no main effect for month of observation on the dependent variable total seizure frequency, F (2, 16) = 1.568, p = 0.239. For the first month of observation, mean total seizure frequency was 12.445 seizures for the entire month; for the second month of observation, $\bar{X}$ = 4.889; and for the third month, $\bar{X}$ = 12.334. Thus the subjects as a group did not have significantly more seizures during one month of observation than during another month of observation.

Differences in seizure frequency at the menstrual and the high progesterone phases of the cycle were not significantly correlated with changes in progesterone level at the menstrual and high progesterone phases of the cycle (r = 0.239, N = 38).

Hypothesis: High Levels of Stress Are Associated With High Seizure Frequency

The second hypothesis, high levels of stress, as measured by the STAI-1, POMS, Moos MDQ, Schedule of Recent Experiences, and Daily Life Event Diaries are associated with high seizure frequency, was examined

Table 2

Means and Analysis of Variance for Seizure Frequency Across Four Stages of the Menstrual Cycle, Anovulatory Cycles Only (N = 7)

	Stage of Cycle				
	Follicular	Periovulatory	High Progesterone	Premenses	Grand Mean
Mean	14.8571	3.4286	5.2857	2.0000	6.3929
SD	21.5749	5.5334	8.3609	4.4721	12.5058

Source of Variation	Sum of Squares	df	Mean Square	F-Test
Between Subjects (Error)	2290.4286	6	381.7381	
Within Subjects	1932.2500	21	92.0119	
Stage of the Menstrual Cycle	706.6786	3	235.5595	3.4597*
Stage of the Menstrual Cycle X Unit	1225.5714	18	68.0873	
Total	4222.6786	27	156.3955	

*p < .05.

Table 3

Seizure Frequency of Ovulatory and Anovulatory Cycles (N = 21)

Types of Cycles		Stage of Cycle				
		Follicular	Periovulatory	High Progesterone	Premenses	Row Marginals
Ovulatory (n = 14)	Mean	10.0714	1.9286	2.0000	1.4286	3.8571
	SD	12.7065	4.1411	4.4202	2.4088	7.8333
Anovulatory (n = 7)	Mean	14.8571	3.4286	5.2857	2.0000	6.3929
	SD	21.5749	5.5334	8.3609	4.4721	12.5058
Column Marginals	Mean	11.6667	2.4286	3.0952	1.6190	4.7024
	SD	15.8093	4.5670	6.0159	3.1381	9.6428

Source of Variation	Sum of Squares	df	Mean Square	F-Test
Between Subjects (Error)	3727.8095	20		
Type of Cycle (Ovulatory vs. Anovulatory)	120.0238	1	120.0238	0.6321
Subjects Within Groups	3607.7857	19	189.8835	
Within Subjects	3989.7500	63		
Stage of the Menstrual Cycle	1380.9881	3	460.3294	28.0337***
Type of Cycle X Stage of Cycle	49.2618	3	16.4206	0.3657
Stage of Cycle X Subjects Within Groups	2559.5001	57	44.9035	

***p < .001.

next. Since the concept of examining each of these independent variables at the four defined stages of the menstrual cycle properly applies mainly to ovulatory cycles, results for ovulatory and anovulatory cycles will again be discussed separately.

Ovulatory Cycles

Since each subject was studied for at least three successive months, a question that needed to be addressed was whether a practice effect occurred; that is, whether the subjects showed a tendency to endorse more or fewer negative mood items with each succeeding month they were studied. A two-way analysis of variance was performed for each of the mood scales, with month and stage of the menstrual cycle being the repeated measure factors. That is, the repeated measure factors "month" and "stage of the menstrual cycle" were analyzed for each of the dependent variables STAI-1, each of the POMS scales, each of the Moos MDQ scales, and the Schedule of Recent Experiences. The unit of analysis was each measurement of the dependent variables for one subject during one ovulatory cycle.

Results of the two-repeated measure factor analysis of variance showed no significance for month, stage of the menstrual cycle, or month by cycle interaction for the dependent measures the Spielberger State Anxiety Inventory, POMS Tension, POMS Depression, POMS Anger, POMS Vigor, POMS Fatigue, POMS Confusion, POMS Total T-Scores, Moos Pain, Moos Concentration, Moos Behavior Change, Moos Autonomic Reactions, Moos Water Retention, Moos Negative Affect, Moos Arousal, Moos Control, and the Holmes and Rahe Weekly Schedule of Recent Experiences. These results apply to ovulatory cycles only. Only for the dependent measure Moos Water Retention a main effect was found for month, F (2, 16) = 5.107, p = .02.

Subjects reported more Water Retention during the first month they were studied ($\bar{X}$ = 8.884) than during succeeding months ($\bar{X}$ = 7.418).

These results indicate that no practice effect occurred for the repeated measures of the dependent variable from month to month, with the exception of Moos Water Retention which was greatest for the first month of study. However, the same two-repeated measure analysis of variance also shows no significant differences in any of the mood measures from one stage of the menstrual cycle to the next. That is, when the subjects were repeatedly measured on the STAI-1, POMS, Moos MDQ, and WSRE variables, no significant differences occurred between these measurements taken at the menstrual, ovulatory, high progesterone, or premenstrual stages of the ovulatory cycles. Table 4 shows the mean values of each of the dependent variables measured at each of the four stages of the menstrual cycle, collapsed across three months of observation. In contrast to the large body of literature reporting increased menstrual and premenstrual negative affect, no significant changes in negative affect between different stages of the menstrual cycle were found for this group of ovulatory epileptic women. We have already determined that this group of epileptic women has a seizure peak at menstruation. Comparison of scores on a variety of mood measures taken at different stages of the menstrual cycle shows no corresponding increase in negative affect at the same time that seizure frequency increases. Another possible hypothesis is that increased negative affect and stress precedes increased seizure frequency, and this hypothesis will be examined shortly.

To investigate the hypothesis that increased negative affect and stress precede increased seizure frequency, stress measured in a stage

Table 4

Mean Values of Dependent Variables Measured at the Four Defined Stages of the Menstrual Cycle, Ovulatory Cycles Only

Variable	Menstruation		Ovulation		High Progesterone		Premenses		Overall F-Test
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Moos Pain	10.065	4.310	10.879	5.547	10.467	4.897	9.148	3.817	0.688
Moos Concentration	13.613	5.723	12.818	5.072	13.367	5.805	12.815	4.000	0.173
Moos Behavior Change	7.065	3.037	7.152	2.583	7.467	3.074	7.704	3.838	0.249
Moos Autonomic Reactions	4.710	1.570	4.788	1.683	4.967	2.025	4.556	1.423	0.282
Moos Water Retention	7.774	2.904	7.424	2.903	7.667	3.004	7.481	3.084	0.090
Moos Negative Affect	16.258	8.242	16.818	8.215	16.833	8.637	16.407	8.283	0.036
Moos Arousal	13.097	5.063	13.273	4.514	12.533	4.787	13.296	4.935	0.157
Moos Control	7.645	2.322	8.303	3.030	7.567	2.565	8.444	3.270	0.729
Spielberger State Anxiety	40.300	12.223	42.788	11.729	44.900	12.472	42.889	13.636	0.659
POMS Tension	38.267	9.451	39.394	9.726	38.500	7.393	37.444	8.621	0.237
POMS Depression	40.267	8.664	39.424	8.414	39.167	7.385	39.185	8.464	0.113
POMS Anger	45.900	9.988	44.121	8.260	45.867	10.095	46.222	9.628	0.306
POMS Vigor	55.467	9.653	55.061	11.786	53.600	9.708	55.111	11.419	0.173
POMS Fatigue	43.200	8.215	43.000	7.935	44.500	9.625	43.074	7.107	0.213
POMS Confusion	40.300	7.448	39.545	6.184	40.567	7.517	41.037	6.856	0.233
POMS Total T-Score	152.467	38.191	150.970	37.560	155.000	38.374	151.852	39.088	0.060
WSRE No. of Occurrences	3.187	5.065	3.879	3.699	3.767	4.645	3.259	4.195	0.188
WSRE Weighted Scores	71.562	109.538	91.909	86.831	78.300	95.234	63.667	78.914	0.481

Note. Number of cycles = 33.

of the menstrual cycle immediately prior to the major seizure flurry in a given cycle was compared to stress in the middle of a seizure-free stage. Since most of the mood variables were measured only four times a month for each subject, an attempt was made to find a testing session for each menstrual cycle that was no more than five days prior to the major seizure flurry of that cycle. A testing session that occurred in the middle of a seizure-free period was also identified for each cycle. Since some women had no seizures during a given menstrual cycle, that cycle was eliminated from the analysis. A total of 36 cycles were included in the analysis that had one period of seizure flurries and one period of no seizures during that cycle. Most of the periods of seizure flurries were during menstruation. Matched t-tests were performed to test the difference in scores on each of the dependent variables between a testing session just prior to a seizure flurry and a testing session that occurred during the midpoint of a seizure-free period. No significant differences were found on the STAI-1 scores, WSRE scores, any of the POMS scores, and any of the Moos MDQ scores when a testing session prior to a seizure flurry was compared to a midpoint seizure-free testing session. Table 5 shows the results of the matched t-tests performed on these variables.

Despite all the negative results in predicting seizure flurries with the standardized mood tests, the Diary of Life Events which the author devised was useful in predicting seizure flurries during menstrual cycles. For each menstrual cycle in which at least one seizure occurred, two time periods were identified. The first time period was three days immediately prior to the greatest seizure flurry of that cycle and the second time period was the midpoint of a period of no seizures during

Table 5

Matched t-Tests for the Difference in Scores on Each of the Dependent Variables Between a Testing Session Just Prior to a Seizure Flurry and a Testing Session That Occurred During the Midpoint of a Seizure-Free Period (N = 36 cycles)

Variable	Mean Difference	Standard Deviation	n	t-Test
Moos Pain	- 0.882	4.770	34	- 1.063
Moos Concentration	0.735	3.657	34	1.155
Moos Behavior Change	0.265	2.524	34	0.602
Moos Autonomic Reactions	- 0.088	2.214	34	- 0.229
Moos Water Retention	- 0.853	2.912	34	- 1.683
Moos Negative Affect	- 0.529	4.603	34	- 0.661
Moos Arousal	- 0.059	3.115	34	- 0.108
Moos Control	- 0.059	1.882	34	- 1.616
Spielberger State Anxiety	- 0.483	9.027	29	- 0.283
POMS Tension	0.793	7.097	29	0.591
POMS Depression	0.345	4.245	29	0.430
POMS Anger	1.897	7.443	29	1.348
POMS Vigor	1.345	6.900	29	1.031
POMS Fatigue	0.172	5.896	29	0.155
POMS Confusion	1.655	5.390	29	1.625
POMS Total T-Score	3.517	23.252	29	0.800
WSRE Weighted Scores	- 16.629	65.460	35	- 1.481

the same cycle. The mean score of all diary ratings was calculated for each individual cycle. The mean was of a rating on a 6-point scale of all the significant life events that the subjects mentioned during a particular menstrual cycle. Next, the mean score for the diary ratings for the three days prior to a seizure flurry and the three days in the midpoint of no seizures was calculated for each cycle. The mean overall diary rating for a given cycle was subtracted from the mean diary score prior to a seizure flurry. The mean overall diary rating for a given cycle was next subtracted from the mean diary score for the midpoint of no seizures for that cycle. Thus each subject's self-rated life stress before a seizure flurry, as well as during a period of no seizures, was compared to her own overall life stress for that particular cycle.

A matched pair t-test was performed to test the difference between self-rated life stress prior to seizures versus life stress during no seizures for all cycles. Since directional hypotheses were made, a one-tailed test was used. The subjects reported significantly more stress in the stage immediately prior to a seizure flurry ($\bar{X}$ = 0.1308) than during a period of no seizures ($\bar{X}$ = - 0.0928), t (35) = 1.7508, $p < .05$. This result suggests that a woman's own identification of personally upsetting life events and evaluation of the relative importance of those events is more useful in predicting seizures than any of the standardized mood or stressful life event scales.

Anovulatory Cycles

The fourteen anovulatory cycles were analyzed by assigning each testing session to one of four time periods that would be equivalent to the follicular, periovulatory, high progesterone, and premenstrual times of an ovulatory cycle. That is, if a subject was seen during menstruation,

that testing session would be assigned to the follicular-equivalent time period; if she was seen midcycle, that testing session would be assigned to the periovulatory-equivalent time period, and so on.

A one-way repeated measure analysis of variance was performed, in which the repeated measure factor was "stage of the menstrual cycle" and the factor levels were follicular-equivalent, periovulatory-equivalent, high progesterone-equivalent, and premenstrual-equivalent testing sessions. The dependent variables were STAI-1, each of the POMS scores, each of the Moos MDQ scores, and the WSRE. The unit of analysis was measurements taken on the dependent variables for one subject during one anovulatory cycle. Separate analyses were done for each dependent variable. Results of the one-way repeated measure ANOVA showed no significant main effects of stage of the menstrual cycle for any of the mood measures. These results appear in Table 6.

Comparison of Ovulatory and Anovulatory Cycles

As previously noted, we found that subjects had twice as many seizures during anovulatory cycles as they did during ovulatory cycles. Also, subjects had their greatest seizure peaks during the menstrual stage and a smaller seizure peak during the high progesterone stage for both ovulatory and anovulatory cycles. In this section the differences in response to the mood scales between the ovulatory and anovulatory cycles is examined.

A one-way repeated measure factor analysis of variance with one grouping factor was performed, in which the repeated measure factor was "stage of the menstrual cycle" and the factor levels were menstruation, ovulation, high progesterone, and premenses. The grouping factor was "cycle status," which had two categories: ovulatory cycles and anovulatory

Table 6

Mean Values of Dependent Variables Measured at Four Defined Stages of the Menstrual Cycle, Anovulatory Cycles Only (N = 14)

Variable	Menstruation		Ovulation		High Progesterone		Premenses		Overall F-Test
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Moos Pain	12.000	5.930	11.000	7.055	9.556	5.014	13.700	6.827	0.667
Moos Concentration	15.500	5.979	15.333	8.069	14.667	5.676	18.100	8.893	0.383
Moos Behavior Change	9.417	4.821	7.333	2.667	8.667	5.850	10.900	6.057	0.746
Moos Autonomic Reactions	4.333	0.624	5.556	3.236	5.111	1.449	5.200	1.778	0.693
Moos Water Retention	5.417	2.060	5.222	1.227	4.667	1.247	6.400	4.079	0.736
Moos Negative Affect	20.833	11.950	16.444	10.584	18.333	10.077	22.500	13.640	0.450
Moos Arousal	11.833	4.687	9.111	3.635	10.667	4.163	12.500	5.971	0.849
Moos Control	9.250	4.284	8.556	3.890	8.222	3.010	9.700	4.562	0.239
Spielberger State Anxiety	47.500	13.763	48.222	14.420	44.667	12.587	46.800	15.854	0.096
POMS Tension	40.417	11.856	39.667	11.508	38.778	8.753	43.000	12.736	0.221
POMS Depression	43.417	11.332	41.667	11.557	41.000	9.274	45.600	12.737	0.284
POMS Anger	51.833	10.286	45.778	9.343	49.444	10.678	51.800	12.711	0.602
POMS Vigor	52.500	10.650	46.778	6.729	50.222	6.696	52.300	12.946	0.639
POMS Fatigue	47.000	12.007	48.889	12.096	47.222	11.183	47.400	11.324	0.046
POMS Confusion	41.417	6.409	43.000	9.345	43.667	6.848	44.200	8.886	0.233
POMS Total T-Score	171.583	36.167	172.000	46.414	169.889	37.793	179.700	51.500	0.091
WSRE No. of Occurrences	1.538	2.308	1.300	1.487	1.000	1.054	2.500	2.975	0.820
WSRE Weighted Scores	34.462	49.598	31.300	36.017	25.222	27.680	50.700	65.131	0.464

cycles. The dependent variables were STAI-1 scores, each of the POMS scales, each of the Moos MDQ scales, and the Schedule of Recent Experiences. The unit of analysis was measurements taken on the dependent variables for one subject during one ovulatory or anovulatory cycle.

Results of the one-way repeated measure factor ANOVA with one grouping factor indicated three statistically significant findings. During anovulatory cycles subjects experienced significantly more anger, as measured by POMS Anger ($\bar{X}$ = 51.253), than during ovulatory cycles ($\bar{X}$ = 45.374), F (1, 44) = 3.999, p = .052. Subjects also experienced significantly more fatigue during anovulatory cycles, as measured by POMS Fatigue ($\bar{X}$ = 48.997) compared to ovulatory cycles ($\bar{X}$ = 43.309), F (1, 44) = 4.222, p = .046. Finally, subjects reported experiencing significantly more water retention during ovulatory cycles ($\bar{X}$ = 7.638) compared to anovulatory cycles ($\bar{X}$ = 5.876), as measured by Moos Water Retention, F (1, 44) = 4.582, p = .038.

Summarizing the results of this section, subjects experienced significantly more anger and fatigue during anovulatory cycles, while experiencing more water retention during ovulatory cycles. Perhaps significant amounts of anger and fatigue are in part responsible for the phenomenon of anovulatory cycles.

Hypothesis: A Combination of Low Levels of Progesterone and High Levels of Stress Is Associated with the Highest Seizure Frequency

Multiple Regression Analysis

The next step in the analysis was an attempt to predict the dependent variable, seizure frequency, from the several independent variables: anticonvulsant blood levels, estrogen and progesterone levels, POMS Profile of Mood States, Spielberger State Anxiety Inventory, Moos Menstrual

Distress Questionnaire, and the Holmes and Rahe Schedule of Recent Experiences. Multiple regression analyses were performed in order to develop prediction equations which would mathematically relate the independent variables to the dependent variable, seizure frequency. The form of multiple regression equation that was used was a step-wise solution; that is, for a given dependent variable, the independent variables are introduced into the equation one at a time until the last step increases the multiple correlation squared by less than 0.01. The multiple regression equations were done using the DATA-TEXT System statistical package (Armor & Couch, 1972). All calculations were done in the double-precision mode since independent variable correlations were very high. Product-moment correlations among all the variables were tested for significance. The predicted and actual scores for the dependent variables for each unit of analysis were printed.

The purpose of the initial multiple regression analysis was to predict the total seizure frequency that might occur at any stage of the cycle from the group of independent variables that were measured at that same stage. The dependent variable, therefore, was total seizure frequency at a given stage of the menstrual cycle while the 21 independent variables were the following measures associated with that stage: total Dilantin level, expressed as μg/ml; estradiol level, expressed as pg/ml; 17-OHP progesterone, expressed as ng/ml; Spielberger State Anxiety; POMS Profile of Mood States Tension, Depression, Anger, Vigor, Fatigue, Confusion, and Total T-Scores; Moos MDQ Pain, Concentration, Behavior Change, Autonomic Reactions, Water Retention, Negative Affect, Arousal, and Control scores; and the Holmes and Rahe Weekly Schedule of Recent Experiences weighted score. The unit of analysis used for this multiple

regression analysis was one testing session for one subject. A total of 168 units of analysis were used for the multiple regression, representing 168 testing sessions for the 14 subjects. Since normative and ipsative values were mixed in the multiple regression analyses, probability statements could not be made: the usual *t* or *F* with its associated probability statements could not be used. Therefore, only *t* values and unique variance are given in reporting the results of the multiple regression analyses. For this same reason, the mixing of normative and ipsative measures, no *p* values or statement of statistical significance for the overall multiple regression analyses could be made. The decision about further interpretation was made on the basis of the magnitude of the multiple *R*.

Results of the last step of this regression analysis appear in Table 7 and the associated correlation matrix appears in Table 8. The multiple correlation squared (R^2) is 0.329. This coefficient seems to merit further analysis and indicates that 32.9% of the variation of the dependent variable total seizure frequency is explained by association with the independent variables POMS Fatigue, State Anxiety, POMS Anger, POMS Vigor, POMS Depression, Holmes and Rahe Weekly Schedule of Recent Experiences, and Moos Pain. Inspection of the standardized regression coefficients indicate that the variables POMS Anger, *t* (160) = 4.24, unique variance = .076, and POMS Fatigue, *t* (160) = 3.31, unique variance = .046, have the greatest relative power to predict the dependent variable seizure frequency. Other significant predictive variables are POMS Vigor, *t* (160) = - 2.49, unique variance = .026, and POMS Depression, *t* (160) = - 2.22, unique variance = .021. However, since the multiple correlation squared is relatively low, the group of variables that appear in Table 7, including POMS Anger and POMS Fatigue, are not good predictors of total

Table 7

Multiple Regression Analysis to Predict the Dependent Variable Total Seizure Frequency Occurring at Any Stage of the Menstrual Cycle from the Group of Independent Variables That Were Measured at That Same Stage of the Cycle (N = 168)

Variable Description	Regression Coefficient	Std. Error of Coefficient	Standardized Coefficient	t-Test	df	Unique Variance
POMS Fatigue	0.2801	0.085	0.295	3.31	160	.046
Spielberger State Anxiety	- 0.1654	0.086	- 0.242	- 1.92	160	.015
POMS Anger	0.3976	0.094	0.448	4.24	160	.076
POMS Vigor	- 0.1672	0.067	- 0.199	- 2.49	160	.026
POMS Depression	- 0.3172	0.143	- 0.328	- 2.22	160	.021
WSRE Weighted Scores	- 0.0143	0.007	- 0.138	- 1.91	160	.015
Moos Pain	0.1637	0.152	0.096	1.07	160	.005
Regression Constant	1.602					
Multiple Correlation Squared	0.329	F = 11.20 with 7 and 160 Degrees of Freedom (p under .001)				
Multiple Correlation	0.573					
Standard Deviation of Residuals	7.540					

Partial Correlations with Dependent Variable for Variables Not Entered

Dilantin Levels	0.012
Estrogen Levels	- 0.088
Progesterone Levels	- 0.030
POMS Tension	0.017
POMS Confusion	- 0.047
POMS Total T-Score	- 0.018
Moos Concentration	0.052
Moos Behavior Change	- 0.009
Moos Autonomic Reactions	- 0.042

Table 8

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at Any Stage of the Menstrual Cycle and the Independent Variables Measured at the Same Cycle Stage

Variable Description	Seizure Frequency	Dilantin Levels	Estrogen Levels	Progesterone Levels
Seizure Frequency	1.000	- 0.092	- 0.096	- 0.005
Dilantin Levels	- 0.092	1.000	- 0.111	- 0.252
Estrogen Levels	- 0.096	- 0.111	1.000	0.299
Progesterone Levels	- 0.005	- 0.252	0.299	1.000
Spielberger State Anxiety	- 0.080	0.061	- 0.062	- 0.110
POMS Tension	- 0.117	0.145	- 0.052	- 0.157
POMS Depression	- 0.022	0.087	- 0.114	- 0.136
POMS Anger	0.292	- 0.123	- 0.119	0.012
POMS Vigor	- 0.126	- 0.271	- 0.041	0.170
POMS Fatigue	0.380	- 0.096	- 0.160	- 0.072
POMS Control	- 0.068	0.060	- 0.154	- 0.168
POMS Total T-Score	0.148	0.085	- 0.121	- 0.159
Moos Pain	0.168	- 0.170	0.058	0.057
Moos Concentration	0.126	- 0.106	- 0.098	- 0.094
Moos Behavior Change	0.153	- 0.051	- 0.079	- 0.011
Moos Autonomic Reactions	- 0.016	- 0.000	0.045	- 0.025
Moos Water Retention	- 0.091	- 0.147	0.117	0.104
Moos Negative Affect	- 0.011	- 0.092	- 0.031	- 0.019
Moos Arousal	- 0.051	- 0.386	0.049	0.243
Moos Control	- 0.009	- 0.085	- 0.042	- 0.005
WSRE Weighted Scores	- 0.129	0.087	- 0.051	0.056

Note. Number of cycle stages measured = 168.

Predicting Seizures at a Given Menstrual Cycle Stage by the Independent Variables Associated With That Stage

Another way of determining the predictors of seizure frequency is to look at the dependent variable, seizure frequency, separately for each of the four stages of the menstrual cycle for which data was collected: menstruation, ovulation, high progesterone, and premenses during ovulatory cycles. Four simultaneous multiple regression analyses were computed. For each of these multiple regression analyses, the dependent measure was total seizure frequency at a given stage of the menstrual cycle (for example, the menstrual stage), and the independent variables were the 21 previously mentioned measures collected at the same stage of the cycle (for example, all the hormonal and mood measures collected at the menstrual stage). The reason for structuring the analyses this way was the consideration that hormone levels and mood states that a woman is experiencing during menstruation might logically be expected to influence seizure frequency at menstruation, while hormone levels and mood states at another stage of the same cycle might logically influence seizure frequency at that other stage. Another way of making this same point is that a totally different weighted set of independent variables might predict seizure frequency at menstruation when hormone values are within a certain range, as compared to seizure frequency at another stage of the cycle when hormone values are within an entirely different range.

Each of these four simultaneous multiple regression equations will be described separately.

The first multiple regression analysis predicts seizure frequency at menstruation for only ovulatory cycles by the 21 independent variables

measured at menstruation and previously described. The unit of analysis for this multiple regression analysis was one testing session at the menstrual stage of the cycle for one subject. A total of 32 units of analysis were included, representing observations during menstruation for 32 ovulatory cycles of a group of 14 subjects.

Results for the last step of this regression analysis appear in Table 9 and the associated correlation matrix appears in Table 10. The multiple correlation squared (R^2) is 0.588, indicating that 58.8% of the dependent variable, total seizure frequency at menstruation during ovulatory cycles, is explained by asscciation with the independent variables POMS Fatigue, POMS Confusion, Moos Behavior Change, Moos Pain, Moos Negative Affect, progesterone levels, Moos Concentration, Moos Control, Moos Autonomic Reactions, and the Weekly Schedule of Recent Experiences, all measured at the menstrual stage of the cycle. Inspection of the standardized regression coefficient indicates that POMS Fatigue, t (21) = 3.38, unique variance = .224, and POMS Confusion, t (21) = - 2.15, unique variance = .090, in order, have the greatest power to predict seizure frequency at menstruation during ovulatory cycles.

The second multiple regression analysis predicts seizure frequency at ovulation, for ovulatory cycles only, by the 21 independent variables measured at ovulation. These 21 independent variables have been previously described in the paragraphs discussing the initial multiple regression analysis. A total of 32 units of analysis were included, representing observations during ovulation for 32 cycles of a group of 14 subjects.

Results for the last step of this regression analysis appear in Table 11 and the associated correlation matrix appears in Table 12. For this analysis, R^2 = 0.865. Inspection of the standardized regression

Table 9

Multiple Regression Analysis to Predict the Dependent Variable Total Seizure Frequency Occurring at Menstruation from the Group of Independent Variables Measured at Menstruation, Ovulatory Cycles Only (N = 32)

Variable Description	Regression Coefficient	Std. Error of Coefficient	Standardized Coefficient	t-Test	df	Unique Variance
POMS Fatigue at Menses	0.7296	0.216	0.629	3.38	21	.224
POMS Confusion at Menses	- 0.5072	0.236	- 0.394	- 2.15	21	.090
Moos Behavior Change at Menses	- 0.4408	0.771	- 0.140	- 0.57	21	.006
Moos Pain at Menses	0.9440	0.532	0.428	1.77	21	.062
Moos Negative Affect at Menses	- 0.5724	0.343	- 0.498	- 1.67	21	.055
Progesterone at Menses	- 1.6063	1.359	- 0.190	- 1.18	21	.027
Moos Concentration at Menses	- 0.5482	0.441	- 0.330	- 1.24	21	.030
Moos Control at Menses	1.1615	1.093	0.282	1.06	21	.022
Moos Autonomic Reactions at Menses	0.9885	1.401	0.163	0.71	21	.010
WSRE Weighted Scores at Menses	- 0.0071	0.015	- 0.081	- 0.48	21	.004
Regression Constant	- 5.231					

Multiple Correlation Squared = 0.588
Multiple Correlation = 0.767
Standard Deviation of Residuals = 7.639

F = 3.00 with 10 and 21 Degrees of Freedom (p = .017)

Partial Correlations with Dependent Variable for Variables Not Entered

Dilantin Levels at Menses	0.031
Estrogen Levels at Menses	- 0.059
Spielberger State Anxiety, Menses	- 0.063
POMS Tension at Menses	0.061
POMS Depression at Menses	- 0.076
POMS Anger at Menses	0.046
POMS Vigor at Menses	- 0.026
POMS Total T-Score at Menses	0.036
Moos Water Retention at Menses	- 0.029

Stepping stopped -- last step increased r^2 by less than 0.010.

Table 10

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at Menstruation and the Independent Variables Measured at Menstruation

Variable Description	Dilantin Levels	Estrogen Levels	Progesterone Levels	State Anxiety	POMS Tension	POMS Depression	POMS Anger	POMS Vigor	POMS Fatigue	POMS Confusion
Dilantin Levels	1.000	- 0.219	0.074	0.143	0.200	0.200	0.033	- 0.233	- 0.087	0.099
Estrogen Levels	- 0.219	1.000	0.136	0.108	0.196	0.033	- 0.036	- 0.170	- 0.054	0.087
Progesterone Levels	0.074	0.136	1.000	- 0.226	- 0.101	0.006	0.060	0.316	- 0.002	- 0.213
Spielberger State Anxiety	0.143	0.108	- 0.226	1.000	0.785	0.794	0.396	- 0.595	0.502	0.665
POMS Tension	0.200	0.196	- 0.101	0.785	1.000	0.789	0.459	- 0.262	0.502	0.616
POMS Depression	0.200	0.033	0.006	0.794	0.789	1.000	0.750	- 0.177	0.664	0.545
POMS Anger	0.033	- 0.036	0.060	0.396	0.459	0.750	1.000	0.196	0.745	0.186
POMS Vigor	- 0.233	- 0.170	0.316	- 0.595	- 0.262	- 0.177	0.196	1.000	- 0.066	- 0.426
POMS Fatigue	- 0.087	- 0.054	- 0.002	0.502	0.502	0.664	0.745	- 0.066	1.000	0.325
POMS Confusion	0.099	0.087	- 0.213	0.665	0.616	0.545	0.188	- 0.426	0.325	1.000
POMS Total T-Score	0.163	0.095	- 0.131	0.866	0.841	0.913	0.694	- 0.404	0.766	0.697
Moos Pain	- 0.255	0.247	0.011	0.468	0.469	0.578	0.475	- 0.140	0.474	0.243
Moos Concentration	- 0.211	0.129	- 0.194	0.675	0.555	0.531	0.347	- 0.367	0.449	0.609
Moos Behavior Change	- 0.167	0.034	0 122	0.442	0.360	0.667	0.760	0.082	0.518	0.267
Moos Autonomic Reactions	- 0.343	0.384	- 0.227	0.318	0.231	0.066	- 0.122	- 0.456	0.079	0.305
Moos Water Retention	- 0.314	0.017	- 0.237	- 0.113	- 0.210	- 0.098	0.079	0.134	- 0.192	- 0.080
Moos Negative Affect	0.090	0.080	- 0.042	0.654	0.607	0.802	0.699	- 0.001	0.511	0.255
Moos Control	0.113	0.122	0.091	0.426	0.398	0.748	0.804	0.172	0.459	0.242
WSRE Weighted Scores	0.130	- 0.285	0.359	0.012	0.005	0.164	0.328	0.349	0.115	- 0.058
Seizure Frequency	- 0.176	0.015	- 0.076	- 0.162	- 0.072	- 0.027	0.207	0.050	0.362	- 0.285

Note. N = 32 cycles.

Table 10 (Continued)

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at Menstruation and the Independent Variables Measured at Menstruation

Variable Description	POMS Total T-Score	Moos Pain	Moos Concentration	Moos Behavior Change	Moos Autonomic Reactions	Moos Water Retention	Moos Negative Affect	Moos Control	WSRE Weighted Scores	Seizure Frequency
Dilantin Levels	0.163	- 0.225	- 0.211	- 0.167	- 0.343	- 0.314	0.090	0.113	0.130	- 0.176
Estrogen Levels	0.095	0.247	0.129	0.034	0.384	0.017	0.080	0.122	- 0.285	0.015
Progesterone Levels	- 0.131	0.011	- 0.194	0.122	- 0.227	- 0.237	- 0.042	0.091	0.359	- 0.076
Spielberger State Anxiety	0.866	0.468	0.675	0.442	0.318	- 0.113	0.654	0.426	0.012	- 0.162
POMS Tension	0.841	0.469	0.555	0.360	0.231	- 0.210	0.607	0.398	0.005	- 0.072
POMS Depression	0.913	0.578	0.531	0.667	0.066	- 0.098	0.802	0.748	0.164	- 0.027
POMS Anger	0.694	0.475	0.347	0.760	- 0.122	0.079	0.699	0.804	0.328	0.207
POMS Vigor	- 0.404	- 0.140	- 0.367	0.082	- 0.456	0.134	- 0.001	0.172	0.349	0.050
POMS Fatigue	0.766	0.474	0.499	0.518	0.079	- 0.192	0.511	0.459	0.115	0.362
POMS Confusion	0.697	0.243	0.600	0.267	0.305	- 0.080	0.255	0.242	- 0.056	- 0.285
POMS Total T-Score	1.000	0.557	0.655	0.583	0.232	- 0.145	0.676	0.581	0.050	0.040
Moos Pain	0.557	1.000	0.606	0.428	0.548	0.317	0.583	0.474	0.239	0.281
Moos Concentration	0.655	0.606	1.000	0.470	0.610	0.332	0.526	0.386	0.047	- 0.111
Moos Behavior Change	0.583	0.428	0.470	1.000	0.035	0.166	0.755	0.740	0.356	- 0.105
Moos Autonomic Reactions	0.232	0.548	0.610	0.035	1.000	0.333	0.128	0.005	- 0.185	0.117
Moos Water Retention	- 0.145	0.317	0.332	0.166	0.333	1.000	0.160	0.197	0.194	- 0.040
Moos Negative Affect	0.676	0.583	0.526	0.755	0.128	0.160	1.000	0.813	0.303	- 0.073
Moos Control	0.581	0.474	0.386	0.740	0.005	0.197	0.813	1.000	0.374	- 0.005
WSRE Weighted Scores	0.050	0.239	0.047	0.356	- 0.185	0.194	0.303	0.374	1.000	- 0.093
Seizure Frequency	0.040	0.281	- 0.111	- 0.105	0.117	- 0.040	- 0.073	- 0.005	- 0.093	1.000

Note. N = 32 cycles.

Table 11

Multiple Regression Analysis to Predict the Dependent Variable Total Seizure Frequency Occurring at Ovulation from the Group of Independent Variables Measured at Ovulation, Ovulatory Cycles Only (N = 32)

Variable Description	Regression Coefficient	Std. Error of Coefficient	Standardized Coefficient	t-Test	df	Unique Variance
Estrogen at Ovulation	0.0200	0.003	0.671	6.79	19	.328
POMS Vigor at Ovulation	- 0.0181	0.025	- 0.075	- 0.73	19	.004
WSRE Weighted Scores at Ovulation	- 0.0098	0.004	- 0.299	- 2.43	19	.042
Moos Behavior Change at Ovulation	0.9460	0.205	0.863	4.61	19	.151
Moos Control at Ovulation	- 0.6136	0.142	- 0.658	- 4.34	19	.133
Moos Autonomic Reactions, Ovulation	- 0.4871	0.193	- 0.292	- 2.52	19	.045
Progesterone Levels at Ovulation	- 0.0787	0.020	- 0.406	- 4.01	19	.114
Dilantin Levels at Ovulation	- 0.0713	0.032	- 0.235	- 2.20	19	.034
Moos Water Retention at Ovulation	- 0.2025	0.129	- 0.207	- 1.57	19	.016
POMS Tension at Ovulation	- 0.1253	0.043	- 0.434	- 2.92	19	.060
Moos Concentration at Ovulation	0.1640	0.095	0.293	1.73	19	.021
Moos Pain at Ovulation	- 0.0784	0.095	- 0.154	- 0.83	19	.005
Regression Constant	7.129					

Multiple Correlation Squared = 0.865
Multiple Correlation = 0.930
Standard Deviation of Residuals = 1.356

F = 10.15 with 12 and 19 Degrees of Freedom (p under .001)

Partial Correlations with Dependent Variables Not Entered

Spielberger State Anxiety, Ovulation	- 0.098
POMS Depression at Ovulation	0.026
POMS Anger at Ovulation	0.079
POMS Fatigue at Ovulation	0 185
POMS Confusion at Ovulation	- 0.054
POMS Total T-Score at Ovulation	0.064
Moos Negative Affect at Ovulation	0.109

Stepping stopped -- last step increased r^2 by less than 0.010.

Table 12

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at Ovulation and the Independent Variables Measured at Ovulation

Variable Description	Dilantin Levels	Estrogen Levels	Progesterone Levels	State Anxiety	POMS Tension	POMS Depression	POMS Anger	POMS Vigor	POMS Fatigue	POMS Confusion
Dilantin Levels	1.000	- 0.182	- 0.434	0.094	0.264	0.115	- 0.056	- 0.174	- 0.039	0.081
Estrogen Levels	- 0.182	1.000	- 0.034	- 0.128	- 0.094	- 0.077	0.086	- 0.147	- 0.174	- 0.171
Progesterone Levels	- 0.434	- 0.034	1.000	- 0.151	- 0.275	- 0.172	0.059	0.222	- 0.061	- 0.244
Spielberger State Anxiety	0.094	- 0.128	- 0.151	1.000	0.736	0.872	0.506	- 0.439	0.463	0.776
POMS Tension	0.264	- 0.094	- 0.275	0.736	1.000	0.733	0.406	- 0.249	0.254	0.631
POMS Depression	0.115	- 0.077	- 0.172	0.872	0.733	1.000	0.645	- 0.477	0.535	0.735
POMS Anger	- 0.056	0.086	0.059	0.506	0.406	0.645	1.000	0.093	0.450	0.271
POMS Vigor	- 0.174	- 0.147	0.222	- 0.439	- 0.249	- 0.477	0.093	1.000	- 0.375	- 0.543
POMS Fatigue	- 0.039	- 0.174	- 0.061	0.463	0.254	0.535	0.450	- 0.375	1.000	0.277
POMS Confusion	0.081	- 0.171	- 0.244	0.776	0.631	0.735	0.271	- 0.543	0.277	1.000
POMS Total T-Score	0.141	- 0.047	- 0.231	0.884	0.751	0.935	0.577	- 0.632	0.648	0.785
Moos Pain	- 0.145	0.188	- 0.055	0.098	- 0.083	0.235	0.536	0.176	0.339	0.019
Moos Concentration	0.010	- 0.012	- 0.220	0.805	0.686	0.752	0.438	- 0.323	0.292	0.717
Moos Behavior Change	0.032	- 0.096	- 0.102	0.577	0.381	0.657	0.756	- 0.025	0.585	0.450
Moos Autonomic Reactions	0.021	0.268	- 0.192	0.211	0.373	0.226	0.011	- 0.132	- 0.106	0.326
Moos Water Retention	- 0.133	0.061	- 0.108	0.057	- 0.009	0.142	0.291	0.105	0.120	0.187
Moos Negative Affect	0.016	0.033	- 0.066	0.716	0.670	0.696	0.697	0.021	0.284	0.466
Moos Control	- 0.193	- 0.003	0.013	0.327	0.029	0.441	0.671	0.153	0.371	0.038
WSRE Weighted Scores	0.181	- 0.055	- 0.231	0.241	0.331	0.365	0.438	0.156	0.256	0.122
Seizure Frequency	- 0.135	0.592	- 0.229	0.011	- 0.111	- 0.031	- 0.059	- 0.388	0.098	0.124

Note. N = 32 cycles.

Table 12 (Continued)

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at Ovulation and the Independent Variables Measured at Ovulation

Variable Description	POMS Total T-Score	Moos Pain	Moos Concentration	Moos Behavior Change	Moos Autonomic Reactions	Moos Water Retention	Moos Negative Affect	Moos Control	WSRE Weighted Scores	Seizure Frequency
Dilantin Levels	0.141	- 0.145	0.010	0.032	0.021	- 0.133	0.016	- 0.193	0.181	- 0.135
Estrogen Levels	- 0.047	0.188	- 0.012	- 0.096	0.268	0.061	0.033	- 0.003	- 0.055	0.592
Progesterone Levels	- 0.231	- 0.055	- 0.220	- 0.102	- 0.192	- 0.108	- 0.066	0.013	- 0.231	- 0.229
Spielberger State Anxiety	0.864	0.098	0.805	0.577	0.211	0.057	0.716	0.327	0.241	0.011
POMS Tension	0.751	- 0.083	0.686	0.381	0.373	- 0.009	0.670	0.029	0.331	- 0.111
POMS Depression	0.935	0.235	0.752	0.657	0.226	0.142	0.696	0.441	0.365	- 0.031
POMS Anger	0.577	0.536	0.438	0.756	0.011	0.291	0.697	0.671	0.438	- 0.059
POMS Vigor	- 0.632	0.176	- 0.323	- 0.025	- 0.132	0.105	0.021	0.153	0.156	- 0.388
POMS Fatigue	0.648	0.339	0.292	0.585	- 0.106	0.120	0.284	0.371	0.256	0.096
POMS Confusion	0.785	0.019	0.717	0.450	0.326	0.187	0.466	0.038	0.122	0.124
POMS Total T-Score	1.000	0.160	0.717	0.610	0.216	0.105	0.605	0.281	0.299	0.108
Moos Pain	0.160	1.000	0.254	0.653	0.016	0.703	0.407	0.695	0.456	- 0.055
Moos Concentration	0.717	0.254	1.000	0.577	0.455	0.212	0.790	0.346	0.264	0.074
Moos Behavior Change	0.610	0.653	0.577	1.000	- 0.026	0.478	0.712	0.716	0.617	- 0.010
Moos Autonomic Reactions	0.216	0.016	0.455	- 0.026	1.000	- 0.088	0.248	- 0.089	- 0.024	0.001
Moos Water Retention	0.105	0.703	0.212	0.478	- 0.088	1.000	0.300	0.380	0.410	- 0.076
Moos Negative Affect	0.605	0.407	0.790	0.712	0.248	0.300	1.000	0.587	0.446	- 0.105
Moos Control	0.281	0.695	0.346	0.716	- 0.089	0.380	0.587	1.000	0.457	- 0.221
WSRE Weighted Scores	0.299	0.456	0.264	0.617	- 0.024	0.410	0.446	0.457	1.000	- 0.279
Seizure Frequency	0.108	- 0.055	0.074	- 0.010	0.001	- 0.076	- 0.105	- 0.221	- 0.279	1.000

Note. N = 32 cycles.

coefficients indicates that the following independent variables are associated with seizure frequency at ovulation, in order of their relative predictive power: estrogen, t (19) = 6.79, unique variance = .328; Moos Behavior Change, t (19) = 4.61, unique variance = .151; Moos Control, t (19) = - 4.34, unique variance = .135; progesterone, t (19) = - 4.01, unique variance = .114; POMS Tension, t (19) = - 2.92, unique variance = .060; Weekly Schedule of Recent Experiences, t (19) = - 2.43, unique variance = .042; Moos Autonomic Reactions, t (19) = - 2.52, unique variance = .045; and Dilantin, t (19) = - 2.20, unique variance = .034.

The third multiple regression analysis predicts seizure frequency at the high progesterone stage of the cycle, for ovulatory cycles only, by the 21 independent variables measured at the high progesterone stage of the cycle. As with the previous two multiple regression analyses, a total of 32 units of analysis were included, representing observations during the high progesterone stage of the cycle for 32 ovulatory cycles of a group of 14 subjects.

Results for the last step of this regression analysis appear in Table 13 and the associated correlation matrix appears in Table 14. For this analysis, R^2 = 0.734. Inspection of the standardized regression coefficients indicates that the following independent variables are associated with seizure frequency at the high progesterone stage of the cycle, in order of their relative predictive power: POMS Anger, t (17) = 2.31, unique variance = .083; POMS Tension, t (17) = - 2.24, unique variance = .078; Moos Concentration, t (17) = 2.61, unique variance = .107; Moos Autonomic Reactions, t (17) = - 2.85, unique variance = .127; progesterone, t (17) = 2.38, unique variance = .089; and Dilantin, t (17) = 2.39, unique variance = .089.

Table 13

Multiple Regression Analysis to Predict the Dependent Variable Total Seizure Frequency Occurring at High Progesterone from the Group of Independent Variables Measured at High Progesterone, Ovulatory Cycles Only (N = 32)

Variable Description	Regression Coefficient	Std. Error of Coefficient	Standardized Coefficient	t-Test	df	Unique Variance
POMS Anger at High Progesterone	0.5320	0.231	0.589	2.31	17	.083
POMS Tension at High Progesterone	- 1.7615	0.787	- 1.416	- 2.24	17	.078
Moos Control at High Progesterone	0.8771	0.873	0.247	1.00	17	.016
Moos Water Retention at High Progesterone	0.9391	0.459	0.308	2.05	17	.065
Moos Concentration at High Progesterone	1.7549	0.672	1.111	2.61	17	.107
POMS Fatigue at High Progesterone	0.2642	0.288	0.279	0.92	17	.013
Moos Negative Affect at High Progesterone	0.0998	0.443	0.094	0.23	17	.001
Moos Autonomic Reactions at High Progesterone	- 4.5279	1.589	- 1.011	- 2.85	17	.127
Progesterone Levels at High Progesterone	0.2020	0.085	0.457	2.38	17	.089
Dilantin Levels at High Progesterone	0.6223	0.260	0.533	2.39	17	.089
POMS Confusion at High Progesterone	0.9259	0.641	0.757	1.44	17	.033
Moos Behavior Change at High Progesterone	- 2.1427	1.208	- 0.721	- 1.77	17	.049
POMS Depression at High Progesterone	- 1.2502	0.785	- 1.013	- 1.59	17	.040
POMS Total T-Score at High Progesterone	0.2268	0.171	0.938	1.33	17	.027
Regression Constant	- 3.171					

Multiple Correlation Squared = 0.734 F = 3.35 with 14 and 17 Degrees of Freedom (p = .011)
Multiple Correlation = 0.857
Standard Deviation of Residuals = 6.511

Partial Correlation with Dependent Variable for Variables Not Entered

Estrogen Levels at High Progesterone	0.247
Spielberger State Anxiety, High Progesterone	0.260
POMS Vigor at High Progesterone	0.000
Moos Pain at High Progesterone	0.037
WSRE Weighted Scores at High Progesterone	0.106

Stepping stopped -- determinant at next step = 0.000000006, which is too small to avoid numerical instability in the solution.

Table 14

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at High Progesterone and the Independent Variables Measured at High Progesterone

Variable Description	Dilantin Levels	Estrogen Levels	Progesterone Levels	State Anxiety	POMS Tension	POMS Depression	POMS Anger	POMS Vigor	POMS Fatigue	POMS Confusion
Dilantin Levels	1.000	- 0.464	- 0.516	0.079	0.245	0.235	- 0.057	- 0.016	- 0.100	0.122
Estrogen Levels	- 0.464	1.000	0.408	- 0.053	- 0.175	- 0.172	- 0.195	- 0.087	- 0.234	- 0.252
Progesterone Levels	- 0.516	0.408	1.000	- 0.229	- 0.261	- 0.120	0.174	0.224	- 0.160	- 0.229
Spielberger State Anxiety	0.079	- 0.053	- 0.229	1.000	0.809	0.790	0.402	- 0.365	0.539	0.741
POMS Tension	0.245	- 0.175	- 0.261	0.809	1.000	0.890	0.405	- 0.327	0.565	0.871
POMS Depression	0.235	- 0.172	- 0.120	0.790	0.890	1.000	0.565	- 0.254	0.579	0.765
POMS Anger	- 0.057	- 0.195	0.174	0.402	0.405	0.565	1.000	0.021	0.324	0.545
POMS Vigor	- 0.016	- 0.087	0.224	- 0.365	- 0.327	- 0.254	0.021	1.000	- 0.247	- 0.408
POMS Fatigue	- 0.100	- 0.234	- 0.160	0.539	0.565	0.579	0.324	- 0.247	1.000	0.457
POMS Confusion	0.122	- 0.252	- 0.229	0.741	0.871	0.765	0.545	- 0.408	0.457	1.000
POMS Total T-Score	0.081	- 0.208	- 0.171	0.796	0.876	0.883	0.642	- 0.504	0.718	0.882
Moos Pain	- 0.189	0.196	0.308	0.374	0.313	0.498	0.596	- 0.117	0.468	0.250
Moos Concentration	- 0.078	- 0.046	0.052	0.759	0.794	0.736	0.531	- 0.281	0.392	0.769
Moos Behavior Change	0.011	- 0.178	0.092	0.616	0.539	0.733	0.763	- 0.060	0.500	0.531
Moos Autonomic Reactions	- 0.086	0.012	0.052	0.409	0.422	0.239	0.376	- 0.454	0.123	0.645
Moos Water Retention	- 0.009	0.358	0.057	0.112	0.221	0.170	0.096	- 0.094	0.045	0.082
Moos Negative Affect	- 0.148	- 0.039	0.087	0.792	0.706	0.745	0.649	- 0.238	0.566	0.674
Moos Control	- 0.032	- 0.044	0.148	0.507	0.417	0.646	0.492	- 0.046	0.460	0.252
WSRE Weighted Scores	0.320	- 0.149	0.050	0.090	0.114	0.367	0.398	0.051	0.089	0.107
Seizure Frequency	- 0.212	0.036	0.398	- 0.036	- 0.144	0.029	0.471	0.104	0.110	- 0.043

Note. N = 32 cycles.

Table 14 (Continued)

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at High Progesterone and the Independent Variables Measured at High Progesterone

Variable Description	POMS Total T-Score	Moos Pain	Moos Concentration	Moos Behavior Change	Moos Autonomic Reactions	Moos Water Retention	Moos Negative Affect	Moos Control	WSRE Weighted Scores	Seizure Frequency
Dilantin Levels	0.081	- 0.189	- 0.078	0.011	- 0.086	- 0.009	- 0.148	- 0.032	0.320	- 0.212
Estrogen Levels	- 0.208	0.196	- 0.046	- 0.178	0.012	0.358	- 0.039	- 0.044	- 0.149	0.036
Progesterone Levels	- 0.171	0.308	0.052	0.092	0.052	0.057	0.087	0.148	0.050	0.398
Spielberger State Anxiety	0.786	0.374	0.759	0.616	0.409	0.112	0.792	0.507	0.090	- 0.036
POMS Tension	0.876	0.313	0.794	0.539	0.442	0.221	0.706	0.417	0.114	- 0.144
POMS Depression	0.883	0.498	0.736	0.733	0.239	0.170	0.745	0.646	0.367	0.029
POMS Anger	0.642	0.596	0.531	0.763	0.376	0.096	0.649	0.492	0.398	0.471
POMS Vigor	- 0.504	- 0.117	- 0.281	- 0.060	- 0.454	- 0.094	- 0.238	- 0.046	0.051	0.104
POMS Fatigue	0.718	0.468	0.392	0.500	0.123	0.045	0.566	0.460	0.089	0.110
POMS Confusion	0.882	0.250	0.769	0.531	0.645	0.082	0.674	0.252	0.107	- 0.043
POMS Total T-Score	1.000	0.516	0.764	0.700	0.506	0.153	0.794	0.518	0.231	0.097
Moos Pain	0.516	1.000	0.419	0.697	0.186	0.510	0.603	0.625	0.531	0.399
Moos Concentration	0.764	0.419	1.000	0.666	0.587	0.169	0.855	0.528	0.049	0.135
Moos Behavior Change	0.700	0.697	0.666	1.000	0.147	0.188	0.792	0.667	0.504	0.358
Moos Autonomic Reactions	0.506	0.186	0.587	0.147	1.000	0.056	0.511	- 0.026	- 0.062	- 0.077
Moos Water Retention	0.153	0.510	0.169	0.188	0.056	1.000	0.153	0.116	0.242	0.158
Moos Negative Affect	0.794	0.603	0.855	0.792	0.511	0.153	1.000	0.571	0.219	0.150
Moos Control	0.518	0.625	0.528	0.667	- 0.026	0.116	0.571	1.000	0.262	0.370
WSRE Weighted Scores	0.231	0.531	0.049	0.504	- 0.062	0.242	0.219	0.262	1.000	0.162
Seizure Frequency	0.097	0.399	0.135	0.358	- 0.077	0.158	0.150	0.370	0.162	1.000

Note. N = 32 cycles.

The fourth multiple regression analysis predicts seizure frequency at the premenstrual stage of the cycle, for ovulatory cycles only, by the 21 independent variables measured at the premenstrual stage of the cycle. A total of 32 units of analysis were included, representing observations during the premenstrual stage of the cycle for 32 ovulatory cycles of a group of 14 subjects.

Results for the final step of this regression analysis appear in Table 15, and the associated correlation matrix appears in Table 16. For this analysis, $\underline{R}^2 = 0.668$. Inspection of the standardized regression coefficients shows that only estrogen levels, $\underline{t}$ (16) = - 2.24, unique variance = .104, are significantly associated with seizure frequency at the premenstrual stage of ovulatory cycles.

Table 17 is a summary table showing the significant results of all the multiple regression analyses. Summarizing the results of the multiple regression analyses described so far and their associated correlation matrices yields the following information:

1. During the menstrual phase of ovulatory cycles, POMS Fatigue positively predicts seizure frequency (standardized coefficient $|\beta| = 0.629$), while POMS Confusion negatively predicts seizure frequency (standardized coefficient $|\beta| = - 0.394$).

2. During the ovulatory phase of ovulatory cycles, estrogen levels positively predict seizure frequency ($\beta = 0.671$), while progesterone ($\beta = - 0.406$) and Dilantin levels ($\beta = - 0.235$) negatively predict seizure frequency. With respect to the mood scales measured at ovulation, Moos Behavior Change positively predicts seizure frequency ($\beta = 0.863$), while Moos Control ($\beta = - 0.658$), Moos Autonomic Reactions ($\beta = - 0.292$), POMS Tension ($\beta = - 0.434$), and the Weekly Schedule of Recent Experiences

Table 15

Multiple Regression Analysis to Predict the Dependent Variable Total Seizure Frequency Occurring Premenstrually from the Group of Independent Variables Measured Premenstrually, Ovulatory Cycles Only (N = 32)

Variable Description	Regression Coefficient	Std. Error of Coefficient	Standardized Coefficient	t-Test	df	Unique Variance
POMS Fatigue at Premenses	0.1414	0.074	0.589	1.92	16	.076
Moos Negative Affect at Premenses	- 0.1167	0.112	- 0.568	- 1.04	16	.022
POMS Anger at Premenses	- 0.0124	0.057	- 0.070	- 0.22	16	.001
POMS Tension at Premenses	- 0.0660	0.127	- 0.333	- 0.52	16	.006
Estrogen Levels at Premenses	- 0.0122	0.005	- 0.434	- 2.24	16	.104
POMS Total T-Score at Premenses	0.0027	0.035	0.060	0.08	16	.000
Moos Behavior Change at Premenses	0.4159	0.198	0.940	2.10	16	.092
Moos Autonomic Reactions at Premenses	- 0.4670	0.269	- 0.394	- 1.73	16	.062
Spielberger State Anxiety at Premenses	0.0490	0.070	0.386	0.70	16	.010
POMS Confusion at Premenses	0.0781	0.105	0.310	0.74	16	.011
WSRE Weighted Scores at Premenses	- 0.0073	0.006	- 0.338	- 1.32	16	.036
Moos Water Retention at Premenses	0.2215	0.141	0.404	1.58	16	.052
POMS Depression at Premenses	- 0.1502	0.126	- 0.745	- 1.20	16	.030
Progesterone Levels at Premenses	- 0.0522	0.047	- 0.274	- 1.11	16	.026
Moos Pain at Premenses	- 0.1860	0.169	- 0.420	- 1.10	16	.025
Regression Constant	1.233					

Multiple Correlation Squared = 0.688 F = 2.15 with 15 and 16 Degrees of Freedom (p = .070)
Multiple Correlation = 0.818
Standard Deviation of Residuals = 1.401

Partial Correlations with Dependent Variable for Variables Not Entered

Dilantin Levels at Premenses	- 0.028
POMS Vigor at Premenses	- 0.000
Moos Concentration at Premenses	- 0.110
Moos Control at Premenses	0.118

Stepping stopped -- determinant at next step = 0.000000007, which is too small to avoid numerical instability in the solution.

Table 16

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at Premenses and the Independent Variables Measured at Premenses

Variable Description	Dilantin Levels	Estrogen Levels	Progesterone Levels	State Anxiety	POMS Tension	POMS Depression	POMS Anger	POMS Vigor	POMS Fatigue	POMS Confusion
Dilantin Levels	1.000	- 0.284	- 0.124	0.194	0.384	0.351	- 0.122	- 0.388	- 0.044	0.407
Estrogen Levels	- 0.284	1.000	0.094	- 0.137	- 0.041	- 0.057	0.110	- 0.083	0.311	- 0.045
Progesterone Levels	- 0.124	0.094	1.000	- 0.320	- 0.162	- 0.283	- 0.144	0.430	0.018	- 0.262
Spielberger State Anxiety	0.194	- 0.137	- 0.320	1.000	0.849	0.867	0.531	- 0.461	0.487	0.753
POMS Tension	0.384	- 0.041	- 0.162	0.849	1.000	0.878	0.407	- 0.407	0.395	0.874
POMS Depression	0.351	- 0.057	- 0.283	0.867	0.878	1.000	0.625	- 0.317	0.474	0.828
POMS Anger	- 0.122	0.110	- 0.144	0.531	0.407	0.625	1.000	0.009	0.569	0.363
POMS Vigor	- 0.388	- 0.083	0.430	- 0.461	- 0.407	- 0.317	0.009	1.000	- 0.272	- 0.382
POMS Fatigue	- 0.044	0.311	0.018	0.487	0.395	0.474	0.569	- 0.272	1.000	0.381
POMS Confusion	0.407	- 0.045	- 0.262	0.753	0.874	0.828	0.363	- 0.382	0.381	1.000
POMS Total T-Score	0.317	0.080	- 0.304	0.877	0.870	0.906	0.650	- 0.569	0.671	0.832
Moos Pain	- 0.019	0.132	0.029	0.217	0.137	0.383	0.570	0.082	0.436	0.165
Moos Concentration	0.239	- 0.249	- 0.297	0.780	0.711	0.819	0.500	- 0.230	0.335	0.785
Moos Behavior Change	0.174	0.184	0.043	0.549	0.621	0.728	0.538	- 0.129	0.551	0.810
Moos Autonomic Reactions	0.461	- 0.340	- 0.175	0.247	0.292	0.194	- 0.027	- 0.286	- 0.032	0.437
Moos Water Retention	0.190	0.065	0.226	- 0.043	- 0.087	0.111	0.199	0.075	0.204	0.031
Moos Negative Affect	- 0.030	- 0.019	- 0.085	0.770	0.646	0.831	0.716	- 0.048	0.454	0.591
Moos Control	- 0.036	0.096	- 0.026	0.478	0.376	0.599	0.700	0.140	0.534	0.338
WSRE Weighted Scores	0.294	- 0.048	0.104	0.451	0.583	0.650	0.493	0.053	0.384	0.586
Seizure Frequency	- 0.054	0.014	- 0.051	- 0.138	- 0.257	- 0.252	- 0.203	- 0.205	0.315	- 0.155

Note. N = 32 cycles.

Table 16 (Continued)

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at Premenses and the Independent Variables Measured at Premenses

Variable Description	POMS Total T-Score	Moos Pain	Moos Concentration	Moos Behavior Change	Moos Autonomic Reactions	Moos Water Retention	Moos Negative Affect	Moos Control	WSRE Weighted Scores	Seizure Frequency
Dilantin Levels	0.317	- 0.019	0.239	0.174	0.461	0.190	- 0.030	- 0.036	0.294	- 0.054
Estrogen Levels	0.080	0.132	- 0.249	0.184	- 0.340	0.065	- 0.019	0.096	- 0.048	0.014
Progesterone Levels	- 0.304	0.029	- 0.297	0.043	- 0.175	0.226	- 0.085	- 0.026	0.104	- 0.051
Spielberger State Anxiety	0.877	0.217	0.780	0.549	0.247	- 0.043	0.770	0.478	0.451	- 0.136
POMS Tension	0.870	0.137	0.711	0.621	0.292	- 0.087	0.646	0.376	0.583	- 0.257
POMS Depression	0.906	0.383	0.819	0.728	0.194	0.111	0.831	0.599	0.650	- 0.252
POMS Anger	0.650	0.570	0.500	0.538	- 0.027	0.199	0.716	0.700	0.493	- 0.203
POMS Vigor	- 0.569	0.082	- 0.230	- 0.129	- 0.286	0.075	- 0.048	0.140	0.053	- 0.205
POMS Fatigue	0.671	0.436	0.335	0.551	- 0.032	0.204	0.454	0.534	0.384	0.315
POMS Confusion	0.852	0.165	0.785	0.610	0.437	0.031	0.591	0.338	0.586	- 0.155
POMS Total T-Score	1.000	0.346	0.737	0.686	0.257	0.077	0.715	0.513	0.560	- 0.075
Moos Pain	0.346	1.000	0.429	0.725	0.004	0.600	0.543	0.678	0.465	0.015
Moos Concentration	0.737	0.429	1.000	0.629	0.410	0.180	0.788	0.642	0.555	- 0.236
Moos Behavior Change	0.686	0.725	0.629	1.000	0.102	0.304	0.750	0.641	0.667	- 0.044
Moos Autonomic Reactions	0.257	0.004	0.410	0.102	1.000	0.110	- 0.057	- 0.089	0.156	- 0.092
Moos Water Retention	0.077	0.600	0.180	0.304	0.110	1.000	0.128	0.349	0.381	0.154
Moos Negative Affect	0.715	0.543	0.788	0.750	- 0.057	0.128	1.000	0.742	0.587	- 0.275
Moos Control	0.513	0.678	0.642	0.641	- 0.089	0.349	0.742	1.000	0.521	- 0.089
WSRE Weighted Scores	0.560	0.465	0.555	0.667	0.156	0.381	0.587	0.521	1.000	- 0.251
Seizure Frequency	- 0.075	0.015	- 0.236	- 0.044	- 0.092	0.154	- 0.275	- 0.089	- 0.251	1.000

Note. N = 32 cycles.

Table 17

Summary of the Significant Results of All the Multiple Regression Analyses and Their Associated Correlation Matrices

Multiple Regression Analysis	Pearson r	Multiple Regression R^2	Standardized Coefficients	DF	Regression Constant	Correlations Between Dilantin, Estrogen, and Progesterone
1. Seizures at any Cycle Stage Predicted by Independent Variables Measured at the Same Cycle Stage	POMS Anger 0.292 POMS Fatigue 0.380	0.329	POMS Anger, 0.448, t = 4.24 POMS Fatigue, 0.295, t = 3.31 POMS Depression, - 0.328, t = - 2.22 POMS Vigor, - 0.199, t = - 2.49	160 160 160 160	1.602	DPH X Prog, - 0.252 Est X Prog, 0.299
2. Seizures at Menstruation Predicted by Independent Variables Measured at Menstruation, Ovulatory and Anovulatory Cycles Only	POMS Fatigue 0.559	0.629	POMS Fatigue, 0.582, t = 4.75 POMS Confusion, - 0.382, t = - 2.92 Moos Pain, 0.473, t = 2.95	37 37 37	11.296	DPH X Prog, 0.418
3. Seizures at Ovulation Predicted by Independent Variables Measured at Ovulation, Ovulatory and Anovulatory Cycles Only	POMS Vigor - 0.382 POMS Fatigue 0.365 WSRE - 0.354	0.752	POMS Vigor, - 0.690, t = - 3.34 POMS Anger, 0.658, t = 2.91 Progesterone, - 0.371, t = - 3.42 Moos Control, - 0.551, t = - 2.86 WSRE, - 0.282, t = - 2.21 Dilantin, - 0.290, t = - 2.49 Moos Concentration, 0.459, t = 2.11 Moos Behavior Change, 0.592, t = 2.52 Moos Water Retention, - 0.247, t = - 2.07	31 31 31 31 31 31 31 31 31	16.935	DPH X Prog, - 0.411
4. Seizures at High Progesterone Predicted by Independent Variables Measured at High Progesterone, Ovulatory and Anovulatory Cycles Only	POMS Anger 0.532 Moos Pain 0.371 Moos Behavior Change 0.394 Moos Control 0.324	0.633	POMS Anger, 0.659, t = 4.49 POMS Tension, - 0.852, t = - 4.52 Moos Concentration, 0.615, t = 3.02 Moos Control, 0.363, t = 2.33 POMS Fatigue, 0.353, t = 2.69 Moos Negative Affect, - 0.523, t = - 2.24	38 38 38 38 38 38	- 12.196	Est X DPH, - 0.388 DPH X Prog, - 0.458 Est X Prog, 0.405
5. Seizures at Premenses Predicted by Independent Variables Measured at Premenses, Ovulatory and Anovulatory Cycles Only	POMS Fatigue 0.488	0.771	POMS Fatigue, 0.710, t = 6.39 Moos Behavior Change, 0.672, t = 3.78 Estrogen, - 0.330, t = - 3.23 Progesterone, - 0.240, t = - 2.31 Moos Autonomic, - 0.294, t = - 2.42	35 35 35 35 35	0.583	

Table 17 (Continued)

Summary of the Significant Results of All the Multiple Regression Analyses and Their Associated Correlation Matrices

Multiple Regression Analysis	Pearson r	Multiple Regression R^2	Standardized Coefficients	DF	Regression Constant	Correlations Between Dilantin, Estrogen, and Progesterone
6. Seizures at Menstruation Predicted by Independent Variables Measured at Menstruation, Anovulatory Cycles Only	POMS Fatigue 0.778					DPH X Proges., 0.774
7. Seizures at Menstruation Predicted by Independent Variables Measured at Menstruation, Ovulatory Cycles Only		0.588	POMS Fatigue, 0.629, t = 3.38 POMS Confusion, - 0.394, t = - 2.15	21 21	- 5.231	
8. Seizures at Ovulation Predicted by Independent Variables Measured at Ovulation, Anovulatory Cycles Only						
9. Seizures at Ovulation Predicted by Independent Variables Measured at Ovulation, Ovulatory Cycles Only	Estrogen 0.592 POMS Vigor - 0.388	0.865	Estrogen, 0.671, t = 6.79 Moos Behavior Change, 0.863, t = 4.61 Moos Control, - 0.558, t = - 4.34 Progesterone, - 0.406, t = - 4.01 POMS Tension, - 0.434, t = - 2.92 WSRE, - 0.299, t = - 2.43 Moos Autonomic Reactions - 0.292, t = - 2.52 Dilantin, - 0.235, t = - 2.20	19 19 19 19 19 19 19 19	7.129	DPH X Proges., - 0.434
10. Seizures at High Progesterone Predicted by Independent Variables Measured at High Progesterone, Anovulatory Cycles Only	POMS Anger 0.678 POMS Fatigue 0.890					

Table 17 (Continued)

Summary of the Significant Results of All the Multiple Regression Analyses and Their Associated Correlation Matrices

Multiple Regression Analysis	Pearson r	Multiple Regression R^2	Standardized Coefficients	DF	Regression Constant	Correlations Between Dilantin, Estrogen, and Progesterone
11. Seizures at High Progesterone Predicted by Independent Variables Measured at High Progesterone, Ovulatory Cycles Only	Progesterone, 0.398 POMS Anger, 0.471 Moos Pain, 0.399 Moos Control, 0.370	0.734	POMS Anger, 0.589, $t = 2.31$ POMS Tension, - 1.416, $t = - 2.24$ Moos Concentration, 1.111, $t = 2.61$ Moos Autonomic React., - 1.011, $t = - 2.85$ Progesterone, 0.457, $t = 2.38$ Dilantin, 0.533, $t = 2.39$	17 17 17 17 17 17		DPH X Estrogen, - 0.464 DPH X Proges., - 0.516 Estrogen X Proges., 0.408
12. Seizures at Premenses Predicted by Independent Variables Measured at Premenses, Anovulatory Cycles Only						
13. Seizures at Premenses Predicted by Independent Variables Measured at Premenses, Ovulatory Cycles Only		0.668	Estrogen, - 0.434, $t = - 2.24$	16	1.233	
14. Seizures at Menstruation Predicted by Independent Variables Measured at the Previous Premenses, Ovulatory & Anovulatory Cycles	POMS Depression, 0.632 POMS Anger, 0.542 POMS Fatigue, 0.569 POMS Total Score, 0.555 Moos Pain, 0.835 Moos Concentration, 0.648 Moos Behavior Change, 0.826 Moos Autonomic React., 0.640 Moos Negative Affect, 0.681					

Table 17 (Continued)

Summary of the Significant Results of All the Multiple Regression Analyses and Their Associated Correlation Matrices

Multiple Regression Analysis	Pearson r	Multiple Regression R^2	Standardized Coefficients	DF	Regression Constant	Correlations Between Dilantin, Estrogen, and Progesterone
15. Seizures at High Progesterone Predicted by Independent Variables Measured at the Previous Ovulation, Ovulatory and Anovulatory Cycles	Moos Pain, 0.336	0.516	State Anxiety, - 1.137, t = - 4.16	37	28.372	
			Moos Behavior Change, 0.717, t = 2.74	37		
			Moos Concentration, 0.700, t = 2.68	37		
			Moos Water Retention, - 0.345, t = - 2.19	37		
			Moos Autonomic React., - 0.333, t = - 2.04	37		
16. Seizures at Premenses Predicted by Independent Variables Measured at the Previous High Progesterone, Ovulatory and Anovulatory Cycles	POMS Fatigue, 0.399	0.764	POMS Fatigue, 0.612, t = 3.52	32	- 2.565	
			Progesterone, - 0.310, t = - 2.75	32		
			Estrogen, 0.389, t = 3.44	32		
			Moos Pain, - 0.521, t = - 2.98	32		
			Moos Behavior Change, 0.561, t = 2.51	32		
			Moos Negative Affect, - 0.600, t = - 2.25	32		

(β = - 0.299) negatively predict seizure frequency. POMS Vigor is negatively correlated with seizure frequency (r = - 0.388).

3. During the high progesterone phase of ovulatory cycles, progesterone levels positively predict seizure frequency (β = 0.457). The mood measures POMS Anger (β = 0.589) and Moos Concentration (β = 1.111) positively predict seizure frequency, while POMS Tension (β = - 1.416) and Moos Autonomic Reactions (β = - 1.011) negatively predict seizure frequency. Moos Pain (r = 0.399) and Moos Control (r = 0.370) are positively correlated with seizure frequency.

4. During the premenstrual phase of ovulatory cycles, estrogen negatively predicts seizure frequency (β = - 0.434).

5. Dilantin levels and progesterone levels are positively correlated during anovulatory cycles at menstruation (r = 0.774). However, Dilantin levels and progesterone levels are negatively correlated at the ovulatory (r = - 0.434) and high progesterone (r = - 0.516) phases of ovulatory cycles.

These results suggest several possible relationships between seizure frequency and the independent variables during ovulatory cycles. If we assume that estrogen and progesterone levels measured at a given phase of the cycle act upon seizure frequency at that same stage of the cycle, no statistically significant relationship between hormone levels and seizure frequency is apparent at menstruation, even though seizures occur more frequently at menstruation than at any other stage of the cycle. Nevertheless, inspection of the absolute levels of progesterone at each stage of the cycle (Figure 1) shows clearly that seizure frequency is highest when progesterone levels are lowest. At ovulation, however, if the ratio of estrogen to progesterone is high, seizure frequency is high (that is,

as estrogen increases and progesterone decreases at ovulation, seizure frequency increases).

Surprisingly, at the high progesterone phase of the cycle, high levels of progesterone are positively correlated with increased seizure frequency. This relationship tends to disconfirm the hypothesis that progesterone protects against seizures when just the relationship between progesterone and seizures is considered. However, at ovulation we previously noted that when the ratio of estrogen to progesterone is high, seizure frequency is high. Estrogen remains high at the high progesterone stage of the cycle, while progesterone is at its peak (Figure 1). Estrogen by itself has long been considered to be a convulsant (Logothetis et al., 1959; Stitt & Kinnard, 1968; Thiry, Heusgem, & Legentil, 1954; Werboff & Corcoran, 1961). The mechanism of action here may be that the high levels of estrogen block some of the presumed protective effect of progesterone. This is an especially likely hypothesis since estrogen and progesterone are positively correlated at the high progesterone stage of the cycle, which means that the more progesterone present, the more estrogen present also.

Another important relationship that exists at the high progesterone phase of the cycle is the highly significant negative correlation between Dilantin and progesterone. Given the fact that the group of epileptic women in this study were compliant on their anticonvulsant medication, a possible interpretation is that the high levels of progesterone are binding Dilantin at the high progesterone phase of the cycle, removing the anticonvulsant effect of Dilantin, and causing women to seize.

At the premenstrual phase of the cycle, decreasing levels of

estrogen are associated with increasing seizure frequency.

In terms of the relationship between the various mood scales and seizure frequency, again assuming that moods measured at a given phase of the cycle act upon seizure frequency at the same stage of the cycle, no one mood scale is consistently associated with higher seizure frequency across all menstrual cycle stages. Increasing levels of POMS Fatigue are associated with increasing seizure frequency at menstruation; increasing levels of Moos Behavior Change are associated with increasing seizure frequency at ovulation; and increasing levels of POMS Anger, Moos Pain, Moos Concentration, and Moos Control are associated with increasing seizure frequency at the high progesterone stage of the cycle. Lower levels of POMS Tension and Moos Autonomic Reactions are associated with increased seizure frequency both at ovulation and at the high progesterone stage of the cycle.

If one would want to speculate about cause-and-effect relationships, a possible interpretation is that fatigue influences seizures at menstruation; low estrogen levels influence seizures premenstrually; and an interaction of hormone balance and a variety of dysphoric mood states influence seizures at ovulation and at the high progesterone stage of the cycle. Inspection of absolute levels of progesterone versus seizure frequency suggests that high seizure frequency at menstruation is associated with low levels of progesterone. At the high progesterone stage of the cycle, high levels of progesterone combined with high levels of estrogen result in a higher seizure frequency. Another relationship at the high progesterone stage of the cycle may be a possible binding effect between Dilantin and progesterone, in which the anticonvulsant properties of Dilantin are weakened resulting in more seizures; and in

those subjects who experienced more anger, pain, and concentration difficulties, an association between increased negative mood and increased seizures.

Table 17 also shows significant correlations between seizure frequency and the 21 independent variables for anovulatory cycles. The only strong relationships are that POMS Fatigue at menstruation is positively correlated with seizure frequency at menstruation, r = 0.778; Dilantin and progesterone are positively correlated at menstruation, r = 0.774; POMS Fatigue at high progesterone is positively correlated with seizure frequency at high progesterone, r = 0.890; and POMS Anger at high progesterone is positively correlated with seizure frequency at high progesterone, r = 0.678.

Predicting Seizures at a Given Menstrual Cycle Stage by the Independent Variables Associated With the Prior Stage

The previous group of multiple regression analyses examined the relationship between seizure frequency at a given stage of the menstrual cycle and the collection of variables measured at the same stage of the cycle. What if a seizure flurry is caused by or related to hormonal and mood changes that occur a few days prior to the seizure flurry? To help answer this question, three more analyses were performed. The first analysis was a product-moment correlation coefficient between seizure frequency at menstruation and the group of 21 independent variables measured at the premenstrual phase of the previous cycle, defined as no more than four days before menstruation occurs. A multiple regression analysis could not be done on this data because there were only 17 units of analysis. The unit of analysis was defined as the menstrual phase of the cycle for a given subject for whom data was also available

on the immediately preceding premenstrual phase. The correlation matrix for this data appears in Table 18, and the significant correlations are summarized in Table 17. Seizures at the menstrual phase of the cycle are strongly positively correlated with several variables measured during the premenstrual phase of the immediately preceding cycle. The correlations with seizures at menstruation are premenstrual POMS Depression, $\underline{r}$ = 0.632; POMS Anger, $\underline{r}$ = 0.542; POMS Fatigue, $\underline{r}$ = 0.569; POMS Total T-Score, $\underline{r}$ = 0.555; Moos Pain, $\underline{r}$ = 0.835; Moos Concentration, $\underline{r}$ = 0.648; Moos Behavior Change, $\underline{r}$ = 0.826; Moos Autonomic Reactions, $\underline{r}$ = 0.640; and Moos Negative Affect, $\underline{r}$ = 0.681. If we make the assumption that a flurry of seizures is related to events occurring shortly before the flurry, then the majority of negative mood states measured by the POMS and Moos scales predict a flurry of seizures at menstruation. In other words, the more negative mood states a subject experiences before menstruation begins, the greater the number of seizures she is likely to experience during menstruation.

The second analysis was a multiple regression analysis which attempted to predict seizure frequency at the high progesterone stage of the cycle by the 21 independent variables measured at the ovulation stage of the same cycle. The measurements taken at ovulation occurred on the average a week before measurements taken at high progesterone. A total of 47 units of analysis were included, representing both ovulatory and anovulatory cycles. Results for the last step of this regression analysis appear in Table 19. For this analysis, $\underline{R}^2$ = 0.516. Inspection of the standardized regression coefficients indicates that the following independent variables measured at ovulation are associated with seizure frequency at the high progesterone stage of the cycle, in

Table 18

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at Menstruation and the Independent Variables Measured at the Previous Premenses

Variable Description	Dilantin Levels	Estrogen Levels	Progesterone Levels	State Anxiety	POMS Tension	POMS Depression	POMS Anger	POMS Vigor	POMS Fatigue	POMS Confusion
Dilantin Levels	1.000	- 0.121	- 0.249	- 0.071	0.129	0.019	- 0.295	- 0.441	- 0.266	0.030
Estrogen Levels	- 0.121	1.000	0.040	- 0.192	- 0.057	- 0.176	- 0.063	- 0.125	0.061	0.181
Progesterone Levels	- 0.249	0.040	1.000	- 0.182	- 0.203	- 0.307	- 0.139	0.532	- 0.032	- 0.195
Spielberger State Anxiety	- 0.071	- 0.192	- 0.182	1.000	0.914	0.826	0.515	- 0.202	0.590	0.765
POMS Tension	0.129	- 0.057	- 0.203	0.914	1.000	0.847	0.503	- 0.292	0.587	0.847
POMS Depression	0.019	- 0.176	- 0.307	0.826	0.847	1.000	0.811	- 0.154	0.783	0.822
POMS Anger	- 0.295	- 0.063	- 0.139	0.515	0.503	0.811	1.000	0.266	0.745	0.531
POMS Vigor	- 0.441	- 0.125	0.532	- 0.202	- 0.292	- 0.154	0.266	1.000	- 0.183	- 0.487
POMS Fatigue	- 0.266	0.061	- 0.032	0.590	0.587	0.783	0.745	0.188	1.000	0.835
POMS Confusion	0.030	0.181	- 0.195	0.765	0.847	0.822	0.531	- 0.487	0.835	1.000
POMS Total T-Score	0.032	0.004	- 0.320	0.805	0.862	0.933	0.695	- 0.413	0.866	0.954
Moos Pain	- 0.177	- 0.195	- 0.099	0.498	0.518	0.827	0.850	0.129	0.758	0.580
Moos Concentration	- 0.038	- 0.216	- 0.193	0.791	0.816	0.922	0.672	- 0.216	0.801	0.849
Moos Behavior Change	- 0.154	- 0.027	0.017	0.305	0.327	0.648	0.661	- 0.042	0.800	0.542
Moos Autonomic Reactions	0.196	- 0.273	- 0.246	0.523	0.671	0.706	0.518	- 0.216	0.483	0.599
Moos Water Retention	- 0.335	- 0.157	0.271	- 0.016	- 0.003	0.219	0.529	0.565	0.157	- 0.033
Moos Negative Affect	- 0.238	- 0.234	- 0.078	0.725	0.671	0.902	0.833	0.146	0.779	0.657
Moos Control	- 0.147	- 0.113	0.005	0.728	0.659	0.786	0.757	0.296	0.579	0.544
WSRE Weighted Scores	- 0.389	- 0.046	0.250	0.116	0.004	0.272	0.621	0.755	0.262	- 0.065
Seizure Frequency	0.019	- 0.301	- 0.317	0.236	0.309	0.632	0.542	- 0.136	0.569	0.421

Note. N = 17 cycles.

Table 18 (Continued)

Pearson's Product-Moment Correlation Coefficients Between the Dependent Variable Total Seizure Frequency Occurring at Menstruation and the Independent Variables Measured at the Previous Premenses

Variable Description	POMS Total T-Score	Moos Pain	Moos Concentration	Moos Behavior Change	Moos Autonomic Reactions	Moos Water Retention	Moos Negative Affect	Moos Control	WSRE Weighted Scores	Seizure Frequency
Dilantin Levels	0.032	- 0.177	- 0.038	- 0.154	0.196	- 0.335	- 0.238	- 0.147	- 0.389	0.019
Estrogen Levels	0.004	- 0.195	- 0.216	- 0.027	- 0.273	- 0.157	- 0.234	- 0.113	- 0.046	- 0.301
Progesterone Levels	- 0.320	- 0.099	- 0.193	0.017	- 0.246	0.271	- 0.078	0.005	0.250	- 0.317
Spielberger State Anxiety	0.805	0.498	0.791	0.305	0.523	- 0.016	0.725	0.728	0.116	0.236
POMS Tension	0.862	0.518	0.816	0.327	0.671	- 0.003	0.671	0.659	0.004	0.309
POMS Depression	0.933	0.827	0.922	0.648	0.706	0.219	0.902	0.786	0.272	0.632
POMS Anger	0.695	0.850	0.672	0.661	0.518	0.529	0.833	0.757	0.621	0.542
POMS Vigor	- 0.413	0.129	- 0.216	- 0.042	- 0.216	0.565	0.146	0.296	0.755	- 0.136
POMS Fatigue	0.866	0.758	0.801	0.800	0.483	0.157	0.779	0.579	0.262	0.569
POMS Confusion	0.954	0.580	0.849	0.542	0.599	- 0.033	0.657	0.544	- 0.065	0.421
POMS Total T-Score	1.000	0.713	0.901	0.632	0.680	0.053	0.772	0.629	0.054	0.555
Moos Pain	0.713	1.000	0.812	0.833	0.743	0.553	0.915	0.714	0.494	0.835
Moos Concentration	0.901	0.812	1.000	0.636	0.748	0.191	0.886	0.725	0.139	0.648
Moos Behavior Change	0.632	0.833	0.636	1.000	0.451	0.293	0.758	0.481	0.376	0.826
Moos Autonomic Reactions	0.680	0.743	0.748	0.451	1.000	0.425	0.622	0.499	0.054	0.640
Moos Water Retention	0.053	0.553	0.191	0.293	0.425	1.000	0.422	0.459	0.684	0.305
Moos Negative Affect	0.772	0.915	0.886	0.758	0.622	0.422	1.000	0.879	0.545	0.681
Moos Control	0.629	0.714	0.725	0.481	0.499	0.459	0.879	1.000	0.680	0.315
WSRE Weighted Scores	0.054	0.494	0.139	0.376	0.054	0.684	0.545	0.680	1.000	0.165
Seizure Frequency	0.555	0.835	0.648	0.826	0.640	0.305	0.681	0.315	0.165	1.000

Note. N = 17 cycles.

Table 19

Multiple Regression Analysis to Predict the Dependent Variable Total Seizure Frequency Occurring at High Progesterone from the Group of Independent Variables Measured at the Previous Ovulation (N = 47)

Variable Description	Regression Coefficient	Std. Error of Coefficient	Standardized Coefficient	t-Test	df	Unique Variance
Moos Pain at Ovulation	0.5111	0.337	0.336	1.52	37	.030
Spielberger State Anxiety at Ovulation	- 0.8130	0.195	- 1.137	- 4.16	37	.227
Moos Behavior Change at Ovulation	2.4733	0.903	0.717	2.74	37	.098
WSRE Weighted Scores at Ovulation	- 0.0310	0.017	- 0.283	- 1.87	37	.046
Moos Concentration at Ovulation	1.0585	0.394	0.700	2.68	37	.094
Moos Water Retention at Ovulation	- 1.1132	0.507	- 0.345	- 2.19	37	.063
Moos Autonomic Reactions at Ovulation	- 1.3966	0.684	- 0.333	- 2.04	37	.055
POMS Vigor at Ovulation	- 0.1358	0.112	- 0.173	- 1.21	37	.019
Dilantin at Ovulation	- 0.0973	0.124	- 0.097	- 0.78	37	.008
Regression Constant	28.372					

Multiple Correlation Squared = 0.516
Multiple Correlation = 0.718
Standard Deviation of Residuals = 7.050

F = 4.38 with 9 and 37 Degrees of Freedom (p = .001)

Partial Correlations with Dependent Variable for Variables Not Entered

Estrogen at Ovulation	- 0.068
Progesterone at Ovulation	- 0.017
POMS Tension at Ovulation	0.114
POMS Depression at Ovulation	- 0.057
POMS Anger at Ovulation	0.032
POMS Fatigue at Ovulation	0.045
POMS Confusion at Ovulation	- 0.085
POMS Total T-Score at Ovulation	0.056
Moos Negative Affect at Ovulation	0.034
Moos Control at Ovulation	- 0.062

Stepping stopped -- last step increased r^2 by less than 0.010.

order of their relative predictive power: Spielberger State Anxiety, t (37) = - 4.16, unique variance = .030; Moos Behavior Change, t (37) = 2.74, unique variance = .098; Moos Concentration, t (37) = 2.68, unique variance = .094; Moos Water Retention, t (37) = - 2.19, unique variance = .063; and Moos Autonomic Reactions, t (37) = - 2.04, unique variance = .055. Only Moos Behavior Change and Concentration difficulties at ovulation are positively correlated with seizures at the high progesterone stage of the cycle.

The third of this group of analyses was a final multiple regression analysis which attempted to predict premenstrual seizure frequency from the 21 independent variables measured at the high progesterone phase of the same cycle. The measurements taken at the high progesterone phase of the cycle occurred an average of five days before measurements taken premenstrually. A total of 47 units of analysis were included. Results for the last step of this regression analysis appear in Table 20. For this analysis, R^2 = 0.764. The following independent variables measured at the high progesterone stage of the cycle are associated with premenstrual seizure frequency, in order of their relative predictive power: POMS Fatigue, t (32) = 3.52, unique variance = .092; progesterone, t (32) = - 2.75, unique variance = .056; estrogen, t (32) = 3.44, unique variance = .087; Moos Pain, t (32) = - 2.98, unique variance = .065; Moos Behavior Change, t (32) = 2.51, unique variance = .047; and Moos Negative Affect, t (32) = - 2.25, unique variance = .037. In this instance, lower levels of progesterone and higher levels of estrogen at the high progesterone stage of the cycle are related to increased premenstrual seizures.

If the assumption is valid that seizure flurries are caused by prior events, so that a time lag exists between a precipitating event and

Table 20

Multiple Regression Analysis to Predict the Dependent Variable Total Seizure Frequency Occurring at Premenses from the Group of Independent Variables Measured at the Previous High Progesterone ($N = 47$)

Variable Description	Regression Coefficient	Std. Error of Coefficient	Standardized Coefficient	t-Test	df	Unique Variance
POMS Fatigue at High Progesterone	0.1924	0.055	0.612	3.52	32	.092
POMS Tension at High Progesterone	- 0.1462	0.127	- 0.357	- 1.15	32	.010
Progesterone at High Progesterone	- 0.0492	0.018	- 0.310	- 2.75	32	.056
POMS Total T-Score at High Progesterone	0.0408	0.034	0.560	1.21	32	.011
Estrogen at High Progesterone	0.0100	0.003	0.389	3.44	32	.087
State Anxiety at High Progesterone	- 0.0826	0.051	- 0.326	- 1.62	32	.019
Moos Pain at High Progesterone	- 0.3340	0.112	- 0.521	- 2.98	32	.065
Moos Water Retention at High Progesterone	0.1585	0.131	0.149	1.21	32	.011
Moos Concentration at High Progesterone	0.1862	0.120	0.341	1.55	32	.018
Moos Behavior Change at High Progesterone	0.4524	0.180	0.561	2.51	32	.047
Moos Negative Affect at High Progesterone	- 0.2107	0.094	- 0.600	- 2.25	32	.037
Moos Autonomic Reactions at High Progesterone	0.5037	0.255	0.304	1.97	32	.029
POMS Confusion at High Progesterone	- 0.1815	0.097	- 0.429	- 1.87	32	.026
POMS Anger at High Progesterone	0.0508	0.054	0.166	0.93	32	.006
Regression Constant	- 2.565					

Multiple Correlation Squared = 0.764 $F = 7.38$ with 14 and 32 Degrees of Freedom (p under .001)
Multiple Correlation = 0.874
Standard Deviation of Residuals = 1.869

Partial Correlations with Dependent Variables for Variables Not Entered

Dilantin at High Progesterone	0.049
POMS Depression at High Progesterone	- 0.074
POMS Vigor at High Progesterone	- 0.074
Moos Control at High Progesterone	- 0.007
WSRE Weighted Scores at High Progesterone	- 0.135

Stepping stopped -- last step increased r^2 by less than 0.010.

the seizures, then a variety of previously existing dysphoric mood states would seem to be related to seizures that occur at menstruation and at the high progesterone phase of the cycle. Notably, estrogen and progesterone levels were not found to be related to seizures at menstruation and at high progesterone in this last set of analyses. However, lower levels of progesterone and higher levels of estrogen, as well as increased fatigue and behavior change at the high progesterone stage of the cycle are related to premenstrual seizures.

Conclusions and Discussion

This study obtained detailed information about the circumstances surrounding epileptic seizures by studying frequency of seizure occurrence in relation to stage of the menstrual cycle; frequency of seizure occurrence in relation to changes in estrogen and progesterone levels during the different stages of the menstrual cycle; and changes in emotional states and stressful life experiences with respect to stage of the menstrual cycle.

The main findings were:

1. Seizure frequency peaks at menstruation for epileptic women. Seizures occur at menstruation more frequently than they do at any other stage of the menstrual cycle.

2. Seizures increase following a period of stressful life events independently of stage of the menstrual cycle, as measured by the Life Events Diary; but no significant differences in any of the standardized mood measures were found from one stage of the menstrual cycle to the next.

3. Measurement of hormonal levels at different stages of the menstrual cycle allowed us to distinguish a group of ovulatory cycles from

an unexpectedly large number of anovulatory cycles. At all stages of the menstrual cycle, seizure frequency was much greater for anovulatory cycles than for ovulatory cycles.

4. Seizures were most common when progesterone levels were lowest.

5. We found that an increase in seizure frequency occurred in association with a fall in progesterone levels.

One of the most striking findings of this study was that thirty percent of all the menstrual cycles of the epileptic sample were anovulatory or showed inadequate luteal production, and sixty percent of the subjects had at least one anovulatory cycle. In addition, seizure frequency during anovulatory cycles was twice as high as during ovulatory cycles. Furthermore, during anovulatory cycles the subjects experienced more overall life stress than during ovulatory cycles. I propose the following mechanisms to explain these findings:

1. Psychological or physical stress results in increased activity of the adrenal glands. While the adrenal gland does not secrete appreciable amounts of estrogen into the circulation under non-stressful circumstances, its normal function does contribute to the total circulating levels of estrogen. This is accomplished by the extragonadal peripheral conversion of C-19 androgenic precursors, such as androstenedione, to estrogens. In this manner, psychological or physical stress may increase the adrenal contribution of estrogenic precursor, and subsequent conversion to estrogen may sustain the blood level of estrogen at a time when a decline is necessary for successful recycling of the menstrual system including a high production of progesterone. Anovulatory cycles will result.

2. This study suggests that progesterone protects against seizures. Anovulatory cycles are by definition deficient in progesterone. When anovulatory cycles are caused by stress, the extragonadal estrogen produced by the adrenals blocks the normal drop in estrogen levels necessary for the production of progesterone and the normal recycling of the menstrual system. Greater reported stress would therefore result in a larger number of anovulatory cycles for the epileptic women in this study, and a larger number of seizures during these anovulatory cycles when progesterone is virtually absent. Also, since high estrogen levels are associated with an increased frequency of seizures among epileptic women, one could expect a higher incidence of seizures in anovulatory cycles than in ovulatory cycles where the protective effect of progesterone is present.

3. Therefore, if stress produces anovulatory cycles which are characterized by high levels of estrogen and low levels of progesterone, and if high levels of estrogen and low levels of progesterone produce seizures (because the normal protective effect of progesterone during the luteal phase of ovulatory cycles is removed), then high levels of stress should be associated with a high frequency of seizures.

4. The basic mechanism therefore is: increased stress leads to increased adrenal production of extragonadal estrogen; increased adrenal production of extragonadal estrogen leads to anovulatory cycles; and anovulatory cycles are deficient in progesterone and have an excess of estrogen, which leads to increased seizure frequency. Anovulatory cycles should therefore be associated with increased seizure frequency, and by this mechanism increased seizure frequency should be highly correlated with emotional distress.

In this study, no changes in mood across the four defined stages of the menstrual cycle were found when the scores of the subjects were averaged. If individual patterns of mood changes were examined with a large enough sample size in a future study, however, two main groups might hypothetically be identified: women who have the highest number of menstrual seizures may also have a significant mood change between menstruation and the other stages of the cycle; while women who have the fewest seizures may not have any mood changes at all between menstruation and the other stages of the cycle. In the present study, all subjects had more seizures at menstruation than at any other stage of the cycle. Future studies might reveal two distinct groups: women who seize primarily at menstruation and women who seize irregularly. Questions for such future studies might be: Are there differences in the incidence of complaints of physical discomfort and psychological stress between women who seize at menstruation as opposed to those who seize irregularly? Do women who complain of the most physical discomfort and psychological stress during menstruation also tend to report more seizures?

Analysis of mood changes and changes in stressful life events before seizures as opposed to changes after seizures for <u>each</u> subject would be very useful in the clinical management of individual cases. Such an analysis would help women become aware of what situations in their particular case predispose to or precipitate seizures.

An important result of this study was that according to the analysis of the Life Events Diary scores, epileptic women do have changes in mood that are not related in a systematic way to the stage of the menstrual cycle, but which do predict seizures. Specifically, changes in mood as measured by stressful life events and a woman's reaction to them,

which are independent of changes in the stage of the menstrual cycle, do predict seizures. Also, analysis of the Life Events Diary scores shows that epileptic women have more negative stressful life events prior to a seizure flurry. The Life Events Diary has the capability of measuring extremely positive life events as well as extremely negative life events, and the relationship that was shown was between negative life events and seizure flurries. An important future project would be to do a qualitative analysis of the Life Events Diary and to look for those specific events that the epileptic women indicated were highly pleasant or highly unpleasant, and particularly those events that preceded seizures. This information could be used to construct a new questionnaire having a standardized item content. Using such a questionnaire, a woman could indicate on a day by day basis which types of life events happened to her, rate those life events, and simultaneously keep an independent record of her seizures.

A limitation of the present study is the small sample size. A better future study might follow larger groups of patients and make comparisons between patients with different types of seizures. Since this study was a prospective study of affective and seizure fluctuations during the menstrual cycle, the sample size was small of necessity and consequently the sample is more likely to be biased. This type of investigation requires highly motivated and cooperative women. The subjects in this study were motivated to participate because they experienced a significant number of seizures despite optimal therapeutic doses of their regular anticonvulsant medication. Many epileptics are completely controlled on their anticonvulsant medication, so this sample cannot be considered to be representative of all epileptic women.

The validity of self-report as a tool to reflect the symptoms accompanying the menstrual cycle can be questioned. In this study, my objectives needed to be revealed to the subjects to some extent in order to elicit their cooperation throughout the course of a lengthy study. The subjects were told that I was investigating whether seizures occurred at a particular time during their menstrual cycle, with the exact time that more seizures were expected to occur being left unspecified. The subjects were also told that depending on the type of seizure pattern they had during their menstrual cycles, additional medication would be offered that might help control their seizures better. The pattern that was expected was not specified in detail until the study was over and some women were offered the medication (oral Provera).

Fluctuations in steroid hormones must be assessed during the menstrual cycle in order to correlate any changes in behavior patterns with the variations in levels of ovarian and pituitary hormones. This was done in this study, and led to the identification of a significant number of anovulatory cycles in which seizure frequency was double that of ovulatory cycles.

Future studies in this area may be more useful in elucidating the hormonal and life stress etiology of epileptic seizures if they meet the following criteria: experimental studies designed for subjects to keep an accurate record of seizures as they occur each day; adequate definition and measurement of subjective changes; determination of each woman's pattern over several cycles; correlation of affective changes with day by day plasma levels of endogenous hormones; and double-blind investigations of subsequent hypotheses.

A final disclaimer needs to be made about the results of the

multiple regression analyses. Since the multiple regression approach mathematically maximizes the amount of variability in the dependent variable which is accounted for by taking advantage of both sample specific and population variation, considerable shrinkage, i.e., decrease in variance accounted for, would be expected on cross validation. Furthermore, the strength of any particular predictor can vary considerably so that the relative importance of predictors may vary quite a bit.

The design of this study is essentially a correlational design because seizure frequency and progesterone level were not manipulated by the experimenter as true independent variables. Therefore, results of these analyses cannot be interpreted in cause-and-effect terms.

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APPENDIX A

APPENDIX

Menstrual Distress Questionnaire

Form A.

Name _____ Marital Status _____

Age _____ Number of Children _____

Today's Date _____ Occupation _____

Write the approximate dates of your most recent menstrual period (flow) in the space marked "A" below. Then write the dates of the menstrual period which preceded the most recent one in the space marked "D".

D	C	B	A
from _____ to _____	other times during most recent cycle	week before most recent flow	most recent flow from _____ to _____

On the next two pages is a list of symptoms which women sometimes experience. Please describe your experience of each of these symptoms during the three different time periods listed below:

Col. 1 during your most recent menstrual flow (the dates delineated by area A on the diagram above),

Col. 2 during the one week before your most recent menstrual flow (area B on the diagram),

Col. 3 during the remainder of your most recent menstrual cycle (area C).

Note: The answers you put in columns 1, 2, and 3 should be accurate for your experience specifically during your most recent menstrual cycle. Please do not simply report your general experience. Also, please report any experience of these symptoms whether or not they seem to you to be related to your menstrual cycle.

For each answer choose the descriptive category listed which best describes your experience of that symptom during that time. Write the number of that description in the space provided. Even if none of the descriptions are exactly correct, choose the one that best describes your experience. Do not leave any blank spaces.

Descriptive Categories

1 - no experience of symptom
2 - barely noticeable
3 - present, mild
4 - present, moderate
5 - present, strong
6 - acute or partially disabling

	1. most recent flow (A)	2. week before (B)	3. remainder of cycle (C)
1. Weight gain			
2. Insomnia			
3. Crying			
4. Lowered school or work performance			
5. Muscle stiffness			
6. Forgetfulness			
7. Confusion			
8. Take naps or stay in bed			
9. Headache			
10. Skin disorders			
11. Loneliness			
12. Feelings of suffocation			
13. Affectionate			
14. Orderliness			
15. Stay home from work or school			
16. Cramps (uterine or pelvic)			
17. Dizziness or faintness			
18. Excitement			
19. Chest pains			
20. Avoid social activities			
21. Anxiety			
22. Backache			
23. Cold sweats			

		1. most recent flow (A)	2. week before (B)	3. remainder of cycle (C)
24.	Lowered judgment			
25.	Fatigue			
26.	Nausea or vomiting			
27.	Restlessness			
28.	Hot flashes			
29.	Difficulty in concentration			
30.	Painful or tender breasts			
31.	Feelings of well-being			
32.	Buzzing or ringing in ears			
33.	Distractable			
34.	Swelling (e.g. abdomen, breasts or ankles)			
35.	Accidents (e.g. cut finger, break dish)			
36.	Irritability			
37.	General aches and pains			
38.	Mood swings			
39.	Heart pounding			
40.	Depression (feeling sad or blue)			
41.	Decreased efficiency			
42.	Lowered motor coordination			
43.	Numbness or tingling in hands or feet			
44.	Change in eating habits			
45.	Tension			
46.	Blind spots or fuzzy vision			
47.	Bursts of energy or activity			

In what ways, if any, was your most recent menstrual cycle unusual?

MENSTRUAL DISTRESS QUESTIONNAIRE

Form T

Name _____

Today's Date _____

On the next two pages is a list of symptoms which women sometimes experience. For each symptom choose the descriptive category listed below which best describes your experience of that symptom today. Circle the number of the category which best describes your experience of the symptom today. Even if none of the categories is exactly correct, choose the one that best describes your experience. Please be sure to circle one number for each symptom. Please also remember to put your name and the date in the blank spaces at the top of this page.

Descriptive Categories

1. No reaction at all
2. Barely noticeable
3. Present, mild
4. Present, moderate
5. Present, strong
6. Acute or partially disabling

1. Weight gain.....	1	2	3	4	5	6
2. Insomnia.....	1	2	3	4	5	6
3. Crying.....	1	2	3	4	5	6
4. Lowered school or work performance....	1	2	3	4	5	6
5. Muscle stiffness.....	1	2	3	4	5	6
6. Forgetfulness.....	1	2	3	4	5	6
7. Confusion.....	1	2	3	4	5	6
8. Take naps or stay in bed.....	1	2	3	4	5	6
9. Headache.....	1	2	3	4	5	6
10. Skin disorders.....	1	2	3	4	5	6
11. Loneliness.....	1	2	3	4	5	6
12. Feelings of suffocation.....	1	2	3	4	5	6
13. Affectionate.....	1	2	3	4	5	6
14. Orderliness.....	1	2	3	4	5	6
15. Stay home from work or school.....	1	2	3	4	5	6
16. Cramps (uterine or pelvic).....	1	2	3	4	5	6
17. Dizziness or faintness.....	1	2	3	4	5	6
18. Excitement.....	1	2	3	4	5	6
19. Chest pains.....	1	2	3	4	5	6

	No reaction	Barely noticeable	Mild	Moderate	Strong	Acute
20. Avoid social activities	1	2		4	5	6
21. Anxiety	1	2	3	4	5	6
22. Backache	1	2	3	4	5	6
23. Cold sweats	1	2	3	4	5	6
24. Lowered judgment	1	2	3	4	5	6
25. Fatigue	1	2	3	4	5	6
26. Nausea or vomiting	1	2	3	4	5	6
27. Restlessness	1	2	3	4	5	6
28. Hot flashes	1	2	3	4	5	6
29. Difficulty in concentration	1	2	3	4	5	6
30. Painful or tender breasts	1	2	3	4	5	6
31. Feelings of well-being	1	2	3	4	5	6
32. Buzzing or ringing in ears	1	2	3	4	5	6
33. Distractable	1	2	3	4	5	6
34. Swelling (e.g. abdomen, breasts, ankle)	1	2	3	4	5	6
35. Accidents (e.g. cut finger, break dish)	1	2	3	4	5	6
36. Irritability	1	2	3	4	5	6
37. General aches and pains	1	2	3	4	5	6
38. Mood swings	1	2	3	4	5	6
39. Heart pounding	1	2	3	4	5	6
40. Depression (feeling sad or blue)	1	2	3	4	5	6
41. Decreased efficiency	1	2	3	4	5	6
42. Lowered motor coordination	1	2	3	4	5	6
43. Numbness or tingling in hands or feet.	1	2	3	4	5	6
44. Change in eating habits	1	2	3	4	5	6
45. Tension	1	2	3	4	5	6
46. Blind spots or fuzzy vision	1	2	3	4	5	6
47. Bursts of energy or activity	1	2	3	4	5	6

NAME_____ DATE_____

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE space under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

IDENTIFICATION

The numbers refer to these phrases.
0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1. Friendly	0	1	2	3	4
2. Tense	0	1	2	3	4
3. Angry	0	1	2	3	4
4. Worn out	0	1	2	3	4
5. Unhappy	0	1	2	3	4
6. Clear-headed	0	1	2	3	4
7. Lively	0	1	2	3	4
8. Confused	0	1	2	3	4
9. Sorry for things done	0	1	2	3	4
10. Shaky	0	1	2	3	4
11. Listless	0	1	2	3	4
12. Peeved	0	1	2	3	4
13. Considerate	0	1	2	3	4
14. Sad	0	1	2	3	4
15. Active	0	1	2	3	4
16. On edge	0	1	2	3	4
17. Grouchy	0	1	2	3	4
18. Blue	0	1	2	3	4
19. Energetic	0	1	2	3	4
20. Panicky	0	1	2	3	4
21. Hopeless	0	1	2	3	4
22. Relaxed	0	1	2	3	4
23. Unworthy	0	1	2	3	4
24. Spiteful	0	1	2	3	4
25. Sympathetic	0	1	2	3	4
26. Uneasy	0	1	2	3	4
27. Restless	0	1	2	3	4
28. Unable to concentrate	0	1	2	3	4
29. Fatigued	0	1	2	3	4
30. Helpful	0	1	2	3	4
31. Annoyed	0	1	2	3	4
32. Discouraged	0	1	2	3	4
33. Resentful	0	1	2	3	4
34. Nervous	0	1	2	3	4
35. Lonely	0	1	2	3	4
36. Miserable	0	1	2	3	4
37. Muddled	0	1	2	3	4
38. Cheerful	0	1	2	3	4
39. Bitter	0	1	2	3	4
40. Exhausted	0	1	2	3	4
41. Anxious	0	1	2	3	4
42. Ready to fight	0	1	2	3	4
43. Good natured	0	1	2	3	4
44. Gloomy	0	1	2	3	4
45. Desperate	0	1	2	3	4
46. Sluggish	0	1	2	3	4
47. Rebellious	0	1	2	3	4
48. Helpless	0	1	2	3	4
49. Weary	0	1	2	3	4
50. Bewildered	0	1	2	3	4
51. Alert	0	1	2	3	4
52. Deceived	0	1	2	3	4
53. Furious	0	1	2	3	4
54. Efficient	0	1	2	3	4
55. Trusting	0	1	2	3	4
56. Full of pep	0	1	2	3	4
57. Bad-tempered	0	1	2	3	4
58. Worthless	0	1	2	3	4
59. Forgetful	0	1	2	3	4
60. Carefree	0	1	2	3	4
61. Terrified	0	1	2	3	4
62. Guilty	0	1	2	3	4
63. Vigorous	0	1	2	3	4
64. Uncertain about things	0	1	2	3	4
65. Bushed	0	1	2	3	4

T D A V F C

MAKE SURE YOU HAVE ANSWERED EVERY ITEM.

POM 021

DC 9216-A

POMS PROFILE SHEET

FEMALE (OP)

Name: _____ Date: _____

T Score	FACTOR						T Score
	Ten	Dep	Ang	Vig	Fat	Con	
80+				28-2			80+
79			48				79
78			47	27			78
77			46	26			77
76			45				76
75			44	25			75
74			42-3				74
73			41	24			73
72			40	23		28	72
71			39				71
70		60	38	22		27	70
69		58-9	37	21		26	69
68		56-7	36		28		68
67	36	55	34-5	20	27	25	67
66	35	53-4	33	19	26	24	66
65	34	52	32		25		65
64	33	50-1	31	18		23	64
63	32	48-9	30		24	22	63
62	31	47	29	17	23		62
61	30	45-6	27-8	16	22	21	61
60		44	26		21	20	60
59	29	42-3	25	15	20		59
58	28	40-1	24	14		19	58
57	27	39	23		19	18	57
56	26	37-8	22	13	18		56
55	25	36	21		17	17	55
54	24	34-5	19-0	12	16	16	54
53	23	32-3	18	11			53
52	22	31	17		15	15	52
51		29-0	16	10	14	14	51
50	21	28	15	9	13		50
49	20	26-7	14		12	13	49
48	19	24-5	13	8	11	12	48
47	18	23	11-2				47
46	17	21-2	10	7	10	11	46
45	16	20	9	6	9	10	45
44	15	18-9	8		8		44
43		17	7	5	7	9	43
42	14	15-6	6	4	6	8	42
41	13	13-4	5				41
40	12	12	3-4	3	5	7	40
39	11	10-1	2		4	6	39
38	10	9	1	2	3		38
37	9	7-8	0	1	2	5	37
36	8	5-6				4	36
35	7	4		0	1		35
34		2-3			0	3	34
33	6	1				2	33
32	5	0				1	32
31	4						31
30	0-3					0	30
T Score	_____	_____	_____	_____	_____	_____	T Score
Raw Score	_____	_____	_____	_____	_____	_____	Raw Score
	Ten	Dep	Ang	Vig	Fat	Con	

POM 040

SCHEDULE OF RECENT EXPERIENCE (SRE)

Part A (Items 1 through 12)

Instructions

For each life event item listed below please do the following:

Think back on the event and decide if it happened to you and when it happened.

If the event did happen, place a check mark in the appropriate time period to the right. The columns are as follows:

PAST WEEK 0 to 6 months ago 6 months to 1 year ago 1 to 2 years ago 2 to 3 years ago

If the event in question did not happen to you in any of the time periods, check under "Does not apply."

	PAST WEEK	0-6 mo ago	6 mo-1 yr ago	1-2 yrs ago	2-3 yrs ago	Does not apply
1. A lot more or a lot less trouble with the boss.						
2. A major change in sleeping habits (sleeping a lot more or a lot less, or change in part of day when asleep).						
3. A major change in eating habits (a lot more or a lot less food intake, or very different meal hours or surroundings).						
4. A revision of personal habits (dress, manners, associations, etc.).						
5. A major change in your usual type and/or amount of recreation.						
6. A major change in your social activities (e.g., clubs, dancing, movies, visiting, etc.).						
7. A major change in church activities (e.g., a lot more or a lot less than usual).						
8. A major change in number of family-get-togethers (e.g., a lot more or a lot less than usual).						
9. A major change in financial state (e.g., a lot worse off or a lot better off than usual).						
10. In-law troubles.						

	Past week	0-6 mo ago	6 mo-1 yr ago	1-2 yrs ago	2-3 yrs ago	Does not apply
11. A major change in the number of arguments with spouse (e.g., either a lot more or a lot less than usual regarding child-rearing, personal habits, etc.).	___	___	___	___	___	___
12. Sexual difficulties.	___	___	___	___	___	___

Part B (Items 13 through 42)

This part is similar to Part A, except that you are now asked to indicate the number of times that an event happened in each of the appropriate time periods.

	Past week	0-6 mo ago	6 mo-1 yr ago	1-2 yrs ago	2-3 yrs ago	Does not apply
13. Major personal injury or illness.	___	___	___	___	___	___
14. Death of a close family member (other than spouse).	___	___	___	___	___	___
15. Death of spouse.	___	___	___	___	___	___
16. Death of a close friend.	___	___	___	___	___	___
17. Gaining a new family member (e.g., through birth, adoption, oldster moving in, etc.).	___	___	___	___	___	___
18. Major change in the health or behavior of a family member.	___	___	___	___	___	___
19. Change in residence.	___	___	___	___	___	___
20. Detention in jail or other institution.	___	___	___	___	___	___
21. Minor violations of the law (e.g., traffic tickets, jaywalking, disturbing the peace, etc.).	___	___	___	___	___	___
22. Major business readjustment (e.g., merger, reorganization, bankruptcy, etc.).	___	___	___	___	___	___
23. Marriage.	___	___	___	___	___	___
24. Divorce.	___	___	___	___	___	___
25. Marital separation from spouse.	___	___	___	___	___	___
26. Outstanding personal achievement.	___	___	___	___	___	___

		(NOT WEEK)	0-6 mo ago	6 mo-1 yr ago	1-2 yrs ago	2-3 yrs ago	Does not apply
27.	Son or daughter leaving home (e.g., marriage, attending college, etc.).	____	____	____	____	____	____
28.	Retirement from work.	____	____	____	____	____	____
29.	Major change in working hours or conditions.	____	____	____	____	____	____
30.	Major change in responsibilities at work (e.g., promotion, demotion, lateral transfer).	____	____	____	____	____	____
31.	Being fired from work.	____	____	____	____	____	____
32.	Major change in living conditions (e.g., building a new home, remodeling, deterioration of home or neighborhood).	____	____	____	____	____	____
33.	Wife beginning or ceasing work outside the home.	____	____	____	____	____	____
34.	Taking on a mortgage greater than $10,000 (e.g., purchasing a home, business, etc.).	____	____	____	____	____	____
35.	Taking on a mortgage or loan less than $10,000 (e.g., purchasing a car, TV, freezer, etc.).	____	____	____	____	____	____
36.	Foreclosure on a mortgage or loan.	____	____	____	____	____	____
37.	Vacation.	____	____	____	____	____	____
38.	Changing to a new school.	____	____	____	____	____	____
39.	Changing to a different line of work.	____	____	____	____	____	____
40.	Beginning or ceasing formal schooling.	____	____	____	____	____	____
41.	Marital reconciliation with mate.	____	____	____	____	____	____
42.	Pregnancy.	____	____	____	____	____	____

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Weekly

SCHEDULE OF RECENT EXPERIENCES (SRE)

Name _____ Date _____ Session # _____

INSTRUCTIONS

For each life event item listed below please do the following:

Think back on the event and decide if it happened to you within the past week, including today.

If, during the course of the last week, any of the items applies to you, place a check mark in the appropriate space to the right. If one of the items should apply more than once during the week, indicate the number of times the event occurred to you within the past week.

If the event in question did not happen to you during the past week, check under "Does not apply."

	Number of times within past week	Does not apply
1. A lot more or a lot less trouble with the boss.	_____	_____
2. A major change in sleeping habits (sleeping a lot more or a lot less, or change in part of day when asleep).	_____	_____
3. A major change in eating habits (a lot more or a lot less food intake, or very different meal hours or surroundings).	_____	_____
4. A revision of personal habits (dress, manners, associations, etc.).	_____	_____
5. A major change in your usual type and/or amount of recreation.	_____	_____
6. A major change in your social activities (e.g., clubs, dancing, movies, visiting, etc.).	_____	_____
7. A major change in church activities (e.g., a lot more or a lot less than usual).	_____	_____
8. A major change in number of family-get-togethers (e.g., a lot more or a lot less than usual).	_____	_____
9. A major change in financial state (e.g., a lot worse off or a lot better off than usual).	_____	_____

Page Two	Number of times within past week	Does not apply
10. In-law troubles.	_____	____
11. A major change in the number of arguments with spouse (e.g., either a lot more or a lot less than usual regarding child-rearing, personal habits, etc.).	_____	____
12. Sexual difficulties.	_____	____
13. Major personal injury or illness.	_____	____
14. Death of close family member (other than spouse).	_____	____
15. Death of spouse.	_____	____
16. Death of a close friend.	_____	____
17. Gaining a new family member (e.g., through birth, adoption, oldster moving in, etc.).	_____	____
18. Major change in the health or behavior of a family member.	_____	____
19. Change in residence.	_____	____
20. Detention in jail or other institution.	_____	____
21. Minor violations of the law (e.g., traffic tickets, jaywalking, disturbing the peace, etc.).	_____	____
22. Major business readjustment (e.g., merger, reorganization, bankruptcy, etc.).	_____	____
23. Marriage.	_____	____
24. Divorce.	_____	____
25. Marital separation from spouse.	_____	____
26. Outstanding personal achievement.	_____	____
27. Son or daughter leaving home (e.g., marriage, attending college, etc.).	_____	____
28. Retirement from work.	_____	____
29. Major change in working hours or conditions.	_____	____
30. Major change in responsibilities at work (e.g., promotion, demotion, lateral transfer).	_____	____

Page Three	Number of times within past week	Does not apply
31. Being fired from work.	_____	_____
32. Major change in living conditions (e.g., building a new home, remodeling, deterioration of home or neighborhood).	_____	_____
33. Wife beginning or ceasing work outside the home.	_____	_____
34. Taking on a mortgage greater than $10,000 (e.g., purchasing a home, business, etc.).	_____	_____
35. Taking on a mortgage or loan less than $10,000 (e.g., purchasing a car, TV, freezer, etc.).	_____	_____
36. Foreclosure on a mortgage or loan.	_____	_____
37. Vacation.	_____	_____
38. Changing to a new school.	_____	_____
39. Changing to a different line of work.	_____	_____
40. Beginning or ceasing formal schooling.	_____	_____
41. Marital reconciliation with mate.	_____	_____
42. Pregnancy.	_____	_____

VALUES OF QUESTIONS ON SCHEDULE OF RECENT EXPERIENCE (SRE)

No.	SRE Question	Mean Value
1	Trouble with boss	23
2	Change in sleeping habits	16
3	Change in eating habits	15
4	Revision of personal habits	24
5	Change in recreation	19
6	Change in social activities	18
7	Change in church activities	19
8	Change in number of family get-togethers	15
9	Change in financial state	38
10	Trouble with in-laws	29
11	Change in number of arguments with spouse	35
12	Sex difficulties	39
13	Personal injury or illness	53
14	Death of close family member	63
15	Death of spouse	100
16	Death of close friend	37
17	Gain of new family member	39
18	Change in health of family member	44
19	Change in residence	20
20	Jail term	63
21	Minor violations of the law	11
22	Business readjustment	39
23	Marriage	50
24	Divorce	73
25	Marital separation	65
26	Outstanding personal achievement	28
27	Son or daughter leaving home	29
28	Retirement	45
29	Change in work hours or conditions	20
30	Change in responsibilities at work	29
31	Fired at work	47
32	Change in living conditions	25
33	Wife begin or stop work	26
34	Mortgage over $10,000	31
35	Mortgage or loan less than $10,000	17
36	Foreclosure of mortgage or loan	30
37	Vacation	13
38	Change in schools	20
39	Change to different line of work	36
40	Begin or end school	26
41	Marital reconciliation	45
42	Pregnancy	40

LIFE EVENTS DIARY

The purpose of this diary is to write down events that happen to you during the day that cause you either a significant amount of upset or that give you a significant amount of pleasure. The events which we would like you to write down are experiences which involve either danger, pain, significant changes in health, status or way of life; the promise of these; or important fulfillments or disappointments.

Please record on the following pages, on a day by day basis, those events in your life that, for better or for worse, interrupted or changed your usual activities.

For example, include events affecting your occupation, your physical health, your living arrangements, your relations with other family members, your friends, or your personal values or beliefs. Include your seizures in each daily list.

Please record these life events, including your seizures, in the order in which they occurred during the day, and please note them in the right hand column according to the following scale:

1 = Extremely Pleasurable -- terrific!
2 = Moderately Pleasurable -- good
3 = Mildly Pleasurable -- nice
4 = Mildly Upsetting -- not too bad
5 = Moderately Upsetting -- bad
6 = Extremely Upsetting -- just awful!

Here is a sample of the type of life events listing that a woman might record:

March 1, 1978

1.	Children missed school bus; had to drive them to school.	3
2.	Husband called from work; won't be home until late tonight, dinner engagement cancelled.	5
3.	Best friend called to say she learned she is pregnant.	2
4.	Children came home for lunch arguing with each other.	4
5.	Mother-in-law called to say she wants to come for an extended visit.	6
6.	Had a seizure.	6
7.	Called best friend, she came over for rest of afternoon.	3

SELF-EVALUATION QUESTIONNAIRE

Developed by C. D. Spielberger, R. L. Gorsuch and R. Lushene

STAI FORM X-1

NAME _____ DATE _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *feel* right now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	①	②	③	④
2. I feel secure	①	②	③	④
3. I am tense	①	②	③	④
4. I am regretful	①	②	③	④
5. I feel at ease	①	②	③	④
6. I feel upset	①	②	③	④
7. I am presently worrying over possible misfortunes	①	②	③	④
8. I feel rested	①	②	③	④
9. I feel anxious	①	②	③	④
10. I feel comfortable	①	②	③	④
11. I feel self-confident	①	②	③	④
12. I feel nervous	①	②	③	④
13. I am jittery	①	②	③	④
14. I feel "high strung"	①	②	③	④
15. I am relaxed	①	②	③	④
16. I feel content	①	②	③	④
17. I am worried	①	②	③	④
18. I feel over-excited and "rattled"	①	②	③	④
19. I feel joyful	①	②	③	④
20. I feel pleasant	①	②	③	④

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SELF-EVALUATION QUESTIONNAIRE

STAI FORM X-2

NAME _____ DATE _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	①	②	③	④
22. I tire quickly	①	②	③	④
23. I feel like crying	①	②	③	④
24. I wish I could be as happy as others seem to be	①	②	③	④
25. I am losing out on things because I can't make up my mind soon enough	①	②	③	④
26. I feel rested	①	②	③	④
27. I am "calm, cool, and collected"	①	②	③	④
28. I feel that difficulties are piling up so that I cannot overcome them	①	②	③	④
29. I worry too much over something that really doesn't matter	①	②	③	④
30. I am happy	①	②	③	④
31. I am inclined to take things hard	①	②	③	④
32. I lack self-confidence	①	②	③	④
33. I feel secure	①	②	③	④
34. I try to avoid facing a crisis or difficulty	①	②	③	④
35. I feel blue	①	②	③	④
36. I am content	①	②	③	④
37. Some unimportant thought runs through my mind and bothers me	①	②	③	④
38. I take disappointments so keenly that I can't put them out of my mind	①	②	③	④
39. I am a steady person	①	②	③	④
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	①	②	③	④

APPENDIX B

Epilepsy Background and History

Patient's Name _____

SECTION A. THIS IS AN EPILEPSY QUESTIONNAIRE. IT IS DESIGNED TO HELP US UNDERSTAND AS FULLY AS POSSIBLE THE SEIZURES THAT YOU ARE HAVING. PLEASE RELAX AND TAKE YOUR TIME.

2. Date of Birth: __ __ (Mo) __ __ (Day) __ __ (Yr)

3. Age: __ __ years

4. Sex: Male _____ Female _____

5. Race:

_____ 1. White
_____ 2. Black
_____ 3. Asian
_____ 4. American Indian
_____ 5. Spanish American
_____ 6. Other (specify) _____

6. Marital Status:

_____ 1. Single
_____ 2. Married
_____ 3. Separated
_____ 4. Divorced
_____ 5. Widowed
_____ 6. Living as married

7. Veteran: _____ 1. Yes _____ 2. No

8. Education (check patient's highest level):

_____ 1. Completed postgraduate training
_____ 2. Attended postgraduate training
_____ 3. Completed college or equivalent
_____ 4. Attended college or equivalent
_____ 5. Completed high school or equivalent
_____ 6. Attended high school (9-12)
_____ 7. Completed grammar school
_____ 8. Attended grammar school (1-8)
_____ 9. No schooling

SECTION B. THERE ARE MANY DIFFERENT KINDS OF SEIZURES; THEREFORE, SOME OR MANY OF THE FOLLOWING QUESTIONS WILL NOT APPEAR TO RELATE TO YOUR CASE. DO NOT LET THIS CONFUSE YOU, SIMPLY ANSWER ALL QUESTIONS AS ACCURATELY AS YOU CAN.

11. How old were you when you had your first spell or seizure? __ __ years

12. Do you have staring spells where you lose contact with people around you for just a few seconds?

_____ 1. Yes (Go to Question 13)
_____ 2. No (Go to Section C, page 4)

13. How long are your staring spells?

_____ 1. Less than 1 second
_____ 2. 1 to 10 seconds
_____ 3. 11 to 120 seconds
_____ 4. 2 to 10 minutes
_____ 5. Greater than 10 minutes

14. Are there any movements observed during your staring spells?

_____ 1. Yes _____ 2. No

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

15. During your staring spells, have your friends or family described you to:

1. Smack your lips or purse your lips?	_____ 1. Yes	_____ 2. No
2. Lick your lips?	_____ 1. Yes	_____ 2. No
3. Flutter your eyelids?	_____ 1. Yes	_____ 2. No
4. Move your hands and play with objects? . .	_____ 1. Yes	_____ 2. No
5. Talk during your staring spells?	_____ 1. Yes	_____ 2. No
6. Walk during your staring spells?	_____ 1. Yes	_____ 2. No

16. Have you found yourself waking up from a spell in a strange place or in an area distant from the area you had been in when your spell started?

_____ 1. Yes _____ 2. No

17. Have you ever attacked and hurt other human beings during your staring spells?

_____ 1. Yes _____ 2. No

18. Do your staring spells suddenly end in a matter of a split second?

_____ 1. Yes _____ 2. No

19. Do you remain confused after your staring spells?

_____ 1. Yes _____ 2. No

20. Describe your feelings immediately preceding your staring spells.

_____ 1. Happy
_____ 2. Sad
_____ 3. No change
_____ 4. Fearful
_____ 5. Other (specify) _____

21. Do you remember events immediately preceding your staring spells?

_____ 1. Yes _____ 2. No

22. Do you remember events during your staring spells?

_____ 1. Yes _____ 2. No

23. Do you remember events during the period of confusion that follows your staring spells?

_____ 1. Yes _____ 2. No

24. How many staring spells have you had in your lifetime?

_____ 1. Less than 10
_____ 2. 11 to 100
_____ 3. Greater than 100

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

25. When did your first staring spell occur?

1. ___ ___ days ago
2. ___ ___ weeks ago
3. ___ ___ months ago
4. ___ ___ years ago

26. When was your most recent staring spell?

1. ___ ___ days ago
2. ___ ___ weeks ago
3. ___ ___ months ago
4. ___ ___ years ago

27. Are your spells becoming more frequent?

_____ 1. Yes, they are more frequent
_____ 2. No, they are remaining the same
_____ 3. No, they are becoming less frequent
_____ 4. It is difficult to tell

28. How many spells have you had this week?

_____ 1. None
_____ 2. Once or twice this week
_____ 3. About every other day
_____ 4. Once a day
_____ 5. Several times a day

29. How many spells have you had this past month?

_____ 1. None
_____ 2. Less than once a week
_____ 3. Once a week
_____ 4. Several times a week
_____ 5. Once a day or more

30. How many spells have you had this past year?

_____ 1. None
_____ 2. 1 to 3
_____ 3. 4 to 12
_____ 4. 13 to 24
_____ 5. Greater than 24

SECTION C. THE FOLLOWING QUESTIONS WILL ASK ABOUT OTHER TYPES OF SEIZURES THAT YOU MAY HAVE HAD.

31. Do you have falling spells where you lose consciousness, shake your arms or legs, or wet your pants?

_____ 1. Yes (Go to Question 32)
_____ 2. No (Go to Section D, page 6)

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

32. Do you lose consciousness with your attacks?

_____ 1. Yes, immediately at the start of an attack
_____ 2. Yes, during the attack
_____ 3. No

33. How often have you lost consciousness?

_____ 1. Not applicable
_____ 2. With one attack only
_____ 3. With less than half of my attacks
_____ 4. With more than half of my attacks
_____ 5. With every attack

34. How long do you remain unconscious?

_____ 1. Not applicable
_____ 2. A few seconds
_____ 3. A few minutes
_____ 4. 15 to 45 minutes
_____ 5. Greater than one hour

IF YOU CHECKED ITEMS 2 OR 3 OF QUESTION 32, CONTINUE TO QUESTION 35. IF YOU CHECKED ITEM 1 OF QUESTION 32, GO TO SECTION E, PAGE 8.

35. Do the first events of an attack consist of unusual movements of a part of the body?

_____ 1. Yes (Go to Question 36)
_____ 2. No (Go to Section D, page 6)

36. How long do the movements last?

_____ 1. Less than one minute
_____ 2. 1 to 5 minutes
_____ 3. 6 to 10 minutes
_____ 4. Greater than 10 minutes

37. Where does this movement start? (Check all that apply)

_____ 1. Foot or leg
_____ 2. Arm or hand
_____ 3. Side of face
_____ 4. Other (specify) _____

38. On which side does this movement start?

_____ 1. Right side
_____ 2. Left side
_____ 3. Right and left sides

39. Does this movement spread to other parts of the body? (Check all that apply)

_____ 1. Not applicable
_____ 2. Foot or leg
_____ 3. Hand or arm
_____ 4. Side of face
_____ 5. Other (specify) _____

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

40. If the movement has spread, where is it located?

_____ 1. Not applicable
_____ 2. Right side
_____ 3. Left side
_____ 4. Right and left sides

41. Do your head and/or eyes turn to one side?

_____ 1. Yes, to the right side
_____ 2. Yes, to the left side
_____ 3. Yes, sometimes to the right or left side
_____ 4. No

SECTION D.

42. Are there any unusual sensations, feelings, dizziness, smells or tastes with your attacks?

_____ 1. Yes (Go to Question 43)
_____ 2. No (Go to Section E, page 8)

43. Have you had any of the following sensations at the start of an attack? (Check all that apply)

_____ 1. Numbness
_____ 2. Tingling or pins and needles
_____ 3. Feelings of hot or cold
_____ 4. Pain
_____ 5. None of these (Go to Question 46)

44. Where do these sensations occur? (Check all that apply)

_____ 1. Face
_____ 2. Trunk
_____ 3. Arms or hands
_____ 4. Legs or feet

45. On which side do these sensations occur?

_____ 1. On the right side
_____ 2. On the left side
_____ 3. On the right and left sides

46. Have you experienced any of the following sensations at the start of an attack? (Check all that apply)

_____ 1. Heart beat slowing down or speeding up
_____ 2. Increased perspiration
_____ 3. Nausea or vomiting
_____ 4. None of these

47. Have you experienced an unusual sensation of smell at the beginning of an attack?

_____ 1. Yes _____ 2. No

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

48. Can you describe this smell?

_____ 1. Yes, (describe) _____
_____ 2. No, but it is a foul smell
_____ 3. No, but it is a pleasant smell
___ ___ 4. Not applicable

49. Have you experienced an unusual sensation of taste at the beginning of an attack?

_____ 1. Yes _____ 2. No

50. Can you describe this taste?

_____ 1. Yes, (describe) _____
_____ 2. No, but it is a foul taste
_____ 3. No, but it is a pleasant taste
_____ 4. Not applicable

51. Have you experienced an unusual sensation in your stomach?

_____ 1. Yes _____ 2. No

52. How would you describe this sensation in your stomach? (Check all that apply)

_____ 1. Not applicable
_____ 2. Nausea
_____ 3. Sinking sensation
_____ 4. Rising sensation
_____ 5. Pain or discomfort
_____ 6. Other (specify) _____

53. Have you experienced any dizziness?

_____ 1. Yes _____ 2. No

54. How would you describe this dizziness? (Check all that apply)

_____ 1. Not applicable
_____ 2. Sense of turning or spinning
_____ 3. Movement of objects around you
_____ 4. Defective balance or staggering
_____ 5. Feelings of lightheadedness, that I am about to faint
_____ 6. Other (specify) _____

55. Have you experienced any hearing changes?

_____ 1. Yes _____ 2. No

56. How would you describe these hearing changes? (Check all that apply)

_____ 1. Not applicable
_____ 2. Ringing in my ears
_____ 3. Noises in my ears
_____ 4. Sounds seem louder than usual
_____ 5. Sounds seem softer than usual
_____ 6. Distortion of sounds
_____ 7. Other (specify) _____

STUDY #118 - FORM 1 (Continued) Patient Study N ___ ___ /___ ___ ___

57. Have you experienced any visual changes?

_____ 1. Yes _____ 2. No

58. How would you describe these visual changes? (Check all that apply)

_____ 1. Not applicable
_____ 2. Blurred vision
_____ 3. Double vision
_____ 4. Sensation of light
_____ 5. Sensation of dark
_____ 6. Sensation of color
_____ 7. Objects appear larger
_____ 8. Objects appear smaller
_____ 9. Shapes are distorted
_____ 10. Hallucinations (visions)
_____ 11. Other (specify) _____

59. Do you have any other unusual sensations not mentioned above?

_____ 1. Yes (describe) _____
_____ 2. No

SECTION E.

60. Have you had any of the following experiences at the start of an attack? (Check all that apply)

_____ 1. A feeling of familiarity when I was in unfamiliar circumstances
_____ 2. A feeling of never having seen something before when it was very familiar to me
_____ 3. Unexplained fear
_____ 4. Thinking about one thing continuously
_____ 5. None of these

61. Have you had any of the following experiences at the start of an attack? (Check all that apply)

_____ 1. Loss of speech or understanding but aware of people around me
_____ 2. Not being in control of my behavior
_____ 3. Hearing a musical theme over and over
_____ 4. None of these

62. Have you ever had (as described by family or friends) prolonged states of behavior changes that you do not remember?

_____ 1. Hours
_____ 2. Days
_____ 3. Weeks
_____ 4. None of these

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

63. Have you experienced any of the following at the start of an attack? (Check all that apply)

_____ 1. Goose bumps
_____ 2. Headaches
_____ 3. Bright spots in front of you
_____ 4. Sensation of floating or being lifted up in the air
_____ 5. None of these

64. Have you experienced any of the following at the start of an attack? (Check all that apply)

_____ 1. Difficulty judging distance
_____ 2. Ceiling looks deeper and farther
_____ 3. Wall looks deeper and farther
_____ 4. People look farther or nearer than usual
_____ 5. None of these

65. Have you experienced any of the following at the start of an attack? (Check all that apply)

_____ 1. Difficulty understanding spoken language
_____ 2. Difficulty explaining your thoughts through the spoken language
_____ 3. Difficulty understanding written words
_____ 4. Difficulty naming objects
_____ 5. None of these

66. Have your family or friends described a prolonged state of confusion where you are noted to perform complex purposeful movements, walk around and exhibit usual eating habits while you appear to be dazed and in a dreamy twilight state?

_____ 1. Yes _____ 2. No

If yes, for how long a time? ___ ___ hours

67. Have you been told that you cry out during an attack?

_____ 1. Yes _____ 2. No

68. Have you been told that your arms or legs jerk during an attack after you have lost consciousness?

_____ 1. Yes
_____ 2. No
_____ 3. Not applicable

69. How long do these movements last?

_____ 1. Not applicable
_____ 2. A few seconds
_____ 3. Up to 3 minutes
_____ 4. 3 to 10 minutes
_____ 5. 11 to 30 minutes
_____ 6. More than an hour
_____ 7. It changes from seizure to seizure

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

70. Which limbs are involved?

_____ 1. Not applicable
_____ 2. Arms
_____ 3. Legs
_____ 4. Arms and legs

71. Which side is involved in this jerking?

_____ 1. Not applicable
_____ 2. Right side
_____ 3. Left side
_____ 4. Right and left sides

72. Have you ever done any of the following during an attack? (Check all that apply)

_____ 1. Bitten your tongue
_____ 2. Lost control of your bladder
_____ 3. Lost control of your bowels
_____ 4. Foam at the mouth
_____ 5. Become stiff all over
_____ 6. Roll your eyes upward
_____ 7. None of these

73. Have you ever injured yourself? _____ 1. Yes _____ 2. No

74. How severe was this injury?

_____ 1. Not applicable
_____ 2. Minor injury that did not require a doctor
_____ 3. Required a doctor but was not serious
_____ 4. Serious injury such as a bone fracture

75. Have others described you as being awake but confused during an attack?

_____ 1. Yes _____ 2. No

76. How long does this last?

_____ 1. Not applicable
_____ 2. A few seconds
_____ 3. A few minutes
_____ 4. An hour
_____ 5. More than an hour

77. Have others described you as engaging in purposeless activity during an attack?

_____ 1. Yes _____ 2. No

78. How long does this behavior last?

_____ 1. Not applicable
_____ 2. A few seconds
_____ 3. A few minutes
_____ 4. An hour
_____ 5. More than an hour

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

79. Have others described you as having great changes in emotion during an attack?

_____ 1. Yes _____ 2. No

80. Do any of the following describe these emotions? (Check all that apply)

_____ 1. Not applicable
_____ 2. Rage or anger
_____ 3. Severe depression
_____ 4. Fear
_____ 5. Pleasure

81. After an attack, do you suffer from (check all that apply):

_____ 1. Muscle soreness
_____ 2. Headaches
_____ 3. Confusion/Disorientation
_____ 4. Tiredness
_____ 5. Anxiety
_____ 6. Combativeness
_____ 7. None of these

82. Do you sleep after an attack?

_____ 1. Yes, for less than an hour
_____ 2. Yes, for an hour or longer
_____ 3. Yes, for the whole day
_____ 4. No

83. Other than your staring spells, when did your first seizure occur?

1. ___ ___ days ago
2. ___ ___ weeks ago
3. ___ ___ months ago
4. ___ ___ years ago

84. How many major attacks have you had (other than your staring spells)?

___ ___ major attacks

85. When was your most recent attack?

1. ___ ___ days ago
2. ___ ___ weeks ago
3. ___ ___ months ago
4. ___ ___ years ago

(IF LESS THAN FOUR ATTACKS, GO TO SECTION F, PAGE 12)

86. Are your attacks becoming more frequent?

_____ 1. Yes, they are more frequent
_____ 2. No, they are remaining the same
_____ 3. No, they are less frequent
_____ 4. It is difficult to tell

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

87. How many attacks have you had this past week?

_____ 1. Not applicable
_____ 2. Several times a day
_____ 3. Once a day
_____ 4. About every other day
_____ 5. Once or twice this week

88. How many attacks have you had this past month?

_____ 1. Not applicable
_____ 2. Once a day or more
_____ 3. Several times a week
_____ 4. Once a week
_____ 5. Less than once a week

SECTION F.

89. On days when I have a major attack:

_____ 1. I go back to what I was doing within an hour after an attack
_____ 2. It takes several hours to recover from an attack
_____ 3. It takes a day or longer to recover from an attack

90. On days when I have short lapses of consciousness:

_____ 1. I go back to what I was doing within an hour after an attack
_____ 2. It takes several hours to recover from an attack
_____ 3. It takes a day or longer to recover from an attack

91. Which of the following describe your situation?

_____ 1. I am not restricted as to the type of work I can do
_____ 2. I can work but there are restrictions
_____ 3. I cannot work at all

92. On the average, how much work do you miss in a month because of your seizures? (Enter NA if patient is retired, unemployed, etc.)

___ ___ days

93. Which of the following describe your situation?

_____ 1. My attacks do not prevent me from enjoying myself in large crowds or being with people I do not know well
_____ 2. Because of my seizures, there are times when I must limit my social activities outside my home
_____ 3. Because of my seizures, I do not feel comfortable around others and must severely limit my contact with other people

94. Have you had a severe head injury?

_____ 1. Yes _____ 2. No

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

95. What type of head injury was this?

_____ 1. Not applicable
_____ 2. Auto accident
_____ 3. Fall
_____ 4. Blow to head
_____ 5. Military injury (wound)
_____ 6. Other (specify) _____

96. Did you have a skull fracture?

_____ 1. Yes
_____ 2. No
_____ 3. Not applicable

97. Did you lose consciousness?

_____ 1. Yes
_____ 2. No
_____ 3. Not applicable

98. How long did you remain unconscious?

_____ 1. Not applicable
_____ 2. A few seconds
_____ 3. A few minutes
_____ 4. An hour
_____ 5. Several hours
_____ 6. A day or longer

99. How long after your head injury did the seizures begin?

1. _____ Not applicable
2. _____ My seizures began before I had the head injury
3. ___ ___ Hours later
4. ___ ___ Days later
5. ___ ___ Weeks later
6. ___ ___ Months later
7. ___ ___ Years later

100. Have you had any of the following illnesses? (Check all that apply)

_____ 1. Meningitis
_____ 2. Encephalitis
_____ 3. Other brain fever
_____ 4. Stroke
_____ 5. Tumor
_____ 6. None of these

101. If you had a stroke, how long after your stroke did the seizures begin?

_____ 1. Not applicable
_____ 2. Several days later
_____ 3. Several weeks later
_____ 4. Several months later
_____ 5. Several years later
_____ 6. My seizures began before I had the stroke

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

102. Was the onset of your seizures associated with another illness?

_____ 1. Yes (specify) _____
_____ 2. No

103. Were you suffering from any of the following with the onset of your seizures? (Check all that apply)

_____ 1. Unusual fatigue
_____ 2. Emotional tension or stress
_____ 3. Poor nutrition or lack of meals
_____ 4. None of these

104. What, if anything, can you do to stop a seizure? (Check all that apply)

_____ 1. Nothing
_____ 2. Walk around
_____ 3. Stop moving
_____ 4. Sit down
_____ 5. Go to bed
_____ 6. Concentrate - mind
_____ 7. Stop talking
_____ 8. Close eyes
_____ 9. Hold self tightly
_____ 10. Other (specify) _____

105. Do you have sudden attacks where you drop to the floor with unconsciousness?

_____ 1. Yes _____ 2. No

106. Do you have sudden attacks where you drop to the floor but do not lose consciousness?

_____ 1. Yes _____ 2. No

107. Do you have sudden attacks were you fall to the floor during short lapses of unconsciousness?

_____ 1. Yes _____ 2. No

108. Which one of these attacks is most common to you?

_____ 1. Short lapses of consciousness
_____ 2. Drop attacks
_____ 3. Unconscious spells with generalized stiffening
_____ 4. Unconscious spells with generalized stiffening followed by jerking movements
_____ 5. Spells with generalized jerking movements alone

109. Does anyone else in your family have spells or seizures? (Check all that apply)

Relationship	Minor Spells			Major Attacks		
	Yes	No	NA	Yes	No	NA
Son	___	___	___	___	___	___
Daughter	___	___	___	___	___	___
Mother	___	___	___	___	___	___
Father	___	___	___	___	___	___
Sister	___	___	___	___	___	___
Brother	___	___	___	___	___	___
Maternal Grandparent	___	___	___	___	___	___
Paternal Grandparent	___	___	___	___	___	___
Aunt	___	___	___	___	___	___
Uncle	___	___	___	___	___	___
Cousin	___	___	___	___	___	___

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

SECTION G. WE WOULD LIKE TO DOCUMENT IN DETAIL THOSE FACTORS, IF ANY, WHICH SEEM TO TRIGGER, INCREASE, DECREASE OR IN ANY OTHER WAY MODIFY THE TYPE OF FREQUENCY OF YOUR SEIZURES. PLEASE ANSWER THE FOLLOWING QUESTIONS AS ACCURATELY AS YOU CAN.

		NEVER 1	2	SOMETIMES 3	OFTEN 4	USUALLY 5	ALWAYS
110.	Is there any cycle your seizures seem to follow? . . .						
	DO YOUR SEIZURES SEEM TO FOLLOW:	1	2	3	4	5	
111.	An hourly cycle?						
112.	A daily cycle?						
113.	A weekly cycle?.						
114.	A monthly cycle?						
115.	A seasonal cycle?.						
116.	An irregular flurry?						
117.	Other cycle?						
118.	Do your seizures occur only upon awakening?.						
119.	Do your seizures occur only during sleep?.						
120.	Do your seizures occur either upon awakening or during sleep?						
	DO YOUR SEIZURES TEND TO OCCUR AT ANY OF THE FOLLOWING TIMES?	1	2	3	4	5	
121.	Morning.						
122.	Noon						
123.	Afternoon.						
124.	Evening.						
125.	Dozing off to sleep.						
126.	Early sleep.						
127.	Late sleep						
128.	On awakening (within first hour)						
129.	Other (specify) _____						

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

DO YOUR SEIZURES TEND TO OCCUR UNDER ANY OF THE FOLLOWING CIRCUMSTANCES?

		1 NEVER	2 SOMETIMES	3 OFTEN	4 USUALLY	5 ALWAYS
130.	Mentally alert and thinking actively					
131.	Awake but relaxed with mind not actively working on a particular topic					
132.	Drowsy					
133.	During active exercising such as walking, running, etc.					
134.	Immediately after exercise, while "catching your breath"					
135.	When physically fatigued from muscular work					
136.	Shortly before meals					
137.	During meals					
138.	After meals					
139.	When bored					
140.	Other (specify) _____					

		1	2	3	4	5
141.	Is your seizure frequency affected by whether you are working or otherwise actively being kept busy?					
142.	In the past 3 months, have you lost sleep some nights (not in bed more than 3 hours)?					
143.	Does lost sleep have any effect on your seizure frequency?					
144.	Do you tend to gain weight or swell up for any reason?					
145.	Does weight gain or swelling have any effect on your seizures?					
146.	In the past 2 years, have you had any illness where you had a fever of greater than 100 degrees?					
147.	Does a fever have any effect on your attacks?					
148.	Have you had other illnesses during the past 2 years such as stomach upsets, broken bones, etc.?					
149.	Have your seizures been affected by other illnesses?					

STUDY #118 - FORM 1 (Continued) Patient Study No. __ __ /__ __ __

	NEVER 1	SOMETIMES 2	OFTEN 3	USUALLY 4	ALWAYS 5
150. Do you smoke?					
151. Does smoking affect your spells?					
152. Have you missed your medication at times?					
153. Do you notice an increase in the number of seizures you have if you miss your medication?					
154. Has the use or excess use of any kind of medicine (including anticonvulsants) seemed to increase your seizures?					
155. Have you used alcohol in the past 2 years?					

156. How often do you use alcohol?

_____ 1. Do not use alcohol
_____ 2. Rare (as on rare social occasions)
_____ 3. Infrequent (1-2 times per month)
_____ 4. Moderate frequency (1-2 times per week)
_____ 5. Frequent (3-4 times per week)
_____ 6. Very frequent (5 or more times per week)

157. Estimate total ounces of alcohol consumed:

_____ 1. Do not use alcohol
__ __ 2. Beer
__ __ 3. Wine
__ __ 4. Liquor
__ __ 5. Other (specify) _____

158. Was your alcohol intake or the effects of the alcohol on your seizures different in earlier years?

_____ 1. Yes _____ 2. No

159. Do various types of alcohol (i.e., beer, wine, liquor) seem to have a different effect on your seizures?

_____ 1. Yes _____ 2. No

If yes, explain _____

_____

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

	NEVER	SOMETIMES	OFTEN	USUALLY	ALWAYS
	1	2	3	4	5
160. Does the use of alcohol at any time seem to increase or decrease the frequency of your seizures?					
161. Do you have seizures while under the influence of alcohol?					
162. Do you have seizures after having alcohol to drink but no longer under the influence of alcohol (i.e., morning after)?					
163. Does your emotional state seem to influence the frequency of your seizures?					

DO ANY OF THE FOLLOWING TEND TO INCREASE YOUR SEIZURE FREQUENCY?	1	2	3	4	5
164. Sudden emotion of any kind (within 1-2 seconds)					
165. A sense of frustration					
166. Following an emotionally stimulating experience (i.e., argument, exciting sports event)					
167. During a period of fearfulness, worry or anxiety					
168. During a time of sadness, weeping or depression					
169. During a period of anger or hostility					
170. When feeling quite happy or joyful					
171. During excitement as in anticipation of some event or when many stimulating things are occurring at the same time					

DO ANY OF THE FOLLOWING TEND TO DECREASE YOUR SEIZURE FREQUENCY?	1	2	3	4	5
172. Sudden emotion of any kind (within 1-2 seconds)					
173. A sense of frustration					
174. Following an emotionally stimulating experience (i.e., argument, exciting sports event)					
175. During a period of fearfulness, worry or anxiety					
176. During a time of sadness, weeping or depression					
177. During a period of anger or hostility					
178. When feeling quite happy or joyful					
179. During excitement as in anticipation of some event or when many stimulating things are occurring at the same time					

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

	CAN AN ATTACK BEGIN OR BE BROUGHT ON BY:	1 NEVER	2 SOMETIMES	3 OFTEN	4 USUALLY	5 ALWAYS
180.	Any specific kind of movement, such as moving one hand, etc.?.					
181.	Contact with a part of the body (rubbing of the hand, leg or other part of the body by clothing, etc.)?					
182.	Loud noises (no specific type)?.					
183.	A specific kind of noise such as music or bells, etc.?					
184.	Suddenly going into an area that is sunny or brightly lit?.					
185.	Flashing lights?					
186.	Exposure to a particular type of odor or taste?. . . .					
187.	Sexual activity?					
188.	Being startled?.					

		1	2	3	4	5
189.	Do your attacks occur while reading?					
190.	Does the type of diet you follow have any effect on your seizures?					
191.	Do allergies affect your seizures?					
192.	Does bowel irregularity affect the frequency of your seizures?.					
193.	Does the use of coffee or tea affect the frequency of your seizures?.					
194.	Do you have periods of thirst related to the occurrence of your seizures?					

SECTION H. TO BE COMPLETED BY WOMEN ONLY.

		1	2	3	4	5
195.	Have you noted a definite relationship of your seizures to the occurrence or appearance of your menstrual period?					
196.	Do your seizures occur before your menstrual period? .					
197.	Do your seizures occur during your menstrual period? .					
198.	Do your seizures occur following your menstrual period?.					
199.	Do your seizures occur in-between your menstrual period?.					

STUDY #118 - FORM 1 (Continued) Patient Study No. ___ ___ /___ ___ ___

200. Have you ever been pregnant?

_____ 1. Yes _____ 2. No

HAVE YOUR SEIZURES BEEN DIFFERENT IN FREQUENCY OR CHARACTER DURING ANY OF THE FOLLOWING:

201. Early pregnancy?

_____ 1. Yes _____ 2. No _____ 3. Not applicable

202. Mid pregnancy?

_____ 1. Yes _____ 2. No _____ 3. Not applicable

203. At the time of delivery?

_____ 1. Yes _____ 2. No _____ 3. Not applicable

204. Within two weeks following delivery?

_____ 1. Yes _____ 2. No _____ 3. Not applicable

205. Did you notice an increase in your seizure frequency while pregnant?

_____ 1. Yes _____ 2. No _____ 3. Not applicable

206. Did you notice a decrease in your seizure frequency while pregnant?

_____ 1. Yes _____ 2. No _____ 3. Not applicable

207. Did your seizures begin about the same year your menstrual period began or stopped?

_____ 1. Yes _____ 2. No

208. Have you ever used birth control pills?

_____ 1. Yes _____ 2. No

209. Has the use of birth control pills had any effect on your seizures?

_____ 1. Yes _____ 2. No _____ 3. Not applicable

DATE COMPLETED: _____ / _____ / _____ FORM COMPLETED BY: _____
(Mo) (Day) (Yr)

EPILEPSY AND THE MENSTRUAL CYCLE

PATIENT INFORMATION

Name _____ Study No._____

Address_____

_____

Telephone(home)_____

(work)_____

Date of birth_____

Social Security #_____

Seizure classification (list controlled and uncontrolled types)
1._____
2._____
3._____

Previous seizure frequency for each type
1._____#/wk., mo., yr.
2._____#/wk., mo., yr.
3._____#/wk., mo., yr.

Age at menarche _____years
(year menstruation began)

	always	usually	rarely
Do you have regular menstrual cycles?	_____	_____	_____
Do you have menstrual cramps?	_____	_____	_____
Do you feel tense just before your period starts?	_____	_____	_____

Have you ever used oral contraceptives (the pill)? yes _____ no _____

If yes, name of drug_____

dates of use_____ = _____months/years

Have you ever used other steroid drugs regularly? yes _____ no _____

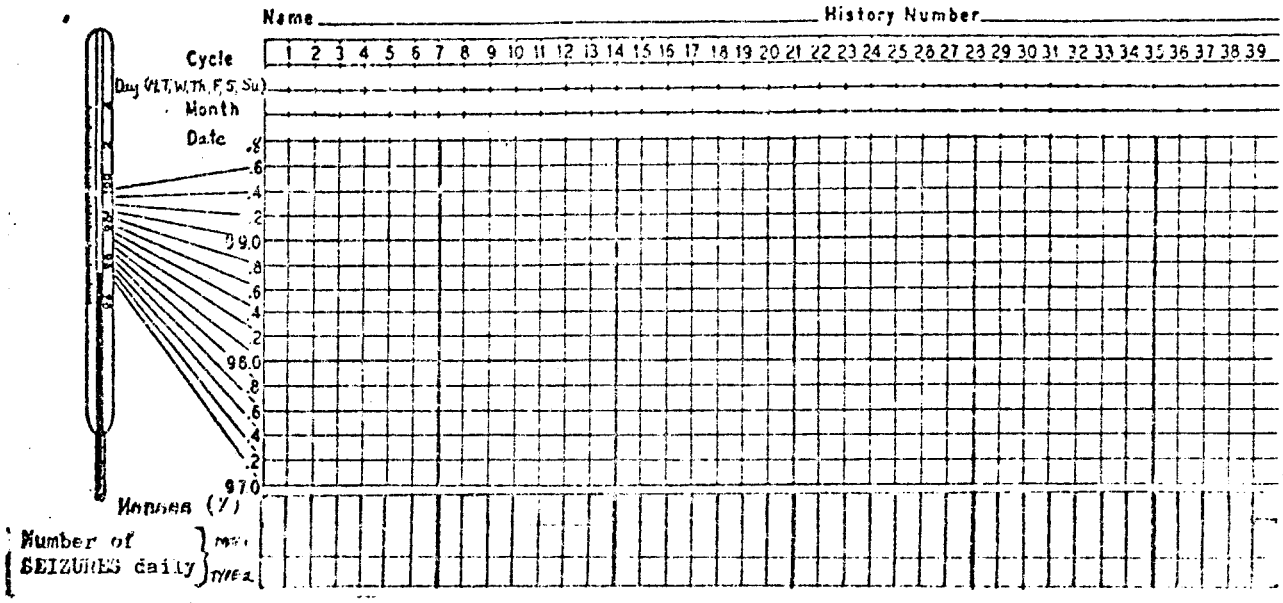
Have you ever been pregnant? yes _____ no _____ # pregnancies___

Completed form 1: Epilepsy Background and History yes_____ no_____

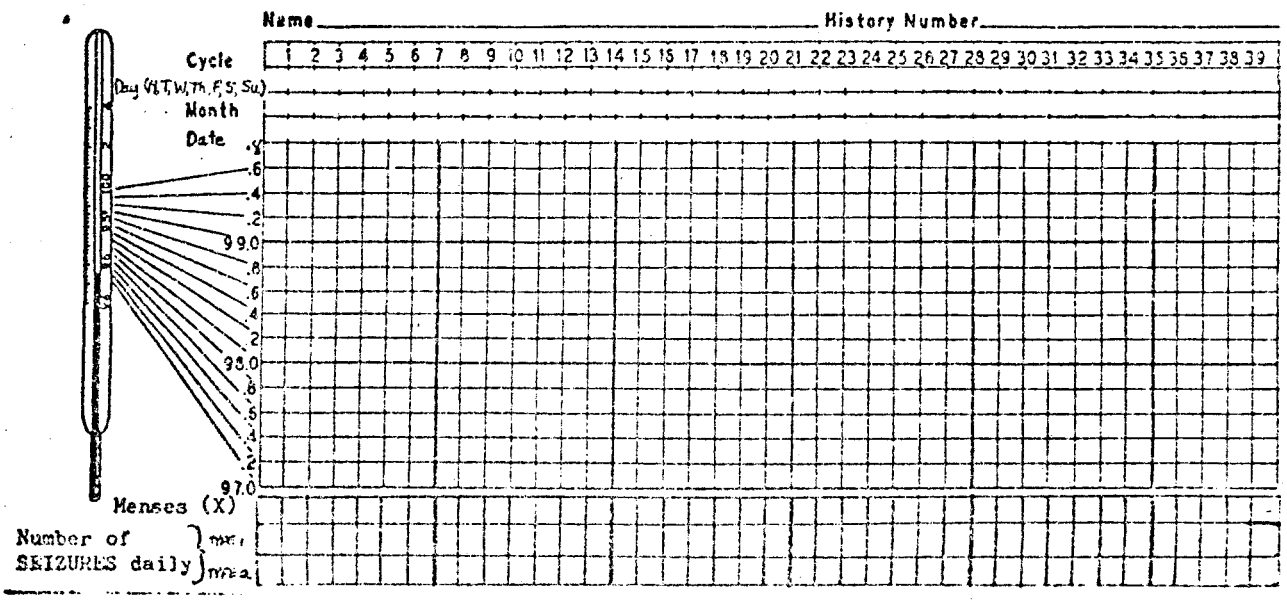
EARLY MORNING TEMPERATURE RECORD and DAILY SEIZURE RECORD, MENSTRUAL CYCLE STUDY

YALE UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY
INFERTILITY AND ENDOCRINE CLINICS

Basal Temperature Record



Basal Temperature Record



PLEASE BRING THIS RECORD WITH YOU TO CLINIC EACH VISIT!

EARLY MORNING TEMPERATURE RECORD and DAILY SEIZURE RECORD, MENSTRUAL CYCLE STUDY

INSTRUCTIONS:

1. Place the thermometer under the tongue for at least a full two minutes immediately after waking in the morning and before arising, eating, drinking or smoking. (Do this every morning).

2. Record the reading on the graph by placing a dot or X at the proper location (be accurate).

3. Insert the date at the top of column in space provided for month and date. Also, insert the day of the week (Monday, Tuesday, Wednesday, etc.) in the space provided.

4. The first day of menstrual flow is considered to be the start of a cycle. Each day of flow should be indicated with an X on the graph starting at extreme left under number one day of cycle.

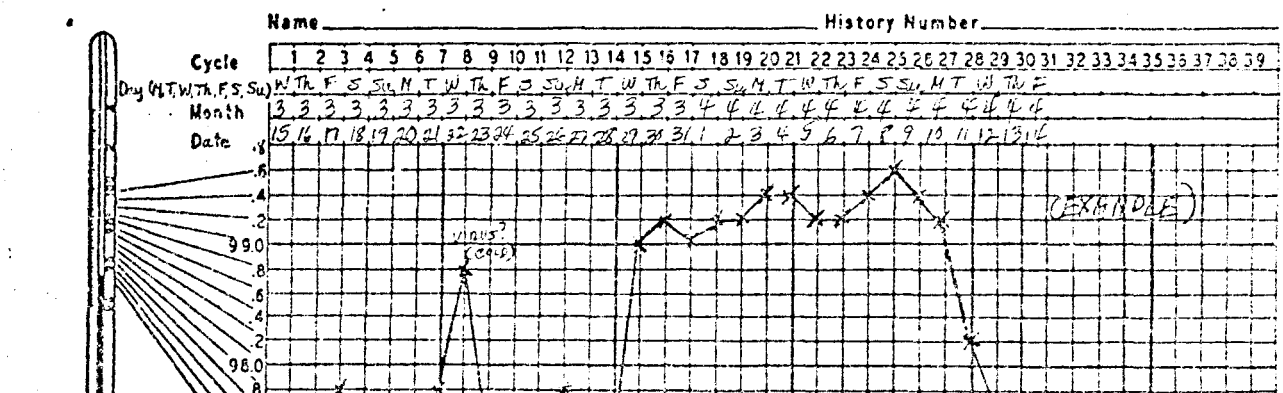
5. Any obvious reasons for temperature variation such as an infection, insomnia or indigestion should be noted on the graph above the reading for that day.

6. Ovulation in some women is detectable by a twinge of pain low on one side of the abdomen or by a few drops of vaginal bleeding about mid-cycle. If this is noticed indicate it on the graph.

7. Please record the number of spells or seizures you have each day, if any, in the space provided on the graph.

8. If you have more than one type of spell or seizure, please keep a separate record for each type. List the first type on one line and the second type on the line below. Another chart is provided for more complete seizure recording.

Basal Temperature Record



Seizure Record

Patient's Name _____ Study No. ___ ___ /___ ___ ___

PLEASE RECORD NUMBER OF SEIZURES EACH DAY. (Record comments on back.)
Please mark FIRST DAY of menstrual period *

MONTH _____ YEAR _____		MONTH _____ YEAR _____		MONTH _____ YEAR _____	
1	_____	1	_____	1	_____
2	_____	2	_____	2	_____
3	_____	3	_____	3	_____
4	_____	4	_____	4	_____
5	_____	5	_____	5	_____
6	_____	6	_____	6	_____
7	_____	7	_____	7	_____
8	_____	8	_____	8	_____
9	_____	9	_____	9	_____
10	_____	10	_____	10	_____
11	_____	11	_____	11	_____
12	_____	12	_____	12	_____
13	_____	13	_____	13	_____
14	_____	14	_____	14	_____
15	_____	15	_____	15	_____
16	_____	16	_____	16	_____
17	_____	17	_____	17	_____
18	_____	18	_____	18	_____
19	_____	19	_____	19	_____
20	_____	20	_____	20	_____
21	_____	21	_____	21	_____
22	_____	22	_____	22	_____
23	_____	23	_____	23	_____
24	_____	24	_____	24	_____
25	_____	25	_____	25	_____
26	_____	26	_____	26	_____
27	_____	27	_____	27	_____
28	_____	28	_____	28	_____
29	_____	29	_____	29	_____
30	_____	30	_____	30	_____
31	_____	31	_____	31	_____

EPILEPSY AND THE MENSTRUAL CYCLE

CLINIC VISIT

Name_____ Study No. _____

Date_____

Weight_____

seizures since last visit _____ calendar returned yes__ no__

average # seizures / month _____

Antiepileptic Drug Phenytoin Phenobarb Primidone Carbamazepine ___

Total daily dose (mg/day)

hours since last dose (hp)

serum concentration
(total µg/ml)

free drug conc. (µg/ml)

% free

estrogen conc. _____pg/ml

progesterone conc._____ng/ml

date last menstrual period started _____(=day 1)

days since first day _____

phase of cycle (adjusted to cycle length_____

Use of adjunct medication since last visit yes ____ no ____

Medication dose dates used why used

Next clinic visit_____

CHECKLIST FOR MENSTRUAL CYCLE STUDY

Name _____ Date _____ Session Number _____

_____ A. Blood Work

_____ 1. Three tubes of blood, red-top. Make sure patient is asked total dose of anticonvulsants that day, and hours since last dose.
_____ 2. Blood spun down, serum labeled, two tubes frozen. One tube to Special Chemistry for anticonvulsant levels.
_____ 3. Save lab slips that come up from Special Chemistry, put on yellow sheets in the Menstrual Study patient's charts.

_____ B. EEG

_____ 1. Electroencephalogram performed.
_____ 2. Paper run labeled with patient name, tape number, Session Number, Time given, Reel number on tape., date.
_____ 3. Tape labelled with patient name, tape number, Session Number, Time given, Reel number on tape., date.
_____ 4. Replace tape and paper run in Janet's office.

_____ C. Epilepsy and the Menstrual Cycle Clinic Visit Chart.

_____ 1. Compare returned thermometers with patient graphs.
_____ 2. Make sure all the following information is recorded:
_____ a. Name.
_____ b. Date.
_____ c. Number of seizures, kind of seizures, and the dates they occurred, for example: 7/14/78 - 2 Petit Male, 1 Grand Mal.
_____ d. Whether calendar was returned for checking or not.
_____ e. Antiepileptic drugs, total daily dose, hours since last dose.
_____ f. Date last Menstrual period started.
_____ g. Use of adjunct medication since last visit.
_____ 3. Make sure diary is up-to-date (green book or steno notebook).

_____ D. Questionnaires

_____ 1. Menstrual Distress Questionnaire, Form T
_____ 2. Weekly Schedule of Recent Experiences (SRE)
_____ 3. POMS Profile of Mood States
_____ 4. Self-Evaluation Questionnaire STAI Form X-1

CHECKLIST FOR MENSTRUAL CYCLE STUDY

Page Two

Name _____ Date _____ Session Number _____

_____ E. Neuropsychological Testing

_____ 1. Grip Strength
_____ 2. Finger Tapping
_____ 3. Pegs
_____ 4. Color Naming
_____ 5. Trunkal Ataxia
_____ 6. Digit Span
_____ 7. Digit Symbol
_____ 8. Trails B
_____ 9. Visual Search

APPENDIX C

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

Invitation to Participate and Description of Project: Part I

You are invited to participate in a study to evaluate the relationship between seizure incidence and menstrual cycles. The purpose of the study is to observe whether some women experience more seizures during a particular phase of the menstrual cycle. Women epileptic patients will be selected to participat in this study. Each woman should have a regular menstrual cycle currently and will report an association with seizures and menstrual cycle; some women will have noticed no pattern of seizure occurrence.

Participation in the 3 month study will require no hospitalization. You will be asked to maintain a calendar (to be provided) recording all seizures including comments about severity of episodes. Daily body temperature and menstrual flow will also be recorded. You will be asked to visit the Epilepsy Laboratory for three months for interview and blood tests on the first and second day of your menstrual flow, two weeks later during mid-cycle, and during the third week of your cycle. (A fourth visit several days before your menses is expected, may be requested). During these laboratory visits three small tubes of blood will be drawn (approximately one ounce), which may cause brief discomfort. EEG recordings will be performed. Each visit will take approximately two hours.

If the study documents an increase in seizure frequency during a phase of the menstrual cycle, the patient may benefit by special additional drug therapy adjusted to known requirements. The general benefit of the study will be a knowledge that cyclic changes in seizure incidence do occur and may require special therapeutic regimens to protect patients when seizures are expected. All possible steps will be taken to maintain confidentiality of all information provided by you. Information obtained from you will become a part of your medical record. If you decide not to participate, or if at any time you wish to terminate participation in the study, you may do so and continue to receive appropriate therapy for your condition. This will have no effect on your care here. You are welcome to ask questions at anytime. Before you sign this form, please ask any questions or any aspect of this study that is unclear to you. You may take as much time as necessary to think this over.

Authorization: I have read the above and decide that _____ (name of subject) will participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

_____
Signature

_____
Relationship (self, parent, guardian, etc.)

_____
Date

_____
Signature of Principal Investigator Telephone

_____
Signature of person obtaining consent Telephone

APPROVAL SHEET

The dissertation submitted by Janet Marie Kamer has been read and approved by the following committee:

Dr. Thomas P. Petzel, Director
Associate Professor of Psychology, Loyola

Dr. Frank J. Kobler
Professor of Psychology, Loyola

Dr. Alan S. DeWolfe
Professor of Psychology, Loyola

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

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

8/11/80
Date

Thomas P. Petzel
Director's Signature