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EPILEPTIC SEIZURES IN WOMEN RELATED TO PLASMA ESTROGEN AND PROGESTERONE DURING THE MENSTRUAL CYCLE

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ABSTRACT

Nine periods in seven women with partial epilepsy have been investigated with respect to frequency of fits, and estrogen-progesterone levels in blood plasma. Six cycles with ovulation showed a positive correlation between the number of secondary generalized seizures and the mean estrogen/progesterone (E/P) ratios and a negative correlation to plasma progesterone levels. Three periods without ovulation showed an increase in the number of fits during days of high estrogen. The number of fits seemed not to be correlated to changes in body weight.

It is generally accepted that an increased frequency of epileptic seizures may occur in conjunction with the menstruation of women (*Gowers* 1885, *Laidlaw* 1965). Given this situation it is not unreasonable to suspect that hormonal variations which normally take place during the menstrual cycle may in fact influence the frequency of seizures. The importance of estrogen and progesterone in this context has already been indicated. *Logothetis et al.* (1959) gave injections of estrogen to women with epilepsy while recording EEG. The EEG's were found to be activated, i.e. the frequency of spikes increased. Seizures were observed in four out of 16 patients in correlation with injections of estrogen administered, while to acertain extent progesterone seemed dicate a diminished electroshock threshold dependent upon the amount of estrogen administered, while to ascertain extent progesterone seemed to have the opposite effect. The anti-convulsive property of progesterone was additionally confirmed by *Spiegel & Wycis* (1945), as well as by *Costa & Bonnycastle* (1952). A report by *Bäckström & Carstensen* (1974) indicates that women with premenstrual tension have higher estrogen and lower progesterone levels on some days pre-menstrually, and a correlation exists between the degree of anxiety and irritability

and the estrogen level in plasma (*Bäckström & Mattsson* 1975). In considering these findings, the present study investigates whether a corresponding correlation exists between the hormonal levels and the seizure frequency of women with epilepsy.

MATERIAL AND METHODS

Methods

Nine periods in seven patients were investigated. The examination periods were divided into two groups: The first group consisted of six cycles in patients with partial epilepsy and with ovulation, the second consisted of three periods in anovulatory patients (see casuistics).

Procedure of investigation: In order to detect possible variations in seizure frequency during one cycle, patients with a high frequency of seizures in spite of medical treatment were chosen. No other criteria were used. On alternate days during the menstrual cycle the patients were weighed and blood samples were taken in order to determine the hormonal content. Blood samples for phenytoin determinations in serum were taken once a week from all patients, except one (SK), 3–7 hours after the morning dose. Amenorrheic patients were subjected to these checks for a period of 1 month. In patients GA and IW two cycles were studied. The rest of the patients did not want to participate in more than one cycle.

Counting of seizures: All patients are known at the neurological clinic at the University Hospital. They had all had previous experience of keeping a record of their seizures, to be showed at their visits to the clinic. The only new feature was the notification in a special diary described below.

At the start of this study the investigator discussed the features of the seizures with each patient and with at least one near relative. No gross intellectual deterioration that invalidated the counting of seizures was noted in any of the patients, excluding MS. The seizure types, as indicated in the casuistics section, are those given by the patient and her relative. The number of seizures per day was recorded by the patient, aided by near relatives. The seizures were noted in a special diary that the patient carried throughout the day. The patients were asked to make notes in their diaries after every seizure and at the same time to indicate the type of seizure as agreed at the beginning of the investigation. A detailed description of each type of seizure was written in the diary under an appropriate head line in order to aid the patient's memory. One patient, EL, who had a large number of partial seizures, carried a handoperated counter. She also frequently had series of three or more generalized seizures, in Figure 7 and Tables 1 and 2, considered as three single generalized seizures. IW sometimes had partial seizures during the night. She reported two to four nocturnal seizures on each occasion, in the diagrams always noted as three seizures. In BA the duration of the aura and not the number of her partial seizures was used. The counting of generalized seizures is believed to have been accurate. The counting of partial seizures may not be exact particularly when they occurred at high frequency.

The patients were neither informed of the normal hormonal blood variations during the menstrual cycle, nor when high or low seizure frequency could be expected. Contacts between the patients and the examination leader were limited during the blood sampling period in order to avoid any bias. After the initial talk about the registration of the seizures, no communication about the seizures occurred between the examiner and the patients.

The recorded number of generalized and partial seizures per day are shown together with plasma estrogen and progesterone levels, estrogen/progesterone ratios, and changes in body weight during the menstrual cycle, in figures drawn for individual patients (Figures 1–6 and 8–10).

The number of generalized and partial seizures, plasma estrogen and progesterone levels and the mean E/P ratios, were calculated on each day of the menstrual cycle for patients with ovulation. The number of seizures per day was correlated to the mean hormonal values using product-moment correlation. Since blood samples were taken every other day only, the hormonal values of the missing days were calculated to be the mean of the day before and the day after the missing day. Statistical significance was calculated according to Fisher's Z transformation (*Fisher* 1958). The occurrence of ovulation was anticipated from a subsequent rise in plasma progesterone. The day when plasma progesterone exceeded 2 ng/ml was used as a reference in order to synchronize the cycles.

Ten days of high E/P ratios during the follicular phase were also compared to 10 days of low E/P ratios during the luteal phase of the patients with ovulation (GA. 1, EL, IW. 1, IW. 2, BA and RO). The sum of the generalized and partial seizures during the 10 days of the respective phase were compared. The number of days free from generalized and partial seizure were also compared. The significance of differences were calculated using Wilcoxon's matched-pairs signed rank test (*Siegel* 1956).

Analytic methods: The levels of estrogen and progesterone in plasma were measured with previously described radioimmunological methods (*Bäckström & Carstensen* 1974) except that precipitation with saturated $(NH_4)_2SO_4$ was used instead of charcoal adsorption. The results are presented in pg/ml and ng/ml. Using SI units, 1 pg/ml of estrogen equals 36.7×10^{-13} M and 1 ng/ml of progesterone equals 31.8×10^{-10} M. The phenotoin level in serum was measured using gas chromatography (*Berlin et al.* 1972) and the therapeutic limits were according to *Buchthal & Lennox-Buchthal* (1972). Other anticonvulsive drugs were not measured.

Patients

Since the patients were known at the neurological clinic at the University Hospital, they had already been thoroughly investigated. The classification of epileptic seizures adopted was that of *Gastaut* (1973).

Patients with Ovulation and Partial Epilepsy

GA, age 36 years

Onset of seizures at age 4, following febrile convulsions.

Menarche: age 13, a slight increase in frequency of seizures was noted during puberty.

Examinations: Neurological and physical examination revealed a slight right (rt) hypesthesia and hemiparesis. Radiology: Skull asymmetry of anterior and middle fossae. Electroencephalogram (EEG): focal epileptic discharges at vertex and lt frontal and central regions.

Medication per day: Phenytoin 0.1 g × 2 (Fenantoin®), ACO), phenobarbital 50 mg × 2 (Fenemal®, ACO), carbamazepine 0.2 g × 2 (Tegretol®, Geigy), diazepam 5 mg × 2 (Valium®, Roche).

Present epileptic seizures: Since age 15 the following seizures have been recorded:

1. *Partial seizures:* Prodrome: fatigue. Aura: short sensation of stiffness, electric shocks, or sensations of movements in rt arm, leg and face. Fit: contractions starting in rt arm, rt leg, or simultaneously in both, then spreading to rt side of the face. Usually no loss of consciousness. Duration: < 1 min. Postictally: slight rt-sided hemiparesis.
2. *Atonic seizures:* Usually occurring in the morning or late in the evening. Without aura she falls atonically to the floor. A milder version of these seizures may occur while lying in bed, consisting of a sensation of falling, without loss of consciousness. Duration $\sim$ 1 min. Postictally: immediate recovery.
3. *Secondarily generalized seizures:* Prodrome: feels awkward the day before. Aura: anxiety and fear. Fit: generalized seizure with loss of consciousness, often occurring during sleep. Duration: a few min or more. Postictally: rapid recovery.
4. *Secondarily generalized seizures: Aura:* stiffness in rt arm, followed by a feeling of moving above or under a table, accompanied by a sensation rising from the abdomen up to the head. Fit: becomes stiff and falls, has a short loss of consciousness, may at times have twitches in rt hand. Duration: a few min. Postictally: rapidly recovered.

Other types of partial epileptic seizures have occasionally been observed, They are, however, extremely rare.

Catamenial period: Seizure types 1 and 2 increase in frequency.

Seizures during hormonal investigation period: (Figures 1 and 8). Partial seizure type I in figures = 1 above, type II = 2.

Summary: 36-year-old woman with partial epilepsy since childhood. The seizures and the EEG findings suggest a lt supplementary sensory-motor epilepsy. The seizures increase in frequency during menstruation.

EL, age 18 years

Heredity: no epilepsy in relatives. Birth: umbilical cord twined around neck. She was cyanotic and was given oxygen. Onset of seizures: age 1.

Menarche: age 13, with an increase in earlier observed interictal personality difficulties.

Examinations: She is rt-handed and is mentally slightly retarded. Radiology: Skull: atrophy of rt middle fossa, intracranial calcifications in rt frontal and lt postcentral-parietal regions. Pneumoencephalography (PEG): widening of rt anterior ventricular horn. EEG: rt frontal-temporal epileptic discharges with secondary bilateral discharges. Epileptic activity is also present in lt centro-parietal region.

At age 15 she was operated upon at the Montreal Neurological Institute with a rt frontal lobectomy, removing the frontal intracerebral calcifications. Microscopy: Tuberous sclerosis.

Postoperatively: her interictal personally improved a great deal, the seizures decreased temporarily in severity and frequency, but at present they are principally [illegible]. Present EEG: frequent focal epileptic discharges in the rt

Present epileptic seizures:

1. *Secondarily generalized seizures:* they often start with an urge to void, followed by a generalized flexion seizure. Duration: < 10 min.
2. *Generalized seizures from the onset:* occurring during motor activities. She gets stiff and falls rapidly forward. Duration: a few min.
3. *Atonic seizures:* complete atonia for a few sec, then immediate recovery.
4. *Epigastric seizures:* informs about "jumps" in her stomach, otherwise behaviorally uninfluenced.

Catamenial period: The seizures usually increase in severity and duration.

Seizures during hormonal investigation period: (Figure 2) Sec. gen. serial seizures = 1 and 2 in series consisting of more than three seizures. Sec. gen. single seizures = 1 and 2 occurring at isolated intervals. Partial seizures = 4.

Summary: 18-year-old girl with partial and generalized epilepsy since infancy, due to tuberous sclerosis. Operated upon at age 15 with a rt frontal lobectomy. Postoperatively: improvement in personality and temporary reduction in frequency and severity of seizures. Positive correlation between the seizures and the catamenial period.

IW, age 30 years

Heredity: no epilepsy. Birth and early development normal. Onset of seizures at age 10.

Menarche: age 14, no change of seizures during puberty.

Examinations: EEG: bilateral, side-alternating epileptic discharges in frontal-temporal regions. Midsphenoidal recording shows lt temporal dominance. Long EEG recording (6 h) reveals rt frontal-temporal dominance.

Medication per day: Phenytoin 0.2 g × 2 (Difhydan®, Leo) carbamazepine 0.6 g × 2 (Tegretol®, Geigy), nitrazepam 5 mg × 1 (Mogadon®, Roche).

Present epileptic seizures:

1. *Secondarily generalized seizures:* usually nocturnal. She thrashes herself violently and often falls out of the bed. There is urinary incontinence and unconsciousness. Duration: a few min. Postictally: drowsy.
2. *Partial seizures:* Procedure: feels tense, is anxious, at times depressed and may have a perservering thought: "must not blaspheme God". Aura: a sudden ascending, intense, disagreeable feeling which may start in her toes. Recently frequent déjà-vu sensations. Fit: grimaces, stops her activities, seems absent. Slight twitches in her arms may occur and she cannot talk. Duration less than a min. Postictally: rapidly recovered.
3. *Partial seizures:* Contractures in limbs often occurring at night as under 1. Unable to speak and perform voluntary movements, consciousness retained, no urinary incontinence. Duration: a few sec. Postictally: rapidly recovered.

Catamenial period: No increase in seizure frequency during days of menstruation. Mother of two children, no changes in seizure frequency during pregnancies.

Seizures during hormonal investigation period: (Figures 3 and 4) Sec, gen. seizures = 1, partial seizures = 2 and 3.

Summary: 30-year-old woman, with partial epilepsy presumably of bitemporal origin, mother of two children. No correlation between catamenial period, pregnancies and seizures.

BA, age 21 years

Heredity: no epilepsy. Birth: premature, with postnatal asphyxia. Weight 1,800 g. Onset of seizures at age 3 years.

Menarche: age 13, increase in number of seizures during puberty.

Examinations: Perimetry shows a lower nasal quadrant anopsia, larger on rt side and a lt paracentral scotoma with a large blind spot. Radiology: slight undefined skull asymmetry. EEG: at age 6–11 repeated EEG's showed side-shifting occipital epileptic discharges. At present the EEG (including sphenoidal and sleep recordings) shows rt frontal epileptic discharges.

Medication per day: Phenytoin 0.2 g × 2 (Epanutin®, Parke-Davis).

Present epileptic seizures:

1. *Partial seizures:* Prodrome: feels nervous, depressed or easily irritable up to 1 day before a seizure. Aura: flickering in front of both eyes, lasting up to an hour or longer, feels dizzy and has cardial palpitations. During flickering in front of eyes she experiences a loss of hearing and feels empty in her head. Fit: minimal twitches may be visible in the eyelids and in the extremities and her face flushes. She may answer correctly during the attack and usually goes to bed while having a fit. No incontinence. Duration 5–10 min. Postictally: tired, but has no aphasia.
2. *Secondarily generalized seizures:* Aura: feeling of nausea, may cry "it comes", then she has a tonic-clonic seizure with loss of consciousness and incontinence. Duration, a few minutes. Postictally: tired, but no aphasia.

Catamenial period: The secondarily generalized seizures often occur in connection with the menstruation.

Epileptic seizures during hormonal investigation period: (Figure 5) Sec. gen. seizures = 2. Partial seizures = the duration of visual aura of 1. See METHODS and DISCUSSION.

Summary: 21-year-old woman with partial epilepsy, the neurological findings and the seizures suggest occipital lesions, but the EEG shows a rt frontal focus. Her seizure frequency increases during menstruation.

RO, age 29 years

Heredity: no epilepsy. Birth: rapid birth at home. Umbilical cord twined around the neck, cyanotic. Onset of epilepsy at age 7 months, with rare seizures up to age 11 years.

Menarche: age 17. Increase in seizure frequency during puberty.

Examination: Radiology: PEG: rt ventricular dilatation in the region of trigonum, which is slightly elevated. EEG: shows focal epileptic discharges in the posterior part of the rt frontal region.

Medication per day: Phenytoin 0.2 g × 2 (Epanutin®, Parke-Davis).

Present epileptic seizures:

1. *Partial seizures:* Prodrome: paraesthesias in lt arm for several hours or a whole day. Aura: feels odd in her head or hears a snap. Pulsations in her lt arm with or without paraesthesias in lt hand. Fit: forced forward flexion of the head, the chin to her chest. Both arms are flexed in front of her. Consciousness is retained and she understands what is said to her, but cannot answer. No urinary incontinence. Duration less than a min. Postictally: a slight paresis in lt leg is noticed. These seizures may occur in clusters.

2. *Generalized seizures from the onset:* rapidly becomes unconscious and falls to the ground. Duration a few sec. Postictally rapidly recovered.
3. *Partial seizures:* She may imagine herself standing on a high mountain, then taking a step forward and falling. At other times she may, for a few min, with consciousness retained, see "only black or white in front of her". She tends to avoid strong sunlight. Travelling in a car through an avenue in sunshine, she once had repeated epileptic fits, the details of which are not described.
4. *Partial seizures:* she feels pin-prick in her lt hand or lt leg. Duration: a few min. Postictally: rapidly recovered.

Catamenial period: usually increase in frequency of seizures during the menstruation. Mother of two children, increase in seizure frequency during pregnancies. There are contradictory notes about the effect of contraceptive pills on her epilepsy.

Seizures during hormonal investigation period: (Figure 6). Sec. gen. seizures = 2, partial seizures = 1.

Summary: 29-year-old woman, with partial and generalized epilepsy since infancy, mother of two children. The seizures suggest a rt sensory-motor and a temporo-parietal lesion. The latter is probably due to local atrophy as evidenced by the PEG. EEG shows a rt frontal focus. Increase in seizure frequency during catamenial period and pregnancies.

Patients with Partial Epilepsy but without Ovulation

GA, age 36 years

See casuistics above.

MS, age 37 years

Onset of seizures at age 22.

Menarche: age 17. At the time of menarche her seizures had not yet started.

Subsequent course: At age 25 she was operated upon for a rt-sided extracerebral chordoma extending from the pontine angle to the clivus, elevating the 3rd ventricle but also encroaching upon the cerebellar vermis. The tumor was only partially removed. A Spitz-Holter valve was later inserted. Postoperatively she has anosmia and decreased corneal reflexes. She has been treated on several occasions in a mental hospital because of maniac psychosis.

EEG (during investigation period) showed a generalized unspecific abnormality and paroxysmal-epileptic discharges from the rt frontal and temporal regions.

Medication per day: Phenytoin 0.2 g × 2 (Difhydan®, Leo), primidone 0.25 g × 2 (Mylepsin®, ICI-Pharma), mephenytoin 0.1 g × 2 (Mesantoin®, Sandoz). The low phenytoin levels (see RESULTS) indicate that the patient did not take the medication as prescribed.

Present epileptic seizures:

1. *Partial seizures* without aura. Fit: she becomes pale, has a staring look, gets stiff and then behaves automatically, getting aggressive. Duration a few min. Postictally: sleepy.
2. *Secondarily generalized seizures:* Prodrome: increasing temperature and shiver-

ing. Aura: ache in her neck and body stiffness. Fit: momentary loss of consciousness and muscle tone, followed by shivering. No incontinence. Duration a few sec. Postictal: sleep up to 20 min.

3. *Partial seizures:* Motor Jacksonian type with jerks in the rt arm and rt side of her face. Occasionally, however, these seizures also occur on the lt side. Duration a few min. Postictally: rt paresis of face and arm. This type of seizure may often be followed by the seizure type described under 1.

Catamenial period: Increase in seizure frequency during the menstruation. She has been amenorrheic for long periods since age 22 when her seizures started. She has been amenorrheic now for 3 years.

Seizures during hormonal investigation period: (Figure 9) Due to the mental state of this patient the seizure registrations were performed by her mother, with whom MS stayed. MS was, however, not psychotic during this period. Sec. gen. seizures = 2, partial seizures = 1.

Summary: 37-year-old woman with partial and secondary generalized epilepsy since age 22 due to a rt extracerebral basal chordoma, partially removed at age 25. Her present seizures and EEG findings suggest a rt frontal-central-temporal lesion. She has been amenorrheic since age 34. Previously increase in the seizure frequency during the catamenial period. She is periodically psychotic.

SK, age 45 years

At age 5 two head traumas: fell from 2 m's height. Unconsciousness for some min. Onset of seizures at age 7.

Menarche: age 14 years. Slight increase in seizure frequency during puberty.

Examinations: EEG: Focal epileptic discharges in the lt frontal-temporal region, and episodic bilateral synchronous discharges. Photic stimulation does not induce epileptic discharges.

Medication per day: Phenytoin 0.1 g × 3 (Epanutin®, Parke-Davis), carbamazepine 0.2 g × 4 (Tegretol®, Geigy), phenobarbital 0.1 g × 1 (Fenemal®, ACO).

Present epileptic seizures:

1. *Partial seizures:* Prodrome: she often has diarrhoea, feels stingy, cannot tolerate flickering lights or noices, nor is she able to read for some time. Aura: sensation of pressure in rt eye or a visual aura during which she sees a red spiral or a reddish carpet or experiences a changed perception of light. Fit: becomes pale, coughs, smacks her lips and strokes her hair with the rt hand. She may then walk around, stumbling over objects. She does experience the surroundings during the attack but is unable to answer. No incontinence. Duration a few min. Postictally: no aphasia.
2. *Secondarily generalized seizures:* Occasionally the aura and fit described in 1. is followed by a tonic-clonic seizure during which she may defecate. No urinary incontinence, but loss of consciousness. Duration a few min. Postictally: sleepy.

   Sometimes the patient may only have an aura. This, however, has not occurred during the hormonal investigation period.

Catamenial period: Usually there was an increase in seizure frequency a few days before and during menstruation. At the time of hormonal investigation the patient had been amenorrheic for 3 months.

Seizures during hormonal investigation period: (Figure 10). Sec. gen. seizures = 2. Partial seizures = 1.

Summary: 45-year-old woman with partial epilepsy. The seizures and EEG suggest a lt frontal and a temporal lesion, possibly involving part of the visual radiation. At present she is amenorrheic, but previously the seizure frequency increased during the catamenial period.

RESULTS

The results are presented in one Figure for each investigation period. The frequency of different seizure types is indicated. Plasma levels of estrogen and progesterone, the estrogen/progesterone ratio, serum phenytoin and body weight changes are also shown. A comparison is made between changes in the hormonal parameters and frequency of different types of seizures. Increases and decreases in seizure frequency are indicated during high or low plasma levels of the hormones. Serum phenytoin and body weight changes are also observed in correlation with seizure frequency.

A. Patients with Ovulation

GA. (Figure 1). GA's plasma estrogen variations during the studied menstrual cycle were normal. The progesterone levels immediately subsequent to ovulation remained between 4–8 ng/ml for 6 days before the plasma levels reached maximum, which may be of importance regarding the effects on the seizure frequency.

During the first days of the cycle there was an increase, especially in partial seizure type I frequency, despite the low concentrations of both estrogen and progesterone. A second rise in seizure frequency was seen during the period of low progesterone and high preovulatory estrogen, particularly in partial seizures type II. After a decrease in frequency during the days of estrogen decrease, around day 15 of the cycle, the frequency of both types of partial seizures rose concomitantly with a rise in estrogen. After some days of increase there was a drop in the seizure rate, first seen in type II and then in type I partial seizures. During the same days plasma progesterone had reached its maximum.

The hormonal changes indicate an activating effect of estrogen and an ameliorating effect of progesterone on the seizure frequency.

Phenytoin in serum showed only small variations and was at the upper therapeutic limit.

There was a stepwise decrease in body weight throughout the cycle of about 2 kg. The steepest decrease was observed between day 9 and

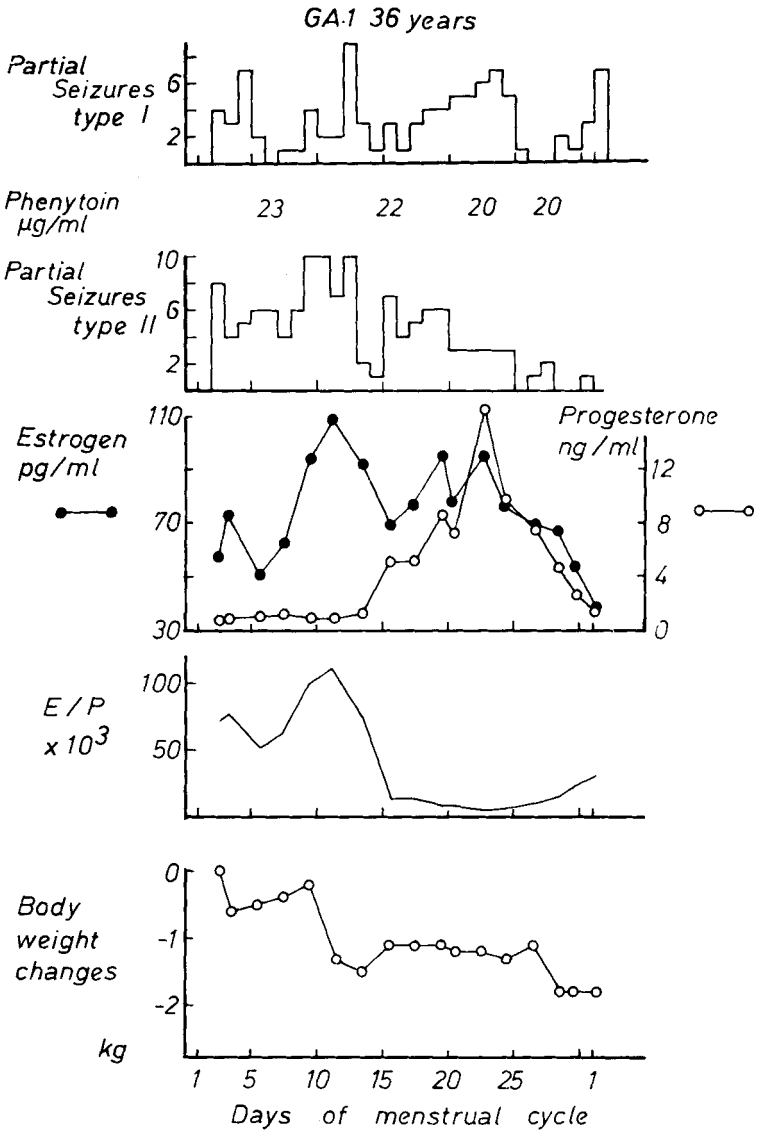

Figure 1.

11, which was concomitant with the preovulatory estrogen peak. There seems to be a tendency towards a positive correlation between partial seizures type II and the changes in body weight.

EL (Figure 2). This patient had somewhat irregular menstrual cycles, the one studied having an excessively long preovulatory phase. Her plasma estrogen levels increased rapidly about day 14 and re-

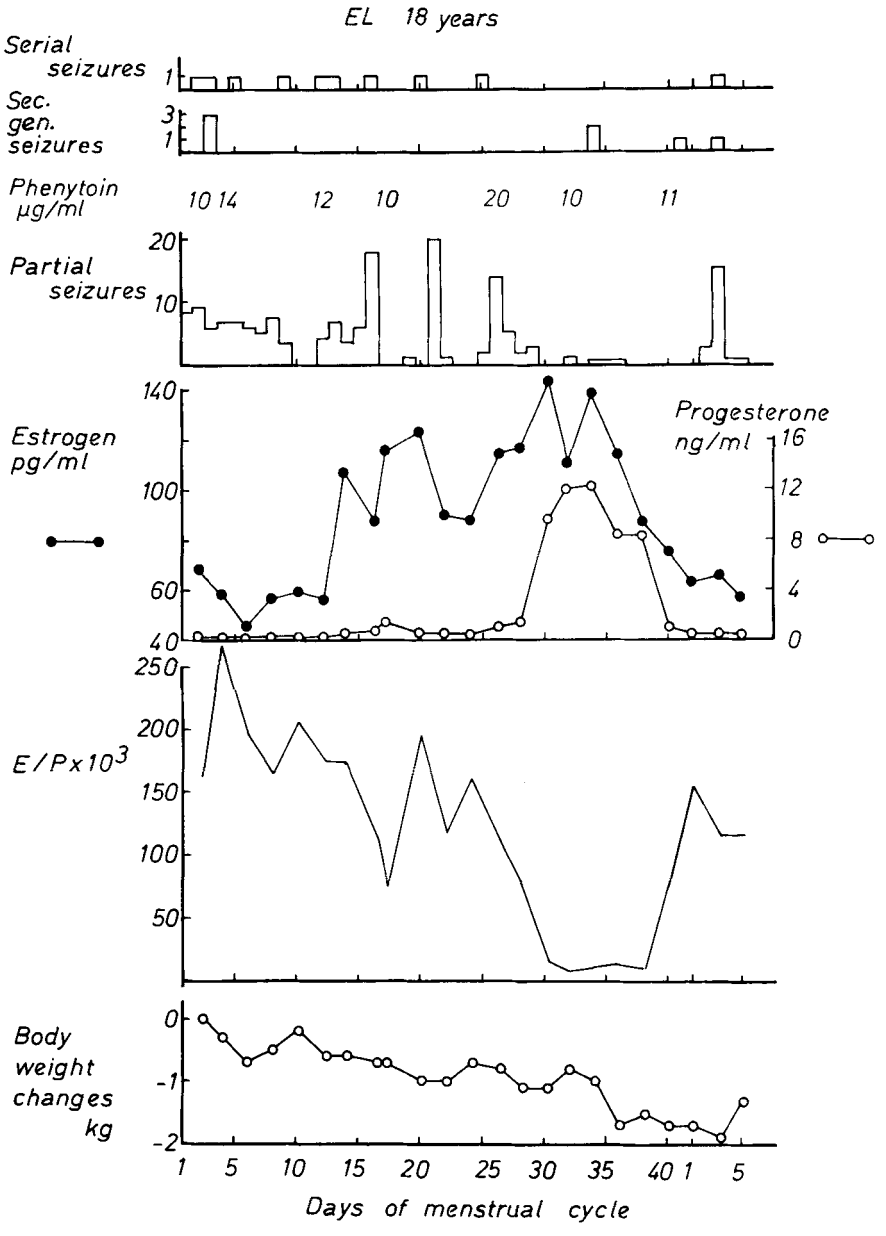

Figure 2.

mained high during the rest of the cycle. When it occurred, the progesterone rise was normal. During this preovulatory phase she had series of generalized seizures every day or at intervals of some days.

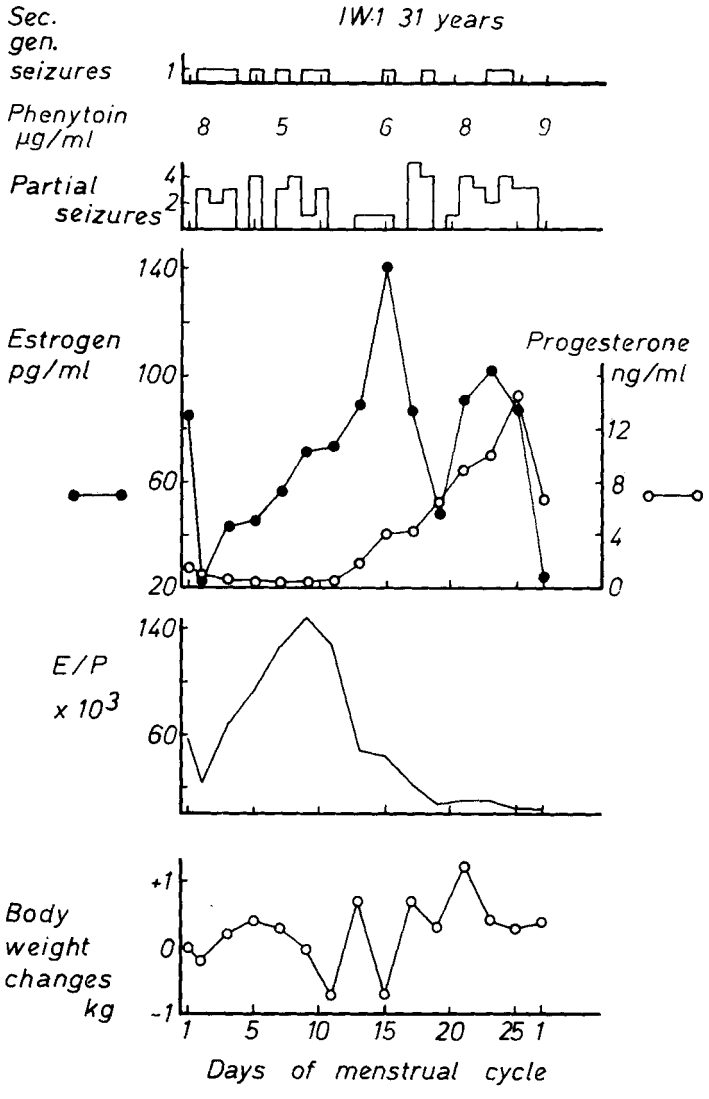

Figure 3.

The series of generalized seizures stopped completely during the luteal phase when the progesterone levels started to rise. She had a few single generalized seizures during the luteal phase and during the menstruations. The number of partial seizures is rather high during the first days of the cycle. During the preovulatory period, at high estrogen levels, a great number of partial seizures were seen, especially on days

16, 21 and 25. When the progesterone levels rose above 2 ng/ml the number of partial seizures decreased.

An ameliorating effect of progesterone on both generalized and partial seizures is likely in this patient.

Phenytoin in serum was within therapeutic levels and showed small variations except on one occasion when the level was doubled, probably caused by an experimental error.

The body weight decreased stepwise throughout the cycle by about 2 kg, it showed no correlation to the seizure frequency.

IW. 1 (Figure 3). Two cycles were studied in this patient. They were both characterized by a climbing progesterone rise. The preovulatory estrogen pattern was normal. However, the luteal estrogen rise was of short duration, only 8 days. In the first cycle she had frequent generalized convulsions during the preovulatory period. During the time of increasing progesterone levels the number of generalized seizures decreased, but did not disappear. The number of partial seizures was high throughout the cycle, and seemingly unaffected by estrogen or progesterone.

Progesterone in this patient seems to have an ameliorating effect on the frequency of generalized seizures, but not on the frequency of partial seizures.

Phenytoin in serum was low and showed small variations only but these were under the therapeutic limit.

The body weight changes were irregular and insignificant.

IW. 2 (Figure 4). This second cycle studied in IW started with decreasing estrogen and progesterone levels. The preovulatory estrogen increase was rapid. In the luteal phase the estrogen rise was of short duration and the levels reached were rather low. Progesterone concentrations showed the same pattern as in the previous cycle. The only generalized seizures occurred when the E/P ratio was elevated. No generalized seizures appeared at high plasma progesterone levels. At this time, however, she had partial seizures every day. In the middle of the cycle, the day after the estrogen peak, a great number of partial seizures occurred. During the luteal phase with both high estrogen and progesterone levels there were also partial seizures every day.

In this cycle the findings point to an ameliorating effect on progesterone on the generalized seizures. An activating effect of the number of partial seizures by estrogen is also probable.

Phenytoin in serum was low and showed small variations, but these were below the therapeutic limit.

She increased about 2 kg in body weight from day 14 to day 26

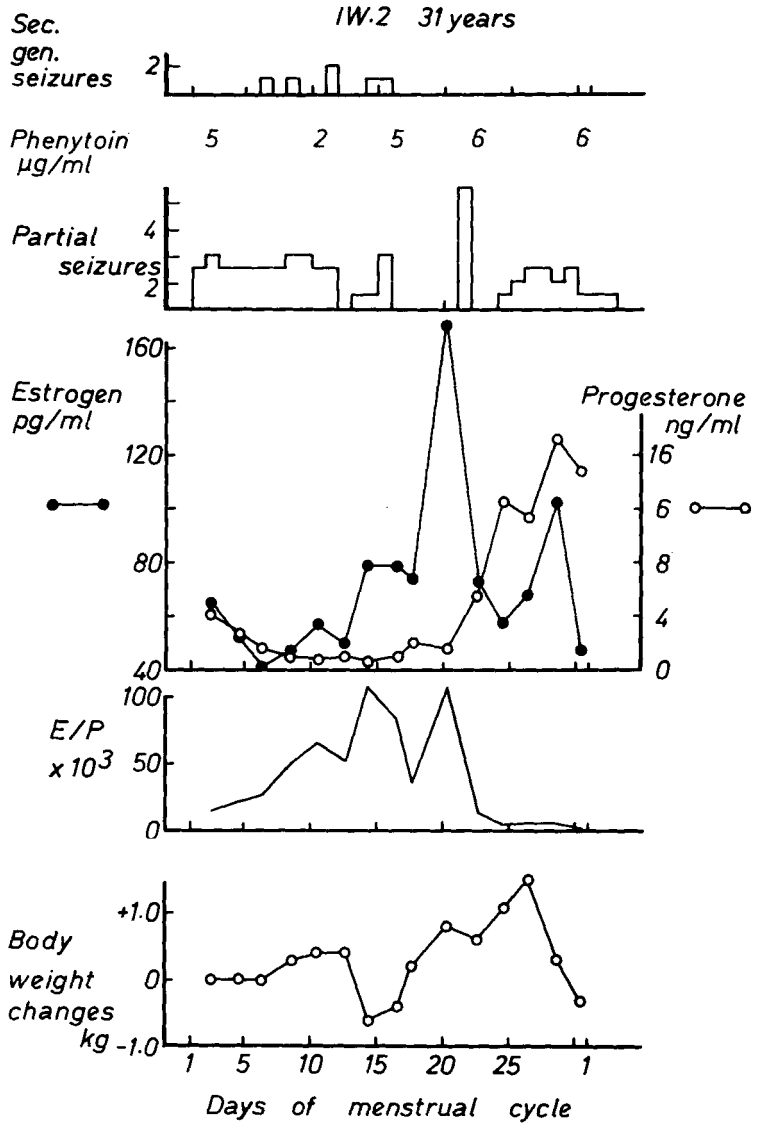

Figure 4.

concomitant with the progesterone rise, however, there was no correlation to the seizure frequency.

Summary (IW. 1 and IW. 2).

Both cycles had a climbing progesterone increase during the luteal

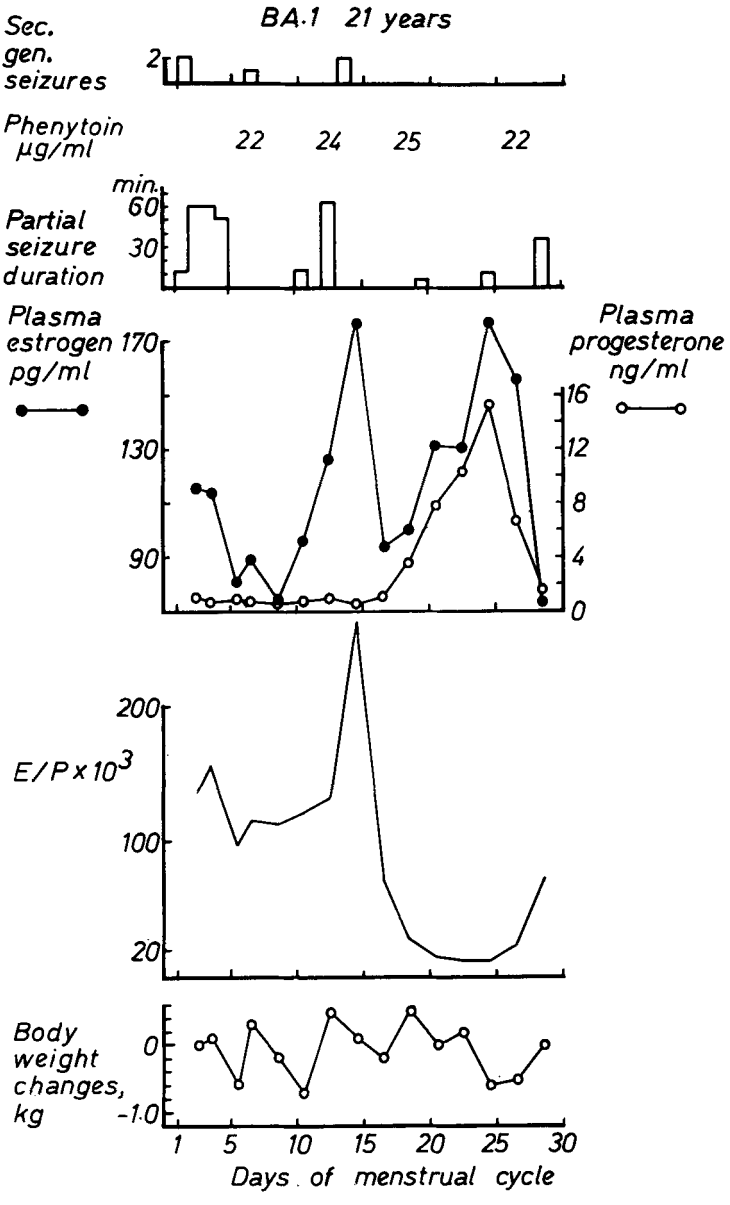

Figure 5.

phases. The luteal estrogen increase was of short duration with rather low levels. In both cycles the generalized seizures seemed to have been ameliorated by progesterone especially in cycle two.

The frequency of partial seizures was, however, unaffected by

progesterone in both cycles. A few days after the preovulatory estrogen peak a high frequency of partial seizures occurred in both cycles especially in cycle IW. 2.

Phenytoin in serum was below the therapeutic limit in both cycles and the partial seizures seemed to be unaffected by progesterone. If this indicates any correlation it cannot be concluded from this patient.

BA (Figure 5). The hormonal variations in this cycle were normal. This patient had only five generalized seizures, all appearing in the follicular phase, two on the second day of menstruation and two during the preovulatory estrogen rise. Her epileptic visual disturbances were of longer duration in the preovulatory and luteolytic phases.

In this case the findings also point to a decreased frequency of generalized fits during high concentrations of progesterone, and a shorter duration of her partial seizure aura during high progesterone. Phenytoin in serum was at high therapeutic levels and showed small variations only.

No significant changes were noted in her body weight.

RO (Figure 6). The preovulatory estrogen and the progesterone pattern were normal in the investigated cycle. The luteal phase was characterized by an abnormally low estrogen increase though the progesterone pattern was normal. Generalized seizures occurred in this patient at three distinct periods, one during the menstruation, one during the preovulatory estrogen peak and one in the luteolytic phase. The partial seizures showed a reversed pattern, with few seizures in the beginning of the cycle and seizures every day during the luteal phase.

Progesterone seems to have decreased the frequency of generalized seizures but not that of the partial seizures. The high estrogen levels seem to increase the number of generalized seizures.

Phenytoin reached moderate therapeutic levels in serum.

No body weight changes were noted, except for a temporary fall on one of the days during menses.

Summary; Cycles with Ovulation

In these six cycles the number of secondarily generalized seizures increased in frequency on two occasions during the menstrual cycle (Figure 7). The first increase was at the beginning of the cycle (A, Figure 7), during the days of menstruation, when the levels of both estrogen and progesterone were low, but just after the rapid decrease in the plasma progesterone levels. The second increase (B, Figure 7) occurred during the time of increasing preovulatory estrogen. During the time of high progesterone levels only a few generalized seizures

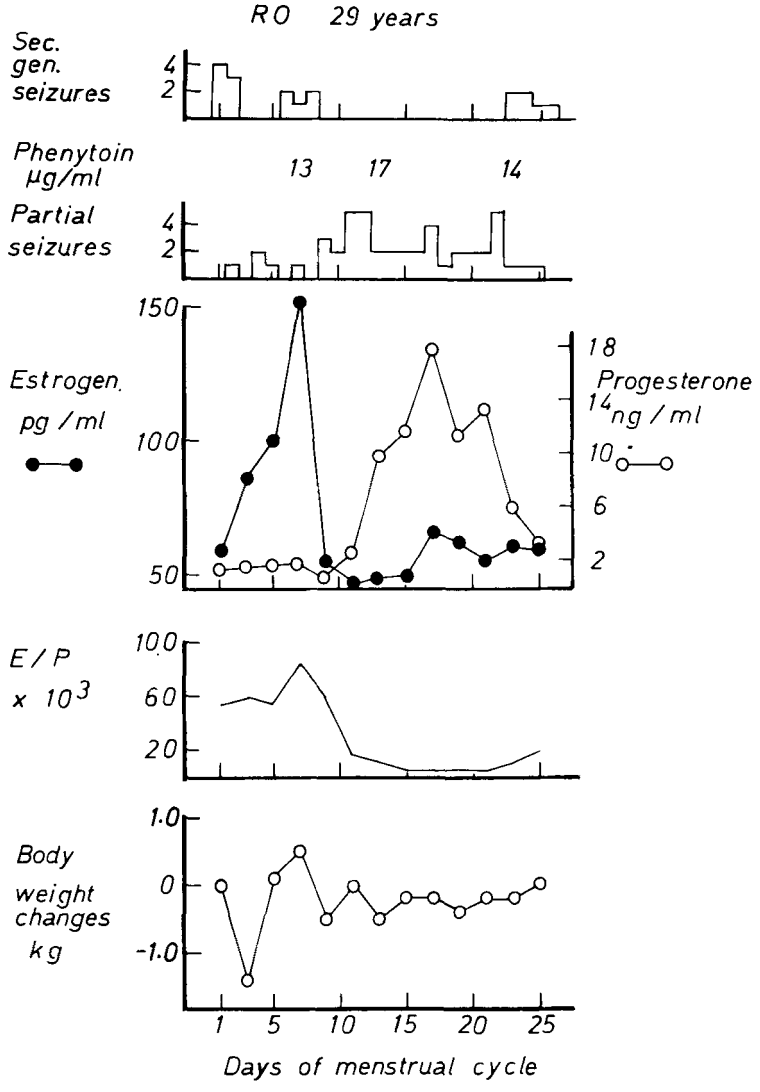

Figure 6.

occurred. There was thus a positive correlation between E/P ratios and the number of generalized seizures per day ($P < 0.005$, Table 1). Furthermore, there was a negative correlation between progesterone levels per day and generalized seizures per day ($P < 0.003$, Table 1). The correlation between the number of generalized seizures and the estrogen levels was also negative ($P < 0.01$, Table 1).

No obvious relationship was seen between the partial seizures and

blood, these workers are also occupationally exposed to mineral oils and their additives. Since some organic components such as methyl n-butyl ketone and hexane may cause polyneuropathy (*Allen et al.* 1975, *Spencer et al.* 1975, *Yamamura* 1969, *Herskowitz et al.* 1971) the development of polyneuropathy in garage workers may be multifactorial.

Our results also confirm the experimental findings of *Schläepffer* (1969) showing that lead intoxication gives rise to a peripheral neuropathy dominated by segmental demyelination and Wallerian degeneration. This idea is experimentally documented, mainly by reduction in conduction velocities.

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B. Patients without Ovulation

GA. 2 (Figure 8). Two cycles were studied in this patient (see GA. 1). The second cycle was remarkably long and therefore the blood sampling was interrupted on the 39th day. The hormonal analysis disclosed a long preovulatory period, and made it probable that she ovulated about day 35. This particular period is included in the unovulatory group because of the long preovulatory phase observed. There were three estrogen peaks during the preovulatory period but progesterone remained low until day 35. In the beginning of the cycle there was an increase in partial seizure frequency during the time when plasma estrogen and progesterone levels were low. After some days, however, the frequency decreased. A second increase in partial seizures was noted when the estrogen levels rose. There was a second decrease in the frequency of fits when the estrogen decreased again. Also during the second estrogen peak the frequency of the partial seizures increased. During a third estrogen peak, however, there was no corresponding increase in seizure frequency.

In general, the findings in this anovulatory cycle indicate that estrogen may increase the frequency of partial seizures.

Phenytoin in serum showed only small variations and was within the therapeutic range. The body weight was mainly unchanged.

MS (Figure 9). This patient has been amenorrheic for 3 years and therefore has variations only in the estrogen levels, the progesterone levels being continuously low. During the first estrogen peak she had a period of several generalized seizures and one partial seizure. During the second estrogen rise she had partial seizures at least once over a period of 4 days. During days 24–30 she had a few partial seizures and one generalized seizure. During this time no increase in estrogen levels was noted. However, changes may have escaped detection because of an interruption in blood sampling for 4 days.

The findings suggest an increase of seizure frequency at high estrogen levels.

Phenytoin in serum was very low or undetectable throughout the period. Only in the first and second sample there were detectable concentrations. (See casuistic section.)

Large fluctuations occurred in her body weight. A tendency towards a negative correlation between seizure frequency and body weight may be seen.

SK (Figure 10). This patient was 45 years old and had been amenorrheic for 3 months. She had low progesterone concentrations throughout the period. During the first days of the period she had decreasing

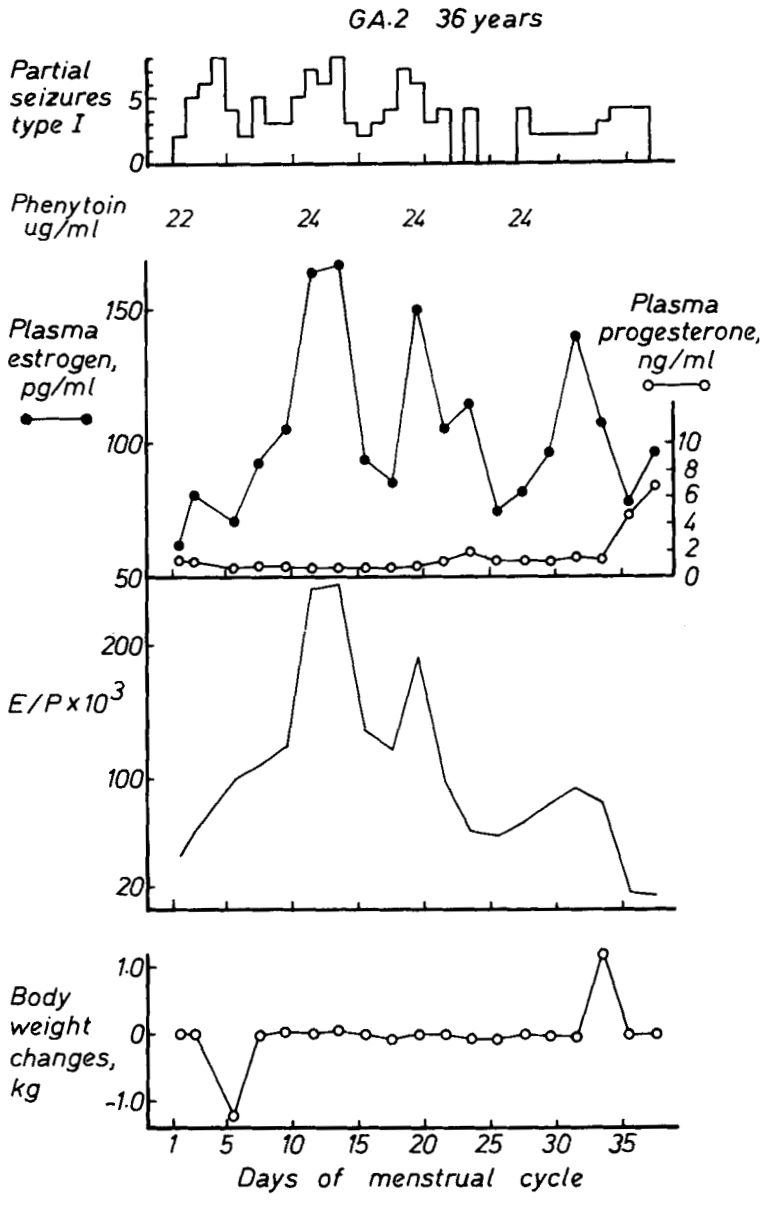

Figure 8.

estrogen levels, then there were several peaks of estrogen with intervals of 7–10 days. She had one generalized and two or more partial seizures every day for 4 days during the early decrease in estrogen levels. On the day of the first estrogen peak she had two generalized

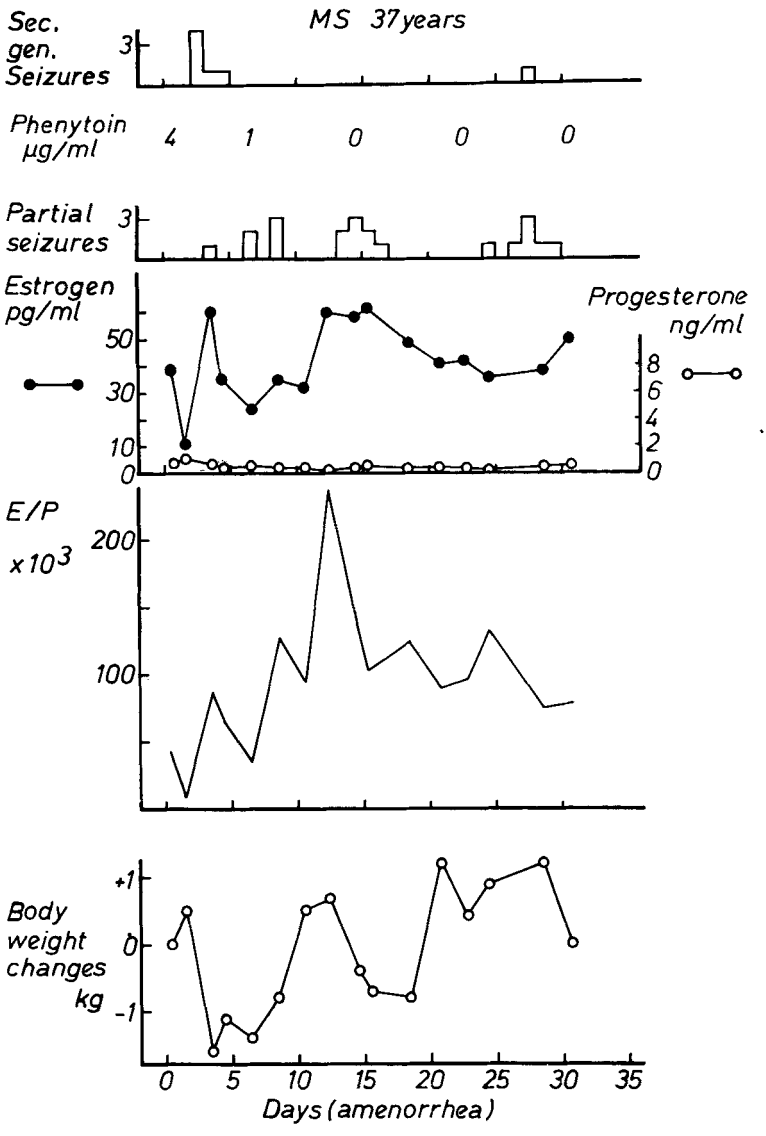

Figure 9.

seizures. During the second estrogen peak she had one generalized and three partial seizures in two days. During the third peak she had seven partial and one generalized seizure and on the day of the fourth estrogen peak, two generalized and two partial seizures were noted.

She had very few partial seizures unrelated to the estrogen peaks

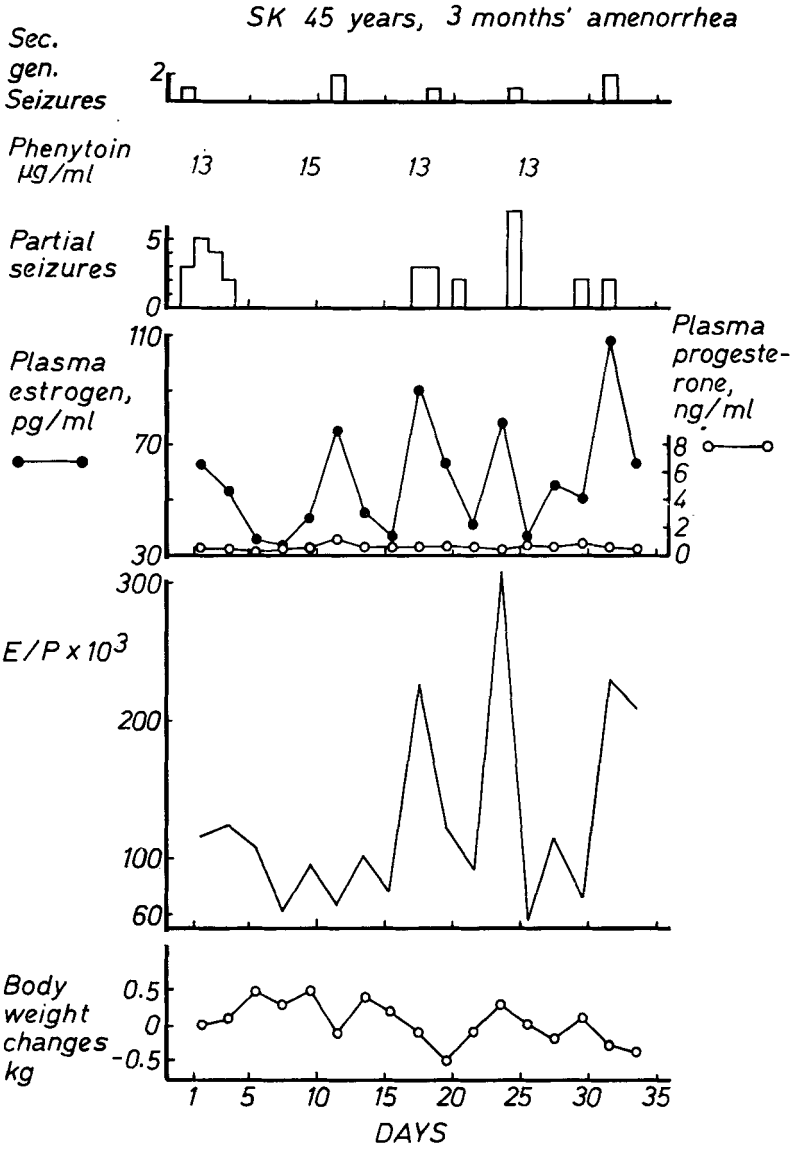

Figure 10.

and no generalized seizures, which indicates an activating effect of estrogen on the seizure frequency.

Phenytoin in serum showed only small variations within the therapeutic range. The body weight showed only small variations.

Summary; Periods without Ovulation

The three periods without ovulation all show variations in plasma estrogen levels, with low and noncluctuating plasma progesterone levels. This makes it easier to recognize effects on seizure frequencies from estrogen alone. It is not necessary to take into account the possible or rebound effects after progesterone. In all three periods there was a positive correlation between plasma estrogen peaks and seizure frequency of both generalized and partial seizures. SK registered only a few seizures which were unrelated to the plasma estrogen peaks. All three periods point in the same direction, indicating an increase in seizure frequency during high plasma estrogen.

DISCUSSION

In a study like this there are inevitably sources of error. The patients themselves have measured the number of fits and no objective registration was made. It had been proved more reliable to have a continuous EEG recording for calculating the number of fits. This was, however, not possible. The errors will be of relevance especially with regard to the number of the partial seizures. Patient IW sometimes did not know if she had had two or four partial seizures. Patient GA, in her second period counted only type I partial seizures. Since the patient's diaries were not checked during the sampling period, this was not discovered until the end of the sampling period. Patient BA had only a few partial seizures. Since the duration of the aura waried a great deal the time of duration has been used in the graphs. The patients may also have forgotten to mark every seizure in the diary. The errors may be of particular importance in phases of high seizure frequency and may obscure an existing correlation between high frequency and high estrogen levels and between high frequency and low progesterone levels. It is unlikely, however, that the patients marked more seizures than they actually had. The relation between E/P ratios and seizure durations might also be influenced, but this was not studied in this investigation, except for some observations on BA who had a longer duration of her aura during the high E/P ratio period.

However, despite these possible errors there is a significant correlation between the mean E/P variations and the number of fits in the patients with ovulation. The results showed that during days of high E/P ratios there is a significantly higher frequency of generalized seizures. On the other hand, during days of low E/P ratios the opposite was observed, as illustrated by the number of seizure-free days.

During high progesterone production there is a decrease in the

number of generalized seizures, followed by an increase when the production of progesterone ceases. This correlates well with *Laidlaw*'s (1956) hypothesis of a rebound after the decrease of progesterone. There is, however, a second peak in the number of generalized seizures during the time of pre-ovulatory estrogen increase. Since the latter coincide with a low concentration of progesterone this supports the hypothesis of an activating effect of estrogen on CNS as suggested by *Logothetis et al.* (1959). The negative correlation observed between the mean estrogen variations and the number of generalized seizures could be explained by an ameliorating effect of progesterone which obscures the effect of estrogen.

Results in favour of the estrogen activation hypothesis are evident in the three patients lacking ovulation, with a greater number of seizures during periods of increased plasma estrogen levels. This is in accordance with animal experiments in which it was found that estrogen lowered the electroshock seizure threshold (*Woolley & Timiras* 1962, *Stitt & Kinnard* 1968), while progesterone raised the seizure threshold (*Woolley & Timiras* 1962, *Spiegel & Wycis* 1945, *Costa & Bonnycastle* 1952).

The positive correlation between the number of partial seizures and E/P ratios was statistically significant but less obvious. The negative correlation between progesterone levels and partial seizures was weaker than that between progesterone and generalized seizures.

The relation between the hormonal status and the occurrence of partial seizures was thus less apparent. In addition, other differences were observed between the patients in this group. In cycle GA. 1 during which only partial seizures occurred, there seemed to be an increase in frequency at high estrogen levels and a decreased frequency at high progesterone levels. A similar pattern of decrease was seen in patient EL, who had both generalized and partial seizures. In patient IW the frequency of partial seizures seemed to be unaffected by progesterone during the luteal phase in the two cycles studied, although there was a decrease in number of generalized seizures. Patient RO behaved differently. She had an increase in number of partial seizures when progesterone levels were high but there were no generalized seizures during this period, which is in line with the observations in the other patients. The differences observed in the relation of partial seizures to the hormonal plasma levels may be related to the location of the epileptic lesions. The present material is too small to allow any conclusions in this respect.

In the etiology of catamenial epilepsy the importance of water retention has frequently been considered. In this investigation, however,

there was no consistent relation between changes in body weight and the number of seizures. Thus no evidence was found indicating a correlation between water retention and frequency of fits. This is also in accordance with the findings of *Ansel & Clark* (1956). Phenytoin in serum was also determined, but only once a week. There is the possibility that the hormones may influence the serum concentration of antiepileptic drugs, as suggested by *Kutt & McDowell* (1968). The hormones may also alter the plasma binding capacity of the antiepileptic drugs. The observed relations between seizure frequency and plasma hormonal levels may therefore act via the antiepileptic drugs. Further investigations are therefore needed to elucidate this possibility. The same reasoning applies also to phenobarbital, the serum concentrations of which should be investigated.

The results obtained here show that during high plasma progesterone levels the number of generalized seizures in female patients with partial epilepsy decreased with a rebound effect at the time of rapid progesterone diminution. Furthermore, during the increase in plasma estrogen the number of generalized seizures concomitantly becomes higher. Furthermore, the frequency of partial seizures in some of the patients seemed to be influenced by estrogen and progesterone in the same way as the generalized seizures. It remains to be shown whether progesterone can be used as a therapeutic drug in female patients with partial epilepsy.

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