PROGESTERONE SUPPOSITORIES AND PESSARIES IN THE TREATMENT OF MENSTRUAL MIGRAINE

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MENSTRUAL MIGRAINE has been known since Hippocrates attributed its symptoms to `agitated blood seeking a way of escape.' The treatment of menstrual migraine with progesterone injections was first described by Singh and his colleagues[14]. This method, which requires frequent intramuscular injections, has been more fully described by Greene and Dalton.[6,19] It was recently shown by Nillius and Johansson[9] that adequate absorption occurs by the rectal and vaginal routes. This has led to the introduction of progesterone suppositories and pessaries, which have revolutionised the treatment of menstrual migraine and their use is evaluated in this paper.

Menstrual migraine is here defined as attacks of severe disabling headaches, always recurring at the same phase of each menstrual cycle. Figure 1 shows the time relationship of migraine to the menstrual cycle in 52 women with menstrual migraine who accurately recorded the dates of their headaches and of menstruation during the months before starting progesterone therapy. Of 512 headaches recorded 36% occurred during the four days immediately before menstruation and 30% occurred during the first four days of menstruation. The highest daily incidence was on the two days immediately preceding menstruation, when 59 headaches were recorded on both days. This is almost a threefold increase on the daily average of 20 headaches.

Menstrual migraine may be provoked by one of three causative factors, tension, water retention or hypoglycaemia.

1. *Tension Migraine,* is usually preceded by one to 14 days of increasingly severe depression, irritability and lethargy finally culminating in a migraine on the immediate premenstrual days or with the onset of menstruation. Occasionally the migraine may be preceded by a day of restless energy of almost manic quality, these are the women who claim they always get a migraine if they 'overdo things.' In the initial case history it is important to note any symptoms of tension, as ideal treatment in these women should include the relief of premenstrual tension as well as of their migraine. They should be asked to mark on a frequency chart the times of tension.

2. *Water Retention Migraine,* in which the attack is preceded or accompanied by weight gain, swollen ankles, bloated abdomen, or breast tenderness. The pain may be concentrated behind the eye, which may appear stony hard during an attack due to the temporary rise in intra-ocular tension during the paramenstruurn.[4] Or there may be nasal obstruction with vacuum headache to engorgement of the sinus membranes.[18]

3. *Hypoglycaemia Migraine.* In these women, going without food for long intervals during the premenstruum may be sufficient to provoke an attack of migraine. Many women manage regularly without breakfast and do a morning's work without food, but it is only during the paramenstruum that this fasting becomes critical and they develop a migraine at midday.

DIAGNOSIS

Two vital diagnostic aids for the task of detecting the precise type of migraine and the operative trigger factor are 'frequency charts' and 'attack forms', which are simple enough for the patient to complete and convey invaluable information to the physician.

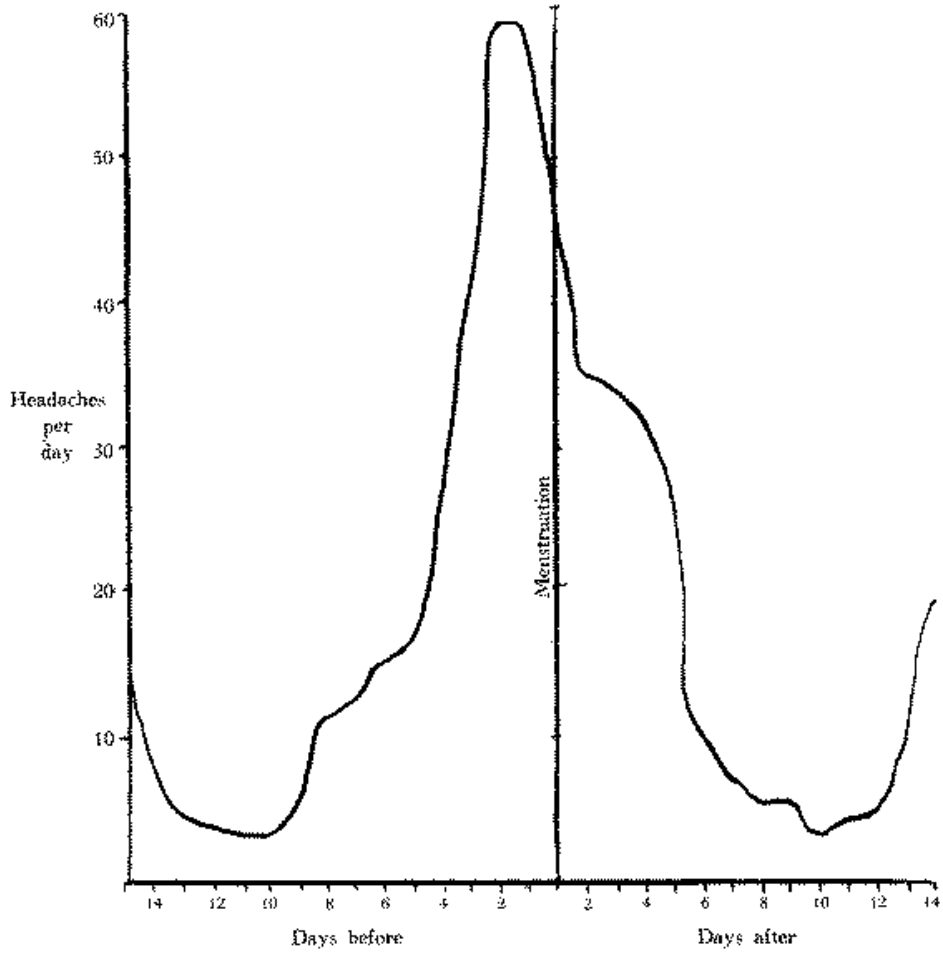

FIG. 1.—Distribution of 512 headaches in relation to menstruation.

Frequency charts enable the physician to establish the day and intensity of each attack, which is marked with an 'H' or 'h' according to severity, and 'P' for period or menstruation. (The letter 'M' is avoided as it could represent both 'migraine' or 'menstruation'). Figures 2-4 demonstrate the charts from three women each with a different presentation time of menstrual migraine. The regular 28 day cycle of a woman taking an estrogen-progestogen contraceptive pill is seen on Figure 4.

Attack Forms (Table 1) are handed out to migraine sufferers, who are asked to complete them in respect of the 24 hours before the onset of an attack, immediately they recover from an attack. The forms give accurate and quick information, which if sought several days later could take time before getting the correct or possibly inaccurate answers. The questions concerning menstruation are worded to cover those having a short cycle of 21 days and a long one of 35 days. The time of onset is helpful in differentiating the types, for water retention migraine tends to wake up the patient in the early hours of the morning or is present on waking. Ten-

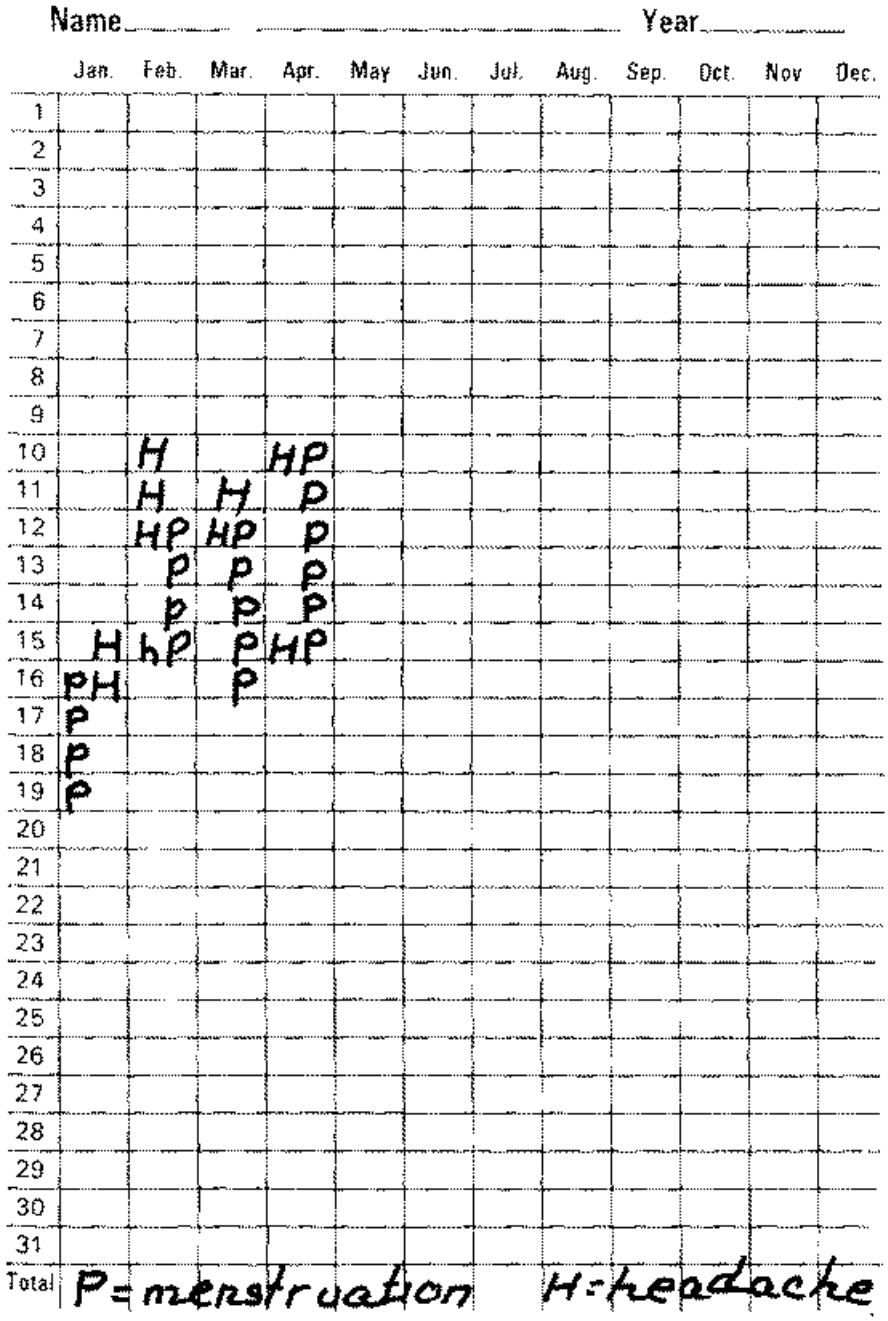

FIGURE 3

sion migraine tends to occur in the evening, and hypoglycemic migraine after an interval of three or more hours without food. The section on itemized food intake and timing, differentiates attacks due to food sensitivities which tend to occur 20 to 24 hours after eating offending foods containing tyramine.[7]

RESULTS

Treatment with progesterone suppositories and pessaries was given to 65 patients, whose frequency chart, covering three months, had confirmed the presence of menstrual migraine. Twenty patients had previously had good control of their menstrual migraine with progesterone injections. Patients were given a choice of the rectal or vaginal route of administration and were started on 200 mg, nocte, but if one method proved unsuccessful or unacceptable another was used. Injections were only used if the other two methods were unsuitable. After three menstrual cycles the patients were assessed and the following three categories of response used:

Good where there had been complete relief of migraine and an acceptable schedule for future treatment found.

Moderate where there had been a reduction in frequency, duration and severity of migraine but not complete abolition; where migraine had been completely abolished but a wholly acceptable method for future treatment had not yet been decided upon; or where additional therapy was required.

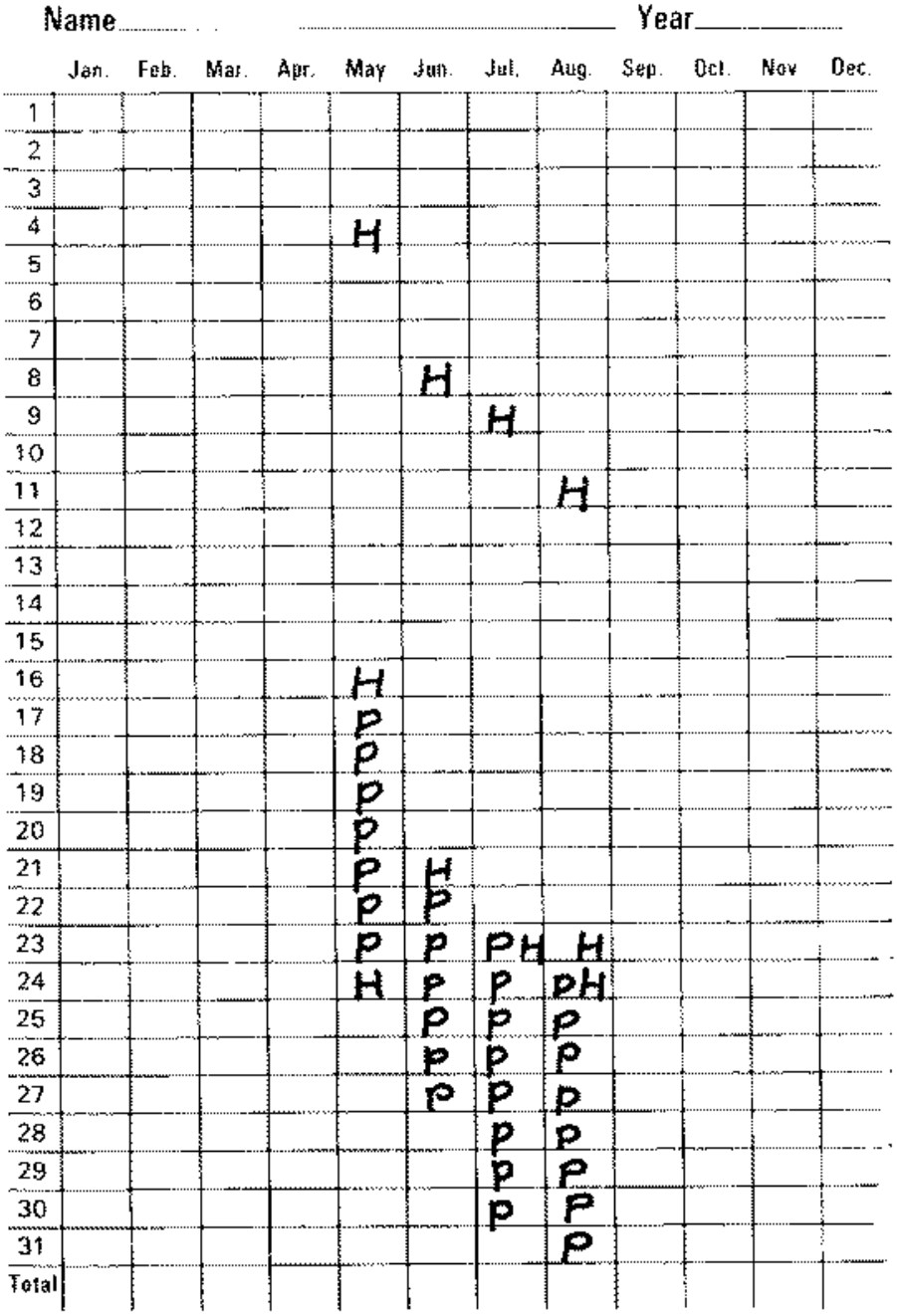

FIGURE 3

Poor where there had been no relief of migraine, or where relief had only occurred with daily progesterone injections which were considered by the patient to be too tiresome for future use and another method of treatment was chosen.

There was a good response to progesterone treatment in 39 women (60%), moderate response in 15 (23%) and poor response in 11 women (17%) (Table 2). Each of the three methods has its advantages and disadvantages. The suppositories can be self administered, although some women have a psychological dislike to inserting them. Suppositories tended to cause diarrhoea 3, anal irritation 2 and flatus 2. The pessaries had a poor absorption in spinsters over 40 years, and there were complaints of difficulty in insertion 3, and dislike of the vaginal discharge 5. Chlorophyll had been added to some pessaries as a deodorant but this green colouring was disliked. The injections usually required dependance on a district nurse, although some managed their own injections or had a skilled husband or friend, who could perform this task daily or on alternate days. The injection needs to be given by deep intramuscular injection into the buttocks, and there were frequent complaints of soreness at the injection site among the thinner women.

Table 3 gives the optimum route of administration in the 34 patients with a good or moderate response. The need for a daily injection was overcome in three women, who were able to have

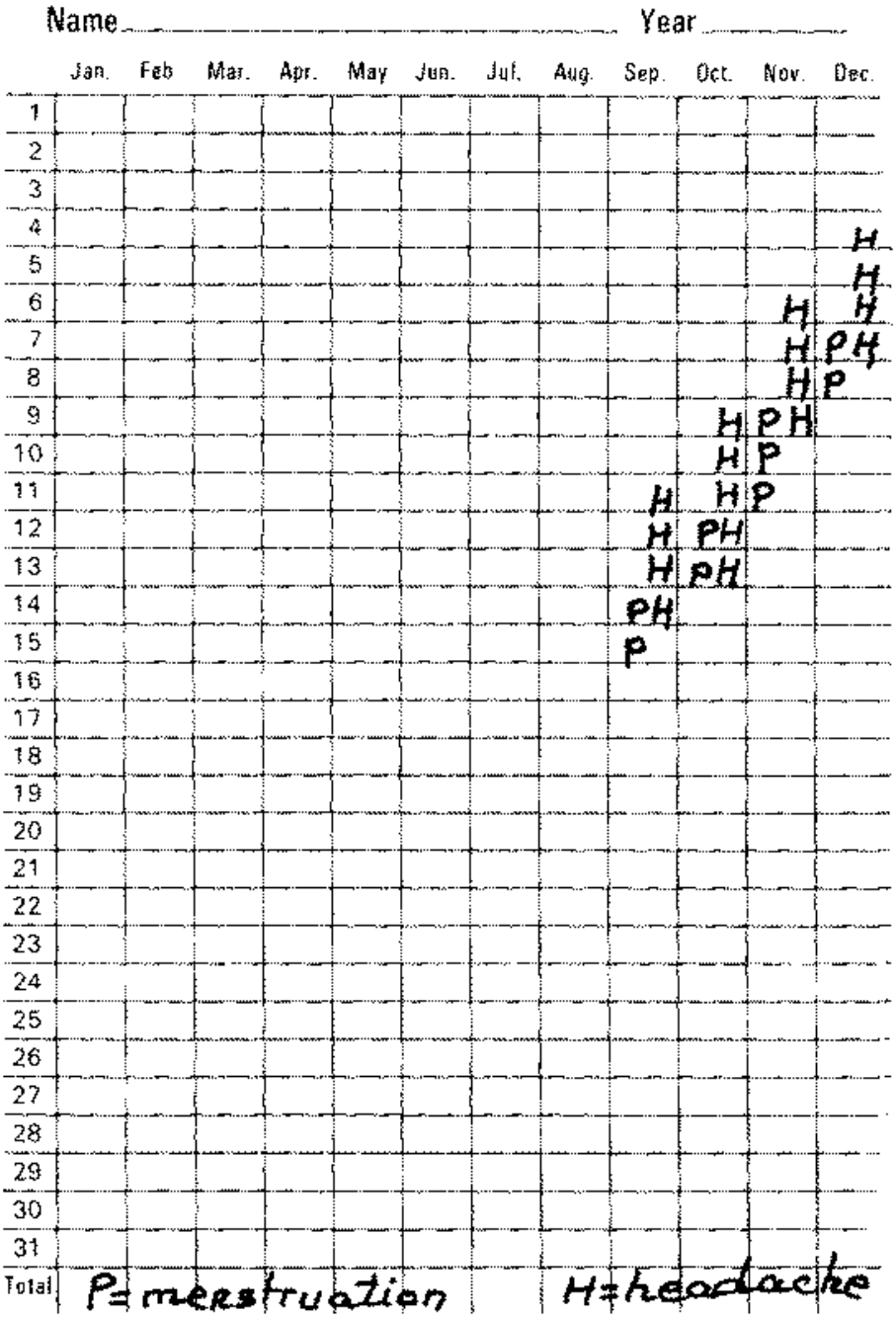

FIGURE 4

an injection and suppository 2, or pessary 1, on alternate days. The dosage and time schedule differed for each individual, being determined by the timing of the symptoms and the length of the menstrual cycle. The same guide lines were used as with the timing of progesterone injections[19], with the usual course being from the 14th day for two weeks. Those with shorter or longer cycles had their course adjusted accordingly. If ovulatory migraine occurred treatment was begun on the 10th day. If the woman was anxious for contraception then the course was started on the 5th day, while if she wished to conceive treatment was started on or after the 18th day. Occasionally treatment postponed the timing of the attack from the paramenstruum to the postmenstruum, in these cases progesterone was continued throughout menstruation in subsequent months. If only partial relief occurred during the first month of treatment the suppositories or pessaries were used morning and night during the subsequent month, whereas if complete relief had occurred the dose was halved or the course shortened, possibly starting on the 21st day instead of the 14th day.

The suppositories and pessaries are available in strengths of 100 and 200mg., but it is quite easy to cut one in half if a smaller dose is required. Many learned to adjust their own dosages, increasing at times of stress or when a migraine appeared imminent. Menopausal women, could sometimes anticipate that they were likely to experience a missed men-

TABLE 1

ATTACK FORM

Name Date Day of week
Time of onset Duration .....
Date last menstruation started .....
Date next menstruation due .....
During the 24 hours *before* the attack:

1. Did you have any special worry, overwork or shock?

2. What had you done during the day?
   Normal work?
   Unusual activity?
   Extra tired?

3. What food had you eaten and when?
   Time Breakfast

   Time Mid-morning
   Time Lunch .....
   .....
   Time Mid-afternoon
   Time Supper
   .....
   Time Evening

   Time Bedtime .....

TABLE 2
Result of Progesterone Therapy

Good	39 patients	60%
Moderate	15 patients	23%
Poor	11 patients	17%
Total	65 patients	100%

struation in one month and would postpone treatment. Each one found her own optimum time in the 24 hours for insertion, many preferring morning. The most frequently successful dosages were suppositories 200mg. die, pessaries 200mg. b.d. and injections 100mg. die. Eighteen of the 20 women who had previously been treated with progesterone preferred either suppositories 13, or pessaries 5, one preferred injections and one was given a progesterone implant.

Nillis and Johannson[9] have shown that the effect of daily progesterone administration is cumulative, therefore it is usually wise to start administration at mid-cycle to have a high enough plasma level during the late premenstruum.

During progesterone therapy other symptomatic treatment was also given. Those with tension migraine sometimes found a mild tranquillizer helpful during the premenstruum. Those with water retention migraine were advised to restrict salt and fluids during the second half of the cycle and some were given a diuretic, during this time. Those with

TABLE 3

Optimum Method of Progesterone Administration

	Good	*Moderate*	*Total*	
	Patients	*Patients*	*Patients*	*%*
Suppositories	22	9	31	57
Pessaries	10	3	13	24
Injections	4	3	7	13
Suppositories and Injections	2	-	2	4
Pessaries and Injections	1	-	1	2
TOTAL	39	15	54	100

hypoglycaemic migraine were advised to avoid an interval without food of longer than three hours during the paramenstruum, thus having mid-morning coffee, afternoon tea and a late night snack in addition to three meals each day. Those worried test these extra snacks would increase their weight were advised that non-fattening foods at frequent intervals would suffice. Otherwise they were taught during the paramenstruum to divide their total daily calorie allowance into six snacks, instead of three meals.

The normal menstruation pattern for each patient was known before the commencement of the trial, and in 18 women there was an alteration, usually postponement of menstruation, during the first course of treatment, but it was possible to correct this in later months. If the progesterone was stopped unexpectedly menstruation was likely to occur within two days, this occurred in those who stopped treatment prematurely due to diarrhoea, vaginal discharge or forgetfulness.

There appears to be a large margin of safety with progestrone. The signs of overdosage, which are rarely encountered, are a dragging pain in the lower abdomen similar to spasmodic dysmenorrhoea, and undue elation or restless tension.

DISCUSSION

The widespread use of progesterone as a method of treatment has been hindered by two factors, firstly the confusion between progesterone and progestones which many think of as synonymous, and secondly the need for frequent deep intramuscular progesterone injections.

Progestogens are synthetic substances having the ability to cause proliferation of oestrogen primed endometrium in the same way as the natural hormone, progesterone. Progestogens may be administered orally, e.g. ethisterone, nor-ethisterone, norgestrel, chlormadinone, or by long acting injections e.g. hydroxyprogesterone caproate, medroxyprogesterone acetate, and many of them are at least ten times more efficacious in this one function than the naturally occurring hormone. However, it is now appreciated that in addition to the ovarian source, progesterone is also formed in the adrenals where it is converted from cholesterol and becomes the precursor of all corticosteroids. Again, progesterone is responsible for the transport of glucocorticoids attached to the alpha-globulin of the plasma. It is one of the few steroids with a high affinity for this binding protein and can cause displacement of cortisol to the free active fraction[20]. These glucocorticoids maintain the liver glycogen and help to maintain the blood sugar levels[13]. Progestogens cannot mimic these actions of progesterone in the synthesis of corticosteroids, nor in the transport of glucocorticoids. Indeed Johansson[8] has shown that progestogens lower the plasma progesterone level. The as-

sociation between menstrual migraine and the administration of oestrogen-progestogen contraceptive pills is well recognised [5,12,17], and it is possible that this is caused by the further lowering of the plasma progesterone level by the progestogens. The failure of progestogens to relieve menstrual migraine[1,2] led to the assumption that there would be a similar failure of the natural hormone, progesterone, while Sachs[21] took it as an indication that the possibility of a specific etiology or treatment for menstrual migraine could be disregarded.

`The Review of Physiological Chemistry"[20] lists some twenty different functions of corticosteroids, but from the etiological angle of menstrual migraine it will only be necessary to consider three, electrolyte metabolism, water retention and glucose metabolism. It would seem that when there is an extra demand for progesterone during the premenstruum a temporary insufficiency may occur of adrenal progesterone resulting in an upset of the corticosteroids concerned with:

1. Electrolyte metabolism, resulting in premenstrual tension, depression, irritability and a tension migraine.

2. Water regulation, which results in a water retention migraine.

3. Glucose metabolism, resulting in a hypoglycaemic migraine.

Menstrual migraine still occurrs cyclically at the menopause, at times of missed menstruation and also following a hysterectomy or oophorectomy[3]. This suggests that the cyclical control of the adrenal progesterone synthesis may be under the control of hypothalamic releasing factors.

Progesterone administered by mouth passes via the portal system to the liver where it is rapidly metabolised. Intra-muscular progesterone has a short half-life time of 20 to 29 minutes[11,16] but Nillius and Johansson found that the plasma progesterone levels remained elevated in most subjects for at least 48 hours, and suggested that during absorption a considerable amount of administered progesterone diffuses into the fat tissues of the body.[10] These depots of progesterone deposited in the fat diffuses into the bloodstream when the plasma levels decline. The disappearance of progesterone after intramuscular injection was found to be slower than after rectal or vaginal administration, which Nillius and Johansson suggest might indicate that the site of injection also serves as a depot for progesterone besides the fat tissue. This view is supported by the clinical observations that injections into the fatty muscles of the buttock cause less local reaction than injections into the thigh or deltoid; progesterone implants are more effective given into the fat of the abdominal wall rather than into the thigh muscles; and soreness at the site of an injection is a more frequent complaint in women with little fat.

The plasma progesterone levels are a reflection of the production of progesterone in the corpus luteum or of the amount circulating in the plasma following administration of exogenous progesterone. It does not monitor the progesterone synthesis within the adrenals. One still awaits a convenient estimation which will reveal those individuals requiring extra progesterone for full adrenal synthesis.

Individuals show marked variations in the duration of menstrual loss, and length of cycle; also in the severity and duration of their attacks of migraine; and the presence or absence of premenstrual tension or water retention. During the pre-menstruum there are marked day-to-day variations in the plasma progesterone levels[15] and in the response to administered progesterone.[9] Therefore it is to be expected that each patient will need to have the duration and dosage of the course of progesterone treatment individually tailored. Somerville[15] treated six patients with menstrual migraine with 25-75 mg. intramuscular progesterone for only 4-5 days before the expected time of an

attack. He eliminated the migraine in one patient, and reduced the duration in a further three. It is reasonable to assume that had Somerville extended the treatment and increased the dosage in his other five patients during the subsequent months of treatment he would have obtained better results.

SUMMARY

Clinical observation assisted by frequency charts enables the relationship between the migraine attack and menstruation to be clearly identified and indicates the time when treatment should begin. An understanding of the role of adrenal progesterone reveals why treatment with progesterone is specific and why progestogens are inadequate. It also illustrates the need for individual tailoring of dosage to ensure an effective response. The ideal treatment is one in which the patient herself can adjust the dosage according to her day-to-day needs. Progesterone suppositories and pessaries fulfill this role.

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Progesterone pessaries and suppositories are available in the U.S. from Mr. Milton Caplan, 424 Equitable Building, Baltimore, Maryland 21202, and in the United Kingdom from Locatell Chemist, 100 Stoke Newington Church Street, London, N. 16.

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