

Three Patterns of Catamenial Epilepsy

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Summary: *Purpose:* On the basis of the neuroactive properties of estradiol and progesterone and the menstrually related cyclic variations of their serum concentrations, we propose the existence of three hormonally based patterns of seizure exacerbation. Because previous reports both support and refute the concept of catamenial epilepsy, we test the hypothesis by charting seizures and menses and measuring midluteal serum progesterone levels to estimate the frequency of epileptic women with catamenial seizure exacerbation.

Methods: One hundred eighty-four women with intractable complex partial seizures (CPS) charted their seizure occurrence and onset of menstruation on a calendar for one cycle during which they had a midluteal blood sample taken for serum progesterone determination on day 22. Levels >5 ng/ml were considered ovulatory. The cycle was divided into four phases with onset of menstruation being day 1: menstrual (M) = -3 to +3, follicular (F) = 4 to 9, ovulatory (O) = 10 to -13, and luteal (L) = -12 to -4. Average daily seizure frequency for each phase was calculated and compared among phases by repeated-measures analysis of variance (ANOVA) and the Student-Newman-Keul's test, separately for ovulatory and anovulatory cycles.

Results: The 1,324 seizures recorded during 98 ovulatory

cycles occurred with significantly greater ($p < 0.001$) average daily frequency during the M (0.59) and O (0.50) phases than during the F (0.41) and L (0.40) phases, offering support for perimenstrual (catamenial 1) and preovulatory (catamenial 2) patterns of seizure exacerbation. The 1,523 seizures recorded during 86 anovulatory cycles occurred with significantly lower ($p < 0.001$) average daily frequency during the F phase (0.49) than during all other phases (M = 0.78, O = 0.74, L = 0.74), offering support for seizure exacerbation throughout the second half of inadequate luteal phase cycles (catamenial pattern 3). Although 71.4% of the women with ovulatory cycles and 77.9% with inadequate luteal phase cycles had seizure exacerbation in relation to one of the three patterns of catamenial epilepsy, approximately one third of the women showed at least a twofold increase in average daily seizure frequency. We propose a twofold or greater increase as a reasonable definition of catamenial epilepsy.

Conclusions: Charting of seizures and menses and determination of day 22 progesterone levels during each cycle may be sufficient to establish the existence of three distinct patterns of catamenial epilepsy. Approximately one third of women with intractable CPS may have catamenial epilepsy. **Key Words:** Epilepsy—Catamenial—Menstrual—Hormones.

We propose the existence of three hormonally based patterns of seizure exacerbation in epilepsy (1). Seizures do not occur randomly in most men and women with epilepsy (2). They tend to cluster in $>50\%$ of cases (2). Seizure clusters in turn may occur with temporal rhythmicity in a significant proportion of men (29%) and women (35%) with epilepsy (3). In women, seizures may cluster in relation to the menstrual cycle; such seizures are commonly termed catamenial epilepsy (4) and may be attributable to (a) the neuroactive properties of steroid hormones and (b) the cyclic variation in serum levels.

Estradiol inhibits γ -aminobutyric acid (GABA) and potentiates glutamatergic transmission (5). It increases neuronal metabolism and discharge rates (5,6). It pro-

motes kindling (7,8) and animal experimental (9), as well as clinical (10) seizure occurrence. Progesterone metabolites such as allopregnanolone, in contrast, are potent barbiturate-like ligands at the GABA-chloride ionophore (11). Progesterone reduces neuronal metabolism (12) and discharge rates (13), and suppresses kindling (14), epileptiform discharges (15), and experimental (16) as well as clinical seizures (17).

Physiological variation in endocrine secretion during the menstrual cycle influences the occurrence of seizures. In ovulatory cycles, seizure frequency shows a statistically significant positive correlation with the serum estradiol/progesterone ratio (18). This ratio is highest during the days before ovulation and menstruation and lowest during the early and midluteal phase (18). The premenstrual exacerbation of seizures has been attributed to the withdrawal of the antiseizure effects of progesterone (19). The premenstrual exacerbation of seizures may also be related to a decrease in serum antiepileptic drug (AED) levels (20,21), which generally de-

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crease in the days before menstruation (20,21). Hepatic mechanisms are implicated (20,21). Specifically, AEDs and gonadal steroids are metabolized by the same microsomal enzyme systems in hepatic cells. The premenstrual decrease in gonadal steroid secretion, therefore, may permit increased metabolism of AEDs, resulting in lower serum levels. Midcycle exacerbations may be due to the preovulatory surge of estrogen unaccompanied by any increase in progesterone until ovulation occurs (18). Seizures are least common during the midluteal phase when progesterone levels are highest (18).

Inadequate luteal phase refers to abnormally low progesterone secretion during the second half of the cycle, regardless of whether ovulation occurs (22). It can be documented by one or more findings, including (a) a failure of the basal body temperature to increase by 0.7°F for at least 10 days during the second half of the menstrual cycle; (b) a serum progesterone level <5.0 ng/ml

during the midluteal phase, generally measured between days 20 and 22 of a 28-day cycle; and (c) a biopsy showing underdeveloped secretory endometrium 8–10 days after ovulation. Serum estradiol/progesterone ratios and seizure frequencies tend to be higher than those in normal ovulatory cycles (18,23).

On the basis of the neuroactive properties of gonadal steroids, the natural cyclic variation of serum estradiol and progesterone concentrations, and clinical observations, the existence of three hormonally based patterns of seizure exacerbation is proposed (Fig. 1): (a) perimenstrual (catamenial pattern 1, C1) and periovulatory (catamenial pattern 2, C2) during normal ovulatory cycles; and luteal, i.e., the entire second half of the cycle (catamenial pattern 3, C3) in inadequate luteal phase cycles.

Results of previous studies both support and refute the existence of cyclic seizure exacerbation in relation to the menstrual cycle. For example, Tauboll et al. (2) demon-

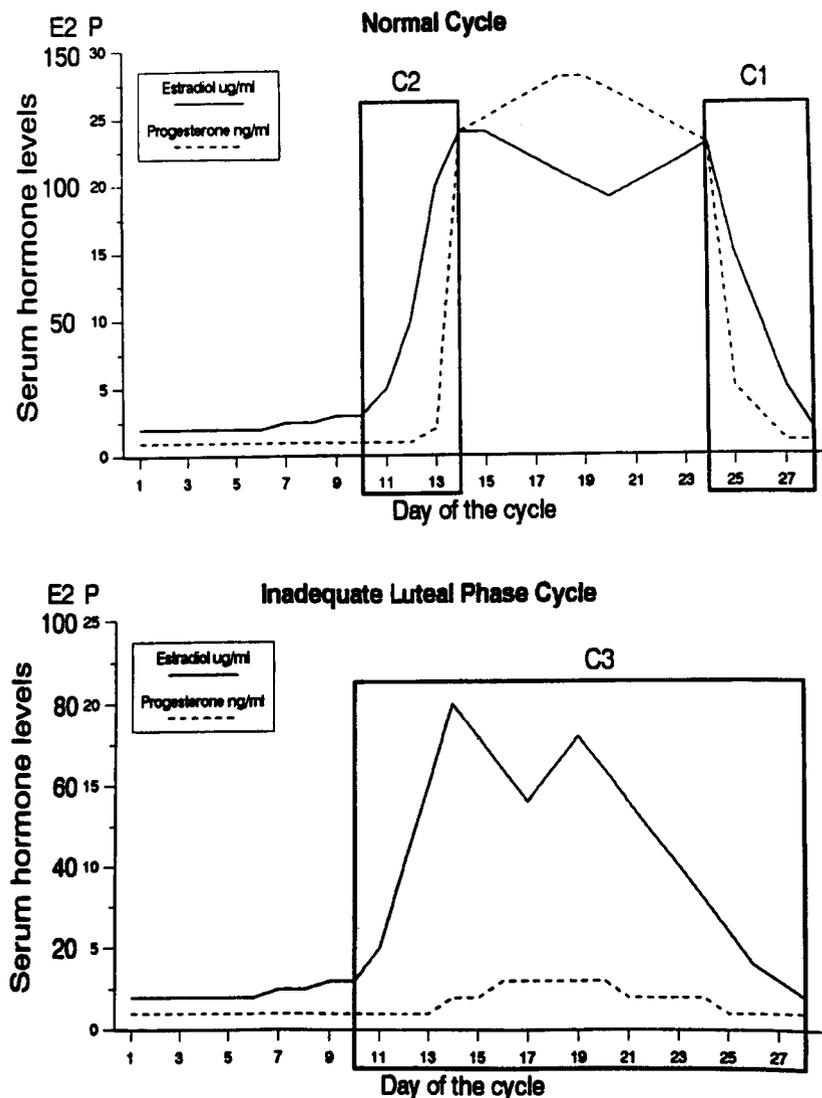


FIG. 1. Three proposed patterns of catamenial epilepsy: perimenstrual (C1) and periovulatory (C2) exacerbations during normal cycles and entire second half of the cycle (C3) exacerbation during inadequate luteal phase cycles.

strated catamenial seizure exacerbation in 78% of women with epilepsy. Laidlaw (19) reported seizure exacerbation in 72%; Rosciszewska (24) reported it in 67%, Ansell and Clarke (25) in 63%, and Gowers (26) in more than half of women with epilepsy. Duncan (27), in contrast, reported catamenial exacerbation in only 12.5% and Dickerson (28) reported it in 10% of women with epilepsy. Almqvist (3) noted a periodicity but could not relate it to a particular phase of the cycle. Finally, Bandler et al. (29) could not identify a periodicity in seizure occurrence in women. Differences in definition of catamenial epilepsy, multiplicity of catamenial exacerbation patterns, variation in cycle intervals, and the occurrence of anovulatory cycles complicate experimental design and mathematical analysis (4). We report a simple method of data collection and analysis and results that support the concept of catamenial epilepsy and the existence of the three previously proposed, hormonally-based patterns of seizure exacerbation (1).

METHODS

The subjects were 184 women aged 18–45 years (mean \pm SD = 28 \pm 5.2) who were consecutively referred for evaluation of intractable epilepsy between 1990 and 1995. All had discrete complex partial seizures (CPS) documented clinically and by focal epileptiform EEG discharges unilaterally or bilaterally in temporal derivatives during interictal and, in some cases, ictal recordings. Secondarily generalized seizures occurred in 62. The subjects used a wide variety of AEDs alone and in various combinations and had documented therapeutic serum levels of at least one drug [monotherapy: carbamazepine (CBZ), 37; phenytoin (PHT), 32; valproate (VPA), 28; phenobarbital (PB), 10; benzodiazepines (BZD), 6; and polytherapy 71], but were not treated with hormones, antidepressants, or major tranquilizers. The women charted their seizure occurrence and onset of menstruation on a calendar for one cycle, during which they had a midluteal blood sample taken for serum progesterone determination on day 22. Levels >5 ng/ml (range 5.0–27.2 ng/ml, $n = 98$) were considered ovulatory; lower levels (range <0.2 –3.4 ng/ml, $n = 86$) were considered consistent with inadequate luteal phase cycles. Cycles <23 or >35 days were not used in the investigation because of the difficulty in distinguishing cycle phases on the basis of a single, day 22 progesterone determination. The cycle was divided into four phases with an adjustment for variable cycle intervals: menstrual (M) = -3 to $+3$, follicular (F) = 4 to 9, ovulatory (O) = 10 to -13 and luteal (L) = -12 to -4 . Onset of menstruation was considered to be day 1 and ovulation was considered to be day -14 . The latter designation was used because ovulation generally occurs 14 days before onset of menstruation regardless of cycle interval. We

adjusted variable cycle intervals for statistical consideration by counting days forward from onset of menstruation to the day before ovulation and backward from onset of the next menstruation to the day of previous ovulation, day -14 , thereby reflecting the physiological variability of follicular phase duration. The three patterns of catamenial epilepsy were defined as follows: C1: greater average daily seizure frequency during the M phase in comparison to the F and L phases in ovulatory cycles; C2: greater seizure exacerbation during the O phase in comparison to the F and L phases in ovulatory cycles; and C3: greater seizure frequency during the O, L, and M phases than during the F phase in inadequate luteal phase cycles. Average daily seizure frequency for each phase was calculated and compared among phases according to the three proposed patterns of catamenial exacerbation by repeated-measures analysis of variance (ANOVA) and Student-Newman-Keul's tests. Comparisons were made separately for normal and inadequate luteal phase cycles.

A plot of the percentage of women with greater seizure frequency versus multiples of greater seizure frequency yielded three descending S-shaped curves (Fig. 4). The curves for C1 and 3 lay higher than the curve for C2 and tended to travel together and overlap each other. We computed the points of inflection for each curve analytically by fitting the curve to an appropriate mathematical model and determining the value of the multiple for which the second derivative equalled zero.

RESULTS

The 1,324 CPS and secondarily generalized seizures recorded during 98 normal cycles (Table 1) occurred with significantly greater ($p < 0.001$) average daily frequency during M (0.59) and O (0.50) phases considered

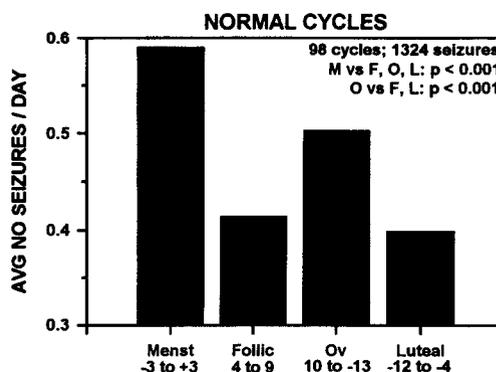


FIG. 2. The average number of daily complex partial and secondarily generalized seizures recorded during 98 normal cycles was significantly greater ($p < 0.001$) during menstrual (M = 0.59) and ovulatory (O = 0.50) phases considered separately than during either the midfollicular (F = 0.41) or luteal (L = 0.40) phase or both combined.

TABLE 1. CPS and secondarily generalized seizure occurrence during various phases of normal menstrual cycles

Seizures	M (6 days)	F (6 days)	O (7.82 days)	L (9 days)
CPS/SGMS (average daily frequency)	347 (0.59)	241 (0.41)	383 (0.50)	353 (0.40)
CPS (average daily frequency)	288 (0.49)	199 (0.34)	322 (0.42)	291 (0.33)
SGMS (average daily frequency)	59 (0.10)	42 (0.07)	61 (0.08)	62 (0.07)

CPS, complex partial seizures; SGMS, secondarily generalized motor seizures; M, menstrual phase; days -3 to 3 (average duration of each phase in parentheses); F, follicular phase, days 4 to 9; O, ovulatory phase, days 10 to -13; L, luteal phase, days -12 to -4; normal, normal luteal phase cycles.

separately than during either the F (0.41) or L (0.40) phase or both combined (Fig. 2). The 1,523 seizures recorded during 86 inadequate luteal phase cycles (Table 2) occurred with significantly lower ($p < 0.001$) average daily frequency during the F phase (0.49) than during any other phase (M = 0.78, O = 0.74, L = 0.74) considered separately or combined (Fig. 3). CPS considered alone during normal cycles also showed a similar statistically significant ($p < 0.001$) predilection for catamenial exacerbation during the M and O phases (1,100 seizures: average daily seizure frequency by phase was M, 0.49; F, 0.34; O, 0.42; L, 0.33), as did secondarily generalized seizures (224 seizures: average daily seizure frequency by phase was M, 0.10; F, 0.07; O, 0.08; L, 0.07; $p < 0.01$). Likewise CPS considered alone during inadequate luteal phase cycles showed a statistically significant predilection for catamenial exacerbation during the M, O, and L phases relative to F (1,015 seizures: average daily seizure frequency by phase M was 0.55; F, 0.33; O, 0.52; L, 0.53; $p < 0.001$), as did secondarily

TABLE 2. CPS and secondarily generalized seizure occurrence during phases of inadequate luteal phase cycles

Seizures	M (6 days)	F (6 days)	O (4.64 days)	L (9 days)
CPS/SGMS (average daily frequency)	402 (0.78)	253 (0.49)	295 (0.74)	573 (0.74)
CPS (average daily frequency)	284 (0.55)	170 (0.33)	207 (0.52)	410 (0.53)
SGMS (average daily frequency)	118 (0.23)	83 (0.16)	88 (0.22)	163 (0.21)

Abbreviations as in Table 1.

generalized seizures (508 seizures: average daily seizure frequency by phase was M, 0.23; F, 0.16; O, 0.22; L, 0.21; $p < 0.001$).

There was no statistically significant difference in the distribution of AED use (Table 3) (ANOVA = NS) between normal and inadequate luteal phase cycles or among the three patterns of catamenial epilepsy (Table 4) (ANOVA = NS).

Seventy (71.4%) of the 98 women with normal cycles showed a catamenial pattern of seizure exacerbation, with 67 showing both C1 and C2 patterns and 3 showing just C1. Sixty-seven (77.9%) of the 86 women with inadequate luteal phase cycles showed a C3 pattern of seizure exacerbation; only 10 (11.6%) showed pattern C1 or 2.

The data show that 71.4% of the women with normal cycles and 77.9% with inadequate luteal phase cycles have seizure exacerbation conforming with one of the three patterns of catamenial epilepsy (Table 5). The number of women with seizure exacerbation, however, decreases in relation to the level of exacerbation in the form of an S-shaped curve (Fig. 4), so that a point of inflection can be calculated for each catamenial pattern of seizure exacerbation. These points, all of which correspond approximately to a twofold (1.62–1.83) multiple of the seizure frequency of the combined F and L phases (Fig. 4), may distinguish women with high and low seizure sensitivity to cyclic and, presumably, hormonal changes. By this criterion, approximately one third of the women showed at least a twofold increase in average daily seizure frequency.

DISCUSSION

Our findings lend support to the concept of catamenial epilepsy and the existence of at least three distinct patterns of seizure exacerbation in relation to the menstrual cycle: (a) perimenstrual (C1, days -3 to 3) and (b) peri-ovulatory (C2, days 10 to -13) in normal cycles, and (c) luteal (C3, days 10 to 3) in inadequate luteal phase cycles. These three patterns can be demonstrated simply

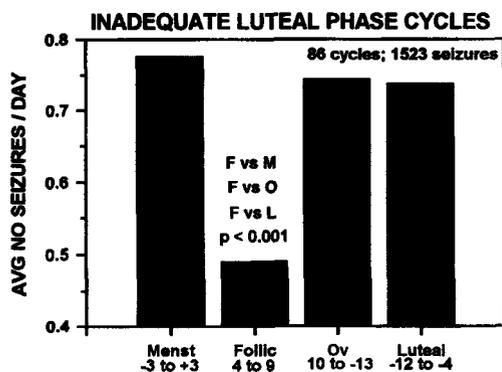


FIG. 3. The average number of daily complex partial and secondarily generalized seizures recorded during 86 inadequate luteal phase cycles was significantly lower ($p < 0.001$) during the midfollicular (F) phase (0.49) than during any other phase [menstrual (M) = 0.78; ovulatory (O) = 0.74; luteal (L) = 0.74] considered separately or combined.

Frequency of Women with Catamenial Epilepsy

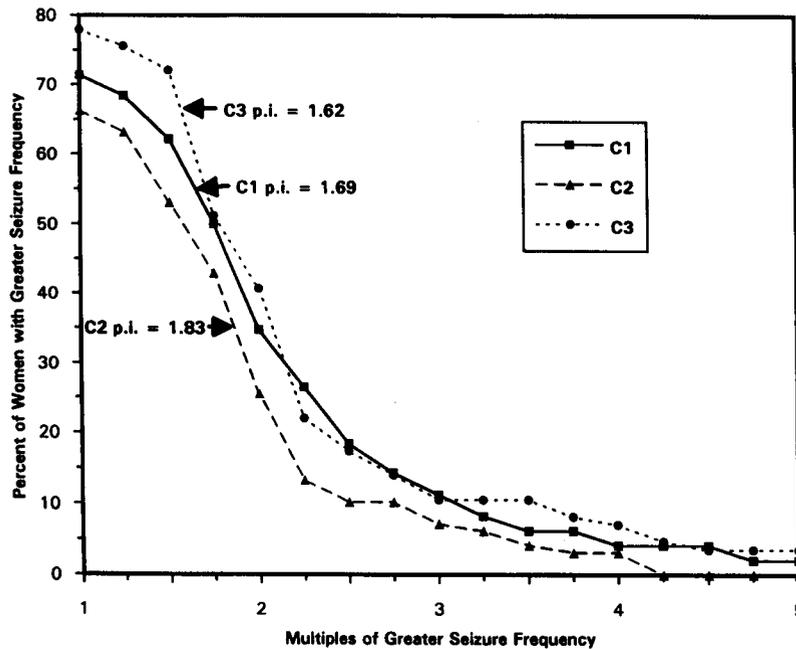


FIG. 4. A plot of the percentage of women with greater seizure frequency during phases of seizure exacerbation in each of the three patterns of catamenial epilepsy (C1, C2, and C3) versus multiples of greater seizure frequency yielded three descending S-shaped curves. Points of inflection (p.i.) were calculated for optimal distinction between women with high and low susceptibility to menstrual cycle and, presumably, hormonal influences on seizure occurrence. A twofold increase in average daily seizure frequency during phases of seizure exacerbation is proposed for the designation of catamenial epilepsy.

by charting menses and seizures and obtaining a midluteal phase serum progesterone level to distinguish between normal and inadequate luteal phase cycles.

The analysis of data allows for variable cycle intervals by fixing the luteal phase duration at 14 days and attributing the variability in total number of cycle days to the ovulatory phase (days 10 to -13). This can be done since (a) ovulation, when it occurs, generally does so 14 days before menstruation; and (b) a progressive preovulatory increase in serum estradiol is almost always present by day 10 and lasts until the day of ovulation in the 23- to 35-day cycles under consideration, thereby conferring an epileptogenic effect throughout this phase (C2) regardless of its precise duration. We considered only 23- to 35-day cycle intervals because of the difficulty in distinguishing cycle phases in shorter and longer cycles on the basis of a single day 22 progesterone determination.

We evaluated only one complete cycle in each woman because only one day-22 serum progesterone level was obtained in the women whose data were considered. Al-

though this design gives equal weight to the overall contribution of each subject in the statistical analysis, it does not provide information regarding the consistency of exacerbation patterns in any one subject.

Both CPS and secondarily generalized seizures showed all three patterns of catamenial seizure exacerbation. In contrast, Backstrom (18) reported catamenial periodicity only for generalized seizures and Helmchen et al. (30) noted it only for partial seizures. In the present study, average daily seizure frequency per woman was 1.47 times greater in inadequate luteal phase cycles (0.691) than in normal (0.469) cycles, and secondarily generalized seizures occurred with almost threefold greater average daily seizure frequency in inadequate luteal phase cycles (0.230) than in normal (0.079) cycles. These findings are consistent with previous observations of greater seizure frequency during inadequate luteal phase cycles (18,23) and lend support to the need for the further investigation of progesterone and its metabolites

TABLE 3. Distribution of AED regimens among women with normal and ILP cycles

AED	Normal, n (%)	ILP, n (%)
Carbamazepine	20 (54.1)	17 (45.9)
Phenytoin	19 (59.4)	13 (40.6)
Valproate	12 (42.9)	16 (57.1)
Barbiturate	6 (60.0)	4 (40.0)
Benzodiazepine	3 (50.0)	3 (50.0)
Polytherapy	38 (53.5)	33 (46.5)

AED, antiepileptic drug; ILP, inadequate luteal phase.

TABLE 4. Distribution of AED regimen in relation to catamenial epilepsy patterns

AED	C1, n(%)	C2	C3
Carbamazepine	15 (75.0)	15 (75.0)	13 (76.5)
Phenytoin	14 (73.7)	13 (68.4)	10 (76.9)
Valproate	9 (75.0)	8 (66.7)	13 (81.3)
Barbiturate	4 (66.7)	4 (66.7)	3 (75.0)
Benzodiazepine	2 (66.7)	2 (66.7)	2 (66.7)
Polytherapy	26 (68.4)	25 (65.8)	26 (78.8)

C1-C3, three patterns of catamenial epilepsy; other abbreviations as in Table 1.

TABLE 5. Occurrence of the three patterns of catamenial epilepsy

Average daily seizure frequency	C1, normal M versus F and L (%)	C2, normal O versus F and L (%)	C3, ILP: M, O and L versus F (%)
>	71.4	68.4	77.9
2×	34.7	25.5	40.7
3×	11.2	7.1	10.5

Abbreviations as in Tables 1 and 4.

in the treatment of intractable seizures (31). Our findings, however, may also be consistent with the possibility that seizures disrupt the normal neuroendocrine modulation of reproductive hormonal secretion and lead to development of reproductive endocrine disorders, menstrual disorders, and infertility (32).

Our results do not show any statistically significant relationship between AED type and the frequency of inadequate luteal phase cycles (Table 3) or patterns of catamenial seizure exacerbation (Table 4). Small numbers in most AED groups, however, preclude a firm negative conclusion. Despite reports of greater (30), lesser (33), and unchanged (2) regularity in seizure occurrence in patients receiving AEDs, in our patients the three catamenial patterns occurred with all types of AED regimens, including both enzyme-inducing and enzyme-retarding varieties. Untreated women were excluded from the investigation.

Each of the three proposed patterns of seizure exacerbation extends beyond the hormonal changes that are postulated to produce it. The designation of C1, for example, as day -3 to 3, includes ≥ 3 days beyond the duration of progesterone withdrawal. Likewise, C2 extends beyond the preovulatory surge of estradiol and ovulatory onset of greater progesterone secretion. C3, like C1, appears to involve the early days of menstruation, a period that extends beyond the withdrawal of progesterone premenstrually. This feature of the proposed patterns of catamenial epilepsy is based on and supported by past clinical observations (1,19,34). One possible explanation is the tendency for seizure clustering, which can imply that "secondary alterations due to a seizure can facilitate the precipitation of a next seizure in the manner of a positive feedback mechanism" (2). Another consideration is that neuroactive steroids may have the capacity to produce changes in the structure and biological activity of surface neuronal excitatory and inhibitory receptors which outlast the brief duration of the hormone-receptor interaction. Specifically, allosterically induced changes may occur in receptor binding, conductance, and subunit composition (35-37), as may morphological changes in hippocampal dendritic spines and synapses (38,39).

Because no single generally used definition of catamenial epilepsy exists, we propose an approach to defi-

nition from the perspective of the severity of seizure exacerbation requisite to qualify for catamenial designation. Table 5 shows that the greater the increase in seizure frequency required to qualify for the designation of a catamenial pattern of seizure exacerbation, the fewer the women who qualify. For example, in a consideration of CPS and generalized seizures together, 71.4% of women in our study qualify as having C1 pattern of seizure exacerbation if they require only a greater average daily seizure frequency during the M phase than during the F and L phases. In contrast, fewer women (34.7%) qualify if a twofold increase in seizure frequency is required and only 11.2% qualify if a threefold increase is required (Table 5).

This type of analysis helps clarify some of the apparent discrepancies in the literature regarding seizure exacerbation at the time of menstruation. For example, our value of 71.4% is similar to the values of 78% of Tauboll et al. (2), 72% of Laidlaw (19), 67% of Rosciszewska (24), and 63% of Ansell and Clarke (25), all of whom used a simply "greater than" criterion for the designation of catamenial epilepsy. In contrast, Duncan et al. (27), who identified 12.5% of women as having catamenial epilepsy, established an approximately sixfold increase in average daily seizure frequency by requiring that three quarters of seizures occur during a 10-day period around menstruation for the designation. Dickerson (28), who reported that only 10% of epileptic women had menstrual seizure exacerbation, studied a chronically institutionalized population with "marked menstrual irregularity." Such irregular cycles are likely to have inadequate luteal phase and would therefore not be expected to show seizure exacerbation only in the menstrual phase (C1) rather than in the entire luteal phase (C3).

Although the precise definition of catamenial epilepsy remains arbitrary, one may maximize the efficiency of distinguishing between women whose seizure occurrence shows a high versus low degree of menstrual cycle and, presumably, hormonal sensitivity by using the points of inflection of the distribution curves (Fig. 4). These points are calculated to be in the vicinity of a twofold (1.62-1.83) increase in seizure frequency for the phases under consideration in comparison to baseline phases. We therefore propose a twofold increase in average daily seizure frequency during the M phase relative to the F and L phases for the designation of a C1 pattern of catamenial seizure exacerbation and a twofold increase in average daily seizure frequency during the O phase relative to the F and L phases for the designation of a C2 pattern of catamenial seizure exacerbation in normal cycles. Similarly, a twofold increase in average daily seizure frequency during the combined O, L, and M phases relative to the F phase should be required for the designation of a C3 pattern of catamenial seizure exac-

erbatation in inadequate luteal phase cycles. By this criterion, approximately one third of women with intractable partial epilepsy would qualify for the designation of catamenial epilepsy. Adoption of a standard, although arbitrary, nomenclature may provide greater uniformity to study designs for investigation of the pathogenesis and treatment of catamenial seizure exacerbation.

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