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THE PREMENSTRUAL SYNDROME

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" Premenstrual tension," as it has hitherto been called, is the commonest of the minor endocrine disorders. The fact that a large number of women suffer from a variety of symptoms, unpleasant at their mildest and at their severest incapacitating, during the ultimate seven to ten days of the menstrual cycle is well known ; but in this country very little has been done to alleviate their distress. This is partly due to the attitude of the patients. Just as, before the days of stilboestrol, women in general accepted the unpleasant symptoms of " the change of life " as a necessary part of the business of being a woman, so still they pass through one week of discomfort in every month, usually without complaining to their doctors but not necessarily without disturbing the tranquillity of their homes. The frequency of the condition is testified to by the fact that in one American factory, employing 1,500 women, 36% applied for treatment in the premenstrual phase (Bickers and Woods, 1951). Israel (1938) stated that symptoms of the kind to be described occur in 40% of otherwise healthy women. It is, we are convinced, equally common in this country, and it is therefore curious that, although many papers on the subject have been published in the U.S.A., we have been able to trace only one in a British journal (Singh *et al.*, 1947), which did not refer to British patients.

The term " premenstrual tension " is unsatisfactory, for tension is only one of the many components of the syndrome. Its use has commonly led to a failure to recognize the disorder when tension is absent or is overshadowed by a more serious complaint. We have preferred to use the term " premenstrual syndrome," but as our investigation has progressed it has become clear that this term also is unsatisfactory. Though the syndrome most commonly occurs in the premenstrual phase, similar symptoms occasionally occur at the time of ovulation, in the early part of the menstrual phase, and even, rarely, in the first day or two after the flow has ceased. The term " menstrual syndrome," though correct, for in each individual the symptoms recur at monthly intervals, may wrongly create the impression that they occur only during menstruation. We have finally decided to retain the term " premenstrual syndrome " in the full realization of its imperfection. The full elucidation of its cause may later suggest a more appropriate and more accurate nomenclature.

The Literature

The first description of the syndrome is that of Frank (1931). He records a condition of indescribable tension and a desire to find relief by foolish actions difficult to restrain. There were often severe headaches and palpable oedema, especially of the face, hands, and feet, accompanied by oliguria and an increase in weight. Sometimes there were diffuse spontaneous subcutaneous haemorrhages, asthma, and, in rare instances, epileptiform seizures. All symptoms were rapidly relieved at the onset of the menstrual flow, but recurred at varying times as the end of the cycle drew near. The condition of the patients became worse if the onset of the flow was delayed. Soon other symptoms with a similar periodicity were observed, including a remarkable degree of oedema, which caused, in two cases described by Thomas (1933), a gain in weight of 12 to 14 lb. (5.4 to 6.4 kg.), relieved on the first day of menstruation by a diuresis of 4.5 litres, continued on the succeeding days.

Sweeny (1934) described tightness of the clothing and stiffness of the hands, and found that 30% of 42 healthy women gained 3 lb. (1.4 kg.) or more in the premenstrual phase. Puech (1942) laid stress on premenstrual asthmatic attacks, rhinorrhoea, fever, and lumbar pain. Israel (1938) recorded ulcerative stomatitis and transient nymphomania. Of 38 patients described by Gray (1941), 5 had nymphomania and 15 some form of " psychosexual disorder." Rubenstein (1942) stressed the incapacitating headache common at this time, in one patient associated with abnormal hunger ; and Morton and McGavack (1946) were inclined to associate this with hypoglycaemia. Morton (1946) drew attention to the frequent association of the other symptoms with pain in the breasts.

Stieglitz and Kimble (1949) found, in a series of 67 patients, that 68% suffered from emotional instability, 65% from headache (in 12 instances amounting to typical migraine), 50% from backache, 47% from depression, 36% from aching in the thighs, and 9% from " bloating " of the abdomen. Of Morton's (1950) 29 patients, all had transient emotional instability, and the majority had pain in the breasts, increased appetite, lower abdominal pain, abdominal bloating, and gain in weight. Almost half had palpable oedema, about one-third had

menstrual irregularity, and a few had nausea and vomiting, increased sexual desire, and pruritus vulvae. One patient had headache, papilloedema, vertigo, and projectile vomiting of a degree suggesting an intracranial tumour. Cooke (1945) reported that 84% of crimes of violence by women occurred during or immediately before the menses. Morton *et al.* (1952), in a study of prison inmates, found that crimes of violence had been committed in 62% of the cases in the premenstrual week, in 19% at mid-cycle, in 17% during menstruation, and in 2% after the end of menstruation.

Analysis of 84 Cases of Premenstrual Syndrome

This series contains the histories of 84 cases of premenstrual syndrome which were treated with ethisterone and/or progesterone, and an analysis of results of treatment in 78 cases. All cases were seen between 1948 and 1952 and attended for a follow-up interview in 1952. Of the 84 patients in the series, 16 were first seen in hospital by R. G. Most of the remainder were collected by K. D. in her own practice (which has a National Health panel of 5,000), after the successful treatment of her own case, and were referred to R. G. Sixteen patients were referred to K. D by her fellow general practitioners.

All the cases had attacks of various symptoms, which occurred during the premenstrual phase, during menstruation or ovulation, or at the time of a missed period, and all cases were symptom-free at other times. All cases included in the series had experienced attacks during each of the last three menstrual cycles; thus any chance coincidence between the attack and menstruation was eliminated. Any case in which the time relationship was not definite was temporarily excluded, the patients being treated symptomatically and asked to keep a calendar.

The "presenting" and other symptoms which occurred during attacks are shown in Table I. "Presenting symptoms" always occurred with each attack, but the other symptoms were not necessarily present with each attack. The site of the premenstrual headache in the 58 cases was: bifrontal, 19; hemicranial, 13; bitemporal, 4; between eyes, 1; behind eyes, 1; over one eye, 12; occipital, 4; vertical, 1; not recorded, 3. In 22 cases the severity necessitated rest in bed, and in 10 cases concomitant symptoms made a diagnosis of migraine inevitable. The visual symptoms noted in these 10 cases of migraine were: photophobia, 4; mistiness, 1; hemianopia, 2; burning pain, 2; flashes of light, 1. Table II shows the sites of premenstrual rheumatism, and Table III the types of skin and mucous lesions.

TABLE I.—*Symptoms*

Symptom	Presenting		Other		Total	
Headache	53	63·1%	5	6·0%	58	69·5%
Nausea	2	2·4%	23	27·4%	25	29·7%
Irritability	2	2·4%	3	3·6%	5	6·0%
Depression	1	1·2%	4	4·8%	5	6·0%
Lethargy	—	—	11	13·1%	11	13·1%
Vertigo	1	1·2%	8	9·5%	9	10·6%
"Rheumatism"	5	6·0%	9	10·6%	14	16·7%
Skin and mucosal lesions	9	10·6%	2	2·4%	11	13·1%
Oedema	1	1·2%	4	4·8%	5	6·0%
Rhinorrhoea	3	3·6%	3	3·6%	6	7·2%
Asthma	4	4·8%	—	—	4	4·8%
Epilepsy, petit mal	3	3·6%	1	1·2%	5	6·0%
,, grand mal	—	—	1	1·2%		
Mastalgia	—	—	2	2·4%	2	2·4%

TABLE II.—*Sites of Premenstrual Rheumatism*

	Presenting Symptom	Other Symptoms	Total
Shoulder	1	1	2
Knees	—	1	1
Feet	2	—	2
Sciatica	2	—	2
Lumbago	2	4	6
Hips	—	1	1
Thighs	—	2	2
Neck	—	1	1
Hands	1	—	1
Total	8*	10	18

* Some patients mentioned more than one site.

TABLE III.—*Types of Premenstrual Skin and Mucous Lesions*

Type	Site	Presenting	Other Symptoms	Total
Acne	Face	1	1	2
	Shoulders and back	2	—	2
Acrocyanosis	Toes	1	—	1
Styes	Eyes	1	—	1
*Seborrhoeic dermatitis	Cubital fossa	—	1	1
*Dry eczema	Neck	1	—	1
*Erythema multiforme	Lower lip	1	—	1
"Glossitis"	Tongue	2 (sisters)	—	2
Total		9	2	11

* Diagnostic label attached by dermatologist.

In view of the suggestion of Salmon (1947) that the onset may be related to sexual dissatisfaction, a search was made for this and other possible psychological causes. No case of sexual maladjustment was found. The incidents (not necessarily significant) associated with the onset of symptoms in our 84 cases were as follows: puberty, 27; childbirth, 15; menopause, 14; widowed, 1; divorced, 1; mumps oophoritis, 1; thyroidectomy, 1; marriage, 3; unknown, 21.

TABLE IV.—*Duration of History of Regular Attacks of Premenstrual Syndrome*

Under 1 year	18	21·4%
1–5 years	35	41·6%
6–10 ,,	10	12·0%
11–15 ,,	9	10·6%
16–20 ,,	7	8·4%
Over 20 years	5	6·0%
	84	100

Menstrual History

Fig. 1 shows the usual time of onset of the attack. In this series 70 patients expected attacks in the premenstrual week, 9 at the onset of menstruation, and 4 during menstruation.

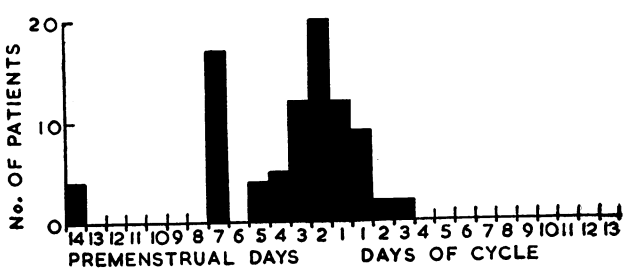

FIG. 1.—Time of onset in relation to flow.

One patient had regular attacks only at ovulation, and 3 had bimensual attacks at ovulation and premenstrually. One of these had ovulatory bleeding. When, as at puberty and in the climacteric, periods are missed, the attacks nevertheless occur on the expected dates. Table V and Fig. 2 show the age at which the first menstrual loss occurred. This was normal in 72 cases, with only 2 cases (2.4%) occurring at the early age of 10 years, and only 5 cases (6%) occurring later than the normal time of onset (arbitrarily assumed to be 11 to 16 years).

Table VI shows the duration of menstrual loss. In only three cases was it abnormally short (two days), and in only one abnormally long (10 days).

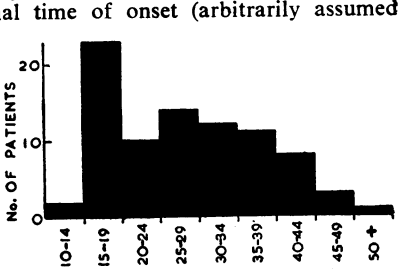

FIG. 2.—Age at onset of symptoms.

TABLE V.—*Age at First Menstrual Period*

	Normal Age Limit										Total
Years:	10	11	12	13	14	15	16	17	18	?	
Cases	2	6	10	19	19	12	6	3	2	5	84
% ..	2·4	7·1	12·0	22·6	22·6	14·2	7·1	3·6	2·4	6·0	100

TABLE VI.—*Average Duration of Menstrual Loss*

Days:	1	2	3	4	5	6	7	8	9	10	?	Total
Cases	—	3	11	17	23	14	12	—	—	1	3	84
% ..	—	3·6	13·1	20·2	27·4	16·7	14·2	—	—	1·2	3·6	100

TABLE VII.—*Length of Menstrual Cycle*

		Normal Length			
Days:	Under 21	21–30	31–42	Irregular	Total
Cases	1	78	4	1	84
%	1·2	92·8	4·8	1·2	100

Table VII, giving the length of the usual menstrual cycles, shows that the cycle exceeded the normal 30 days in four cases only—in women aged 16, 17, 30, and 31 years. The series is conspicuous for the normality of the menstrual history. An irregular cycle had been present in one woman of 49 for twelve months, and presumably heralded the climacteric. In one woman of 27 ovulatory bleeding had occurred regularly at the 14th to 15th day of a 28-day cycle, and she also suffered from migraine at this time. In this respect our experience differs from that of Singh *et al.* (1947), who found a high incidence of abnormal menses.

Two patients had "slight" dysmenorrhoea—that is, the patient had some discomfort relieved by simple analgesics, but the pain was not sufficient to interfere with normal work or necessitate lying down. The other 82 patients had no dysmenorrhoea. One case of associated severe dysmenorrhoea has since been observed.

Effect of Pregnancy

TABLE VIII.—*Parity of Series*

	Our Series	Registrar-General's Figures (Ages 15–45)
Single women	13 (15·5%)	43·2%
Married, no children ..	13 (15·5%)	13·3%
,, 1 child	25 (29·6%)	18·3%
,, 2 children	11 (13·1%)	14·4%
,, 3 ,, ...	13 (15·5%)	5·7%
,, 4 ,, ...	5 (6·0%)	2·7%
,, 5 or more children	4 (4·8%)	2·4%

Table VIII shows the parity of the series. The patients conceived easily and none had required medical advice on account of infertility. Most had their children in close succession, and all but two married women who had not had a child in the previous twelve months stated that they were practising some form of contraception. Three normal deliveries and one miscarriage at ten weeks occurred during treatment.

TABLE IX.—*Health After First Trimester of Pregnancy*

More energetic, symptom-free	36 (62·1%)
Symptom-free	18 (31%)
Symptoms (depressed 2, migraine 1, asthma 1) ..	4 (6·9%)
	58 (100)

Table IX shows the state of health of the patient after the first trimester. After the third month of pregnancy the premenstrual symptoms ceased in all but four patients, and 36 patients reported feeling more energetic than usual.

Toxaemia occurred in 11 of 58 parous women and complicated 21 of 128 pregnancies, thus accounting for the following obstetrical complications: surgical induction, 12; caesarean section, 4; forceps, 2; stillbirth, 3; sterilization, 1.

In 5 out of 11 cases the premenstrual syndrome began after the pregnancy complicated by toxaemia. The possible association between the syndrome and toxaemia is under further investigation.

Effect of Childbirth

In all cases in which the syndrome existed before pregnancy the attacks occurred with increased severity at the first menstruation after childbirth. Three patients with migraine had an attack during the puerperium; 15 dated the onset of regular attacks from childbirth.

In seven cases childbirth was followed by increasing weight and lethargy in addition to the premenstrual syndrome, a condition easily misdiagnosed as myxoedema, but which responded to ethisterone or progesterone therapy.

In view of the frequency of the syndrome no sound conclusions about familial incidence can be drawn from so small a series. It may, however, be worthy of note that the mothers of 29 of our patients had suffered from migraine: of these, 14 suffered from attacks which were related to menstruation and which ceased at the menopause. Seven of our patients reported similar conditions in their sisters, in five instances in relation to menstruation. One patient reported that her father suffered from migraine. Two patients who were cousins were able to trace premenstrual migraine in four generations.

Is Water Retention the Cause of the Syndrome?

That the symptoms are due to water retention is strongly suggested by the oliguria and gain in weight which announces their arrival and the diuresis and loss of weight which accompanies their relief at, or soon after, the onset of menstruation. To the observations already quoted may be added those of Thorn, Nelson, and Thorn (1938), who found a premenstrual gain in weight of more than 1 kg. in 48% of healthy women, and, be it noted, a mid-menstrual gain in 76%. They showed that at neither time was the gain attributable to increased intake of food, an important point in view of the increased appetite occasionally reported. Morton (1950) found that in his series of cases of "premenstrual tension" a higher proportion (52%) gained weight and that 45% had pitting oedema. Bickers and Woods (1951) found a good correlation between the gain in weight and the severity of the symptoms, and reproduced them by injections of "pitressin." Relief of the symptoms by various diuretic measures has been reported. Greenhill and Freed (1940) claimed success in all their patients treated with ammonium chloride and a diet low in sodium, and in a later and larger series (Greenhill and Freed, 1941) in 34 patients out of 40. Thorn and Emerson (1940) were successful with a diet low in sodium and high in potassium. Stieglitz and Kimble (1949), in order to avoid the chloride ion, preferred ammonium nitrate and obtained relief in 91% of their patients. Argonz and Abinzano (1950) treated 30 patients with large doses of vitamin A because of its reported diuretic effect, and claimed success in every case. Bickers and Woods (1951) relieved all symptoms with the new diuretic pyralamine-8-bromotheophylline, which reduced the average gain of weight from 5.2 to 1.4 lb. (2.4 to 0.6 kg.). Their results were less good with ammonium chloride, which reduced the gain only to 4.3 lb. (2 kg.). Vainder (1951) was successful in 153 cases treated with "pyrabom" (pyralamine-8-bromotheophylline).

Nevertheless, it is necessary to be on guard against too ready an explanation of the syndrome *solely* by water retention. Thorn, Nelson, and Thorn (1938), as we have seen, found that a gain in weight occurred more often at mid-cycle than in the premenstrual phase. Similar symptoms do sometimes occur at the time of ovulation, but they are far less common. Thorn and Emerson (1940) were disposed to explain this by the experimental fact that progesterone and oestradiol both have the capacity to cause water retention, and that, whereas only oestradiol is operative at mid-cycle, both are present before menstruation; but, for reasons which will later be obvious, this explanation is not

acceptable. In our series, symptoms occurred at mid-cycle in only four cases. Such women usually have two attacks, and sometimes these last long enough to merge with each other, especially when the cycle is short and the gap between menstruation and ovulation therefore also short. One unfortunate Irishwoman complained: "I only feel well when I am poorly." If we include mastalgia with the other symptoms we can assure ourselves that a factor other than water retention is involved. Greenhill and Freed (1941) noted that this symptom, alone in the syndrome, was not improved by dehydration, a fact which we have repeatedly confirmed.

Moreover, observation of a patient by one of us in 1938 (Fig. 3) suggests that a factor other than water retention

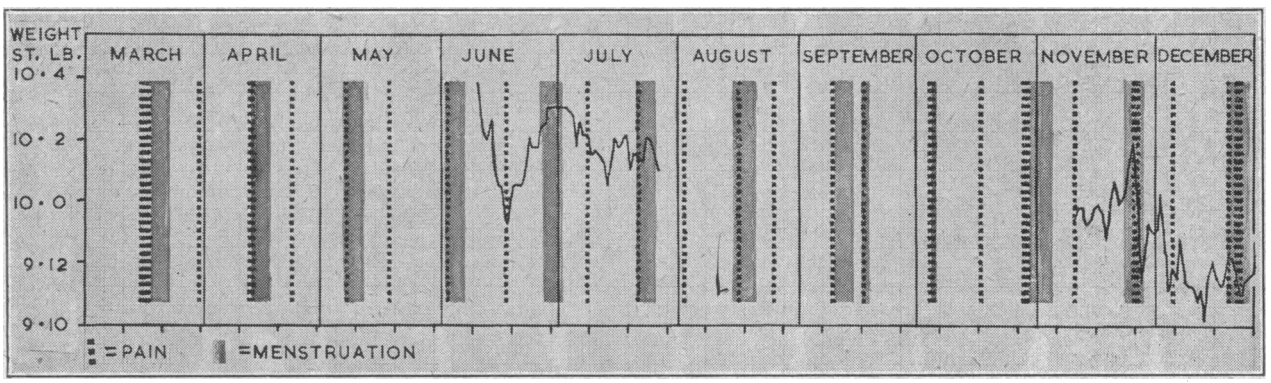

FIG. 3.—Occurrence of pain in relation to 11 menstrual cycles, together with weight changes during four cycles in a patient.

may sometimes be involved. She complained of attacks of migraine, occurring usually at intervals of a fortnight. She was intelligent and co-operative, and kept careful notes of her symptoms over a period of 11 cycles. During four cycles she plotted her weight day by day. These 11 cycles varied in length from 24 to 27 days. The attacks were of two kinds, occurring either during the interval or near the beginning of menstruation. The intermenstrual attacks, which all lasted for one day only, occurred nine times on the 14th or 15th days before menstruation. The two exceptions occurred on the 10th day before (when, uniquely in this study, no menstrual attack succeeded it) and on the 17th day before (when, again uniquely, it was accompanied by uterine haemorrhage and succeeded by a scanty menstrual flow). The menstrual attacks occurred in 10 cycles. They varied in length from one to three days, and their onset varied between the third day before the beginning of the flow to the second day after the beginning of the flow, in this way differing from the majority, in which all attacks were premenstrual.

It is important to observe that in the cycle in which there was an intermenstrual but no premenstrual attack, the weight dropped sharply by over 4 lb. (1.8 kg.) in the first half of the intermenstruum (the attack occurring at the nadir) and rose again by almost 4 lb. (1.8 kg.) in the second half (without any attack at the zenith). In the succeeding cycle weight changes were far less obvious and bore no relation to the attacks. Later in the series of cycles, one was observed in which the intermenstrual attack occurred before the nadir, though the premenstrual attack occurred at the zenith, and one in which an attack occurred intermenstrually before the nadir and premenstrually without a significant rise. Such observations enjoin some caution in assuming that water retention is the sole cause of intermenstrual and premenstrual or early menstrual migraine.

Another difficulty to be overcome arises from the reported effects of sterols in treatment. Oestrogens, androgens, and progestogens all have the property of causing water retention (Thorn and Engel, 1938; Kenyon *et al.*, 1940). Thorn, Nelson, and Thorn (1938) estimated that the relative potencies of the common sterols in this respect were, represented in "dog units," oestradiol 700, progesterone 400, oestrone 200–300, pregnanediol 140, testosterone 80, and testosterone propionate 25. Despite this, as we shall see, there is ample evidence of the effectiveness in treatment of progesterone, testosterone, testosterone propionate, and methyltestosterone. Still more surprising is the statement of Chiray *et al.* (1940) and Rubenstein (1942) that occasional cases respond to oestrogens, a claim we have been unable to confirm. Moreover, Singh *et al.* (1947) were able to induce attacks with oestrogens.

Though at first sight the water-retaining properties of progesterone and testosterone appear incompatible with their success in treatment, a hypothetical explanation may be suggested. The effects of progesterone on the excretion of oestradiol may more than counterbalance its weaker direct effect on water metabolism. That progesterone has this effect is shown by the observations of Smith and Smith (1931, 1938), which have been amply confirmed (Burrows, 1945).

Why Does Water Retention Occur?

The fact that two peaks of oestradiol secretion occur in each normal menstrual cycle—one at the time of ovulation and one in the premenstrual phase—suggests a hypothetical explanation of the retention of water at these times. That oestrogens are capable of causing water retention is well known, especially from the observations of Zuckerman and his colleagues (Krohn and Zuckerman, 1937; Aykroyd and Zuckerman, 1938; Zuckerman *et al.*, 1938).

Direct evidence of an excess of oestrogens at the time of the occurrence of symptoms is of doubtful validity. Frank (1931) and Frank *et al.* (1934), it is true, claimed that their patients' blood contained twice the normal amount of "ovarian hormone," and that after the relief of symptoms by *x* rays applied to the ovaries the ovarian hormone level became normal; but the difficulties inherent in the estimation of ovarian hormones in blood make it necessary to accept the statement with reserve. Morton found that vaginal smears were suggestive of excessive oestrogenic activity. On the other hand, Frank's suggestion of a high renal threshold for oestrogens was found by Israel (1938) in fewer than half his patients, which led him to suggest that the cause of the trouble was not so much a high level of oestradiol as a lack of antagonism by progesterone.

The concept of an abnormally high oestradiol/progesterone ratio has much in its support. Greenblatt (1940) contested the suggestion because in most of his patients he found a normal progestational pattern in their endometria and a normal excretion of pregnanediol; though he also noted a deficient excretion of oestrogens. Gray (1941) failed to find any correlation between the premenstrual syndrome and anovular cycles, and in the series reported by Bickers and Woods (1951) the basal temperature curve was invariably biphasic and the endometrial pattern progestational. Provenzano (1944) found a normal pattern in 12 out of 15 patients. It should, however, be pointed out that the hypothesis that the cause of the syndrome is an abnormally high

oestradiol/progesterone ratio does not at all depend on the demonstration of a consistently high level of the former or low level of the latter, since only the ratio between the two is on trial.

The hypothesis is supported by several observations. Morton (1946) has reviewed the evidence that painful breasts, so common a feature of the syndrome, are due to a high oestrogenic level, and he (Morton, 1950) was able to induce the syndrome artificially by the administration of large doses of oestrogens in two castrates and one post-menopausal woman, thus confirming the earlier observations of Singh *et al.* (1947). That the administration of progesterone is effective in relieving it was shown by Gray (1941), Puech (1942), and Albeaux-Fernet and Loublie (1946), and has been amply confirmed by ourselves. The hypothesis is further supported by the experimental evidence produced by Gillman (1942), who showed that progesterone administered to baboons reduces oestrogenic perineal swelling to normal in from four to seven days, an observation confirmed by Krohn (1951). Herlant (1939) had previously suggested that this effect was due to the suppression of the gonadotrophic activity of the pituitary by progesterone, but Krohn pointed out that the effects are too rapid for such an explanation and thought that a direct antagonism in this respect between oestrogens and progesterone was a more likely explanation. The pregnanediol output was subnormal in 10 of Morton's (1950) 29 patients, the endometrial pattern showed progestational deficiency in 22, and the basal temperature curve was "anovular" in 23.

Water Retention and the Oestradiol/Progesterone Ratio

If water retention due to an abnormally high oestradiol/progesterone ratio is the cause of the symptoms, how is it brought about? Several explanations have been postulated. Is there, for instance, a change in the metabolism of sodium, a sodium retention bringing about a water retention? Thorn, Nelson, and Thorn (1938) and Thorn and Emerson (1940) found that the excretion of sodium and chloride is decreased before and increased after both ovulation and menstruation. Morton (1950) found at these times a diminished excretion not only of sodium but also of potassium and chloride. Danforth *et al.* (1946) failed to find any consistent fluctuation in sodium or potassium metabolism, but confirmed the common rise in weight reported by other workers and found it to be associated with a decline in haematocrit and plasma proteins. Greisheimer *et al.* (1946) found no constant menstrual change in the blood, in *p*H, CO_2 content, chloride, or total base either in the premenstrual syndrome or in the controls, and concluded that the menstrual cycle is not characterized by any regular change in the acid-base equilibrium of the serum. Males showed as much fluctuation as females. The success of the treatment of the premenstrual syndrome by reduction in sodium intake has been noted above.

Many points are still obscure and several difficulties in interpretation have yet to be overcome; it does, however, appear that the best working hypothesis is that which postulates a cyclical change in sodium (and therefore in water) metabolism which occurs to a slight extent in healthy women and to an exaggerated extent in sufferers from the premenstrual syndrome. The rhythm of this change seems to be controlled by the level of oestradiol in the tissues, and this in its turn to be under the partial control of progesterone. Excessive water retention may therefore be present even with a fairly low level of oestradiol if progesterone is entirely lacking; or absent even with a very high level of oestradiol if progesterone is present in adequate amounts. It is the oestradiol/progesterone ratio which determines whether or not symptoms occur.

Symptomatology

If this hypothesis is correct a ready explanation of many of the symptoms is available.

Migraine and lesser degrees of headache may well be due to an increased hydration within the indistensible cranium. We have seen a male patient suffering from the oliguria and water retention which so often follow epidemic encephalitis who had frequent attacks of the severest migraine which were entirely prevented by the reduction of salt and water in his diet and the administration of urea. That urea is a useful treatment in some cases of migraine was always taught by Sir Walter Langdon-Brown and has been often confirmed by many workers—for example, Brown (1943)—and on other grounds water retention has been incriminated in migraine by the work of Földes (1933) and of Goldzieher (1941). Bickers and Woods (1951) produced the symptoms of the premenstrual syndrome by the injection of "pitressin" and found a close correlation between the consequent gain in weight, the severity of the symptoms, and the subsequent diuresis. The occasional epileptiform fits may be looked upon as the natural counterpart of the pitressin–water test for epilepsy.

There is no evidence that fluid retention causes bronchospasm. Indeed, the persistence over several days of premenstrual "asthma" suggests that the bronchial obstruction may be due to a less transient cause. A more prolonged obstruction by swelling of the mucosa may be present, though we have not yet confirmed this suggestion by bronchoscopy. The relationship between hyperaemia and oedema of the upper respiratory tract and the pelvic organs has long been recognized. It has been briefly reviewed by Greene (1943). The relationship was known to Hippocrates and was brought to the attention of the moderns by Mackenzie as early as 1884. He observed that the nasal mucosa of women becomes congested before the menstrual periods and that actual bleeding may then occur ("vicarious menstruation"). Some women, as Hoseason (1938) pointed out, suffer at this time from rhinorrhoea. Mortimer *et al.* (1936, 1937, 1939) showed that in monkeys there is an increase in colour of the nasal mucosa at monthly intervals coincident with the swelling of the sexual skin. The nasal changes were, indeed, 8% more regular as a sign of ovarian activity than menstrual bleeding itself, and were most obvious in the fertile months of September and October. Immature and adult monkeys of both sexes, whether intact or castrate, react to oestrogenic treatment by reddening of the nasal mucosa, which occurs even if the nasal tissue is transplanted elsewhere (Bachman *et al.*, 1936).

The papers from the Montreal school were followed by several clinical reports of good results in the treatment of atrophic rhinitis by injections or local applications of oestrogenic substances. That these results may be accounted for by the selective concentration of oestrogens in the nose is suggested by the experiments of Fisher *et al.* (1936). The immediate effect of this concentration is local vasodilatation, as Reynolds and Foster (1940) showed. Apart from their specific action, oestrogens produce hyperaemia in many tissues (Hechter *et al.*, 1940) and it is natural that this hyperaemia should be greatest in those tissues in which a concentration of oestrogens occurs. This hyperaemia is due to the liberation of acetylcholine in these situations (Reynolds, 1939; Reynolds and Foster, 1940), and effects similar to those of oestrogens may indeed be obtained by spraying the nose with neostigmine (Bernheimer and Soskin, 1940), The rhinorrhoea of the premenstrual syndrome—and perhaps the asthma as well—is thus explicable by the excessive local activity of oestradiol which would be expected *ex hypothesi*. The oedematous nasal mucosa may lead to blocking of the exits from the nasal sinuses and consequent "vacuum headaches."

The occasional association of premenstrual mastodynia with the commoner symptoms can be plausibly explained by the relatively high oestrogenic level without involving the consequent water retention. The evidence that the "painful nodular breast" is caused by excessive oestrogenic stimulation has been reviewed by Morton (1946) and by Greene (1950).

That so-called rheumatic pains may be due to water retention is well recognized. The rather ill-defined pain and tenderness in the soft tissues of obese women (often referred

to as "fibrositis" and "panniculitis") usually responds well to a dehydrating regime. A possible explanation has been offered by Copeman (1949).

The dermatoses of the premenstrual syndrome are less readily explicable on the present hypothesis. The explanation must await further work on the relationship between steroid metabolism and the state of the human skin. That such a relationship exists is clinically obvious. The laboratory evidence has been reviewed by Burrows (1945).

Treatment of the Syndrome

It has been indicated that numerous treatments have been suggested in the past. These include the following.

Dehydration.—References to this method of treatment have been cited in the discussion on the possibility that water retention is the cause of the syndrome. There seems little doubt that in a fair proportion of cases it is effective. It was not adopted in the present series. It has been tried by one of us (R. G.) in earlier cases with occasional success. It is greatly disliked by the patients, and only those suffering from the severest symptoms can be bothered with it for more than a few months. The newer diuretics have not been tried.

Androgens.—The "literature" of the subject leaves little doubt that androgens may be useful (Greenblatt, 1940; Albeaux-Fernet and Loublie, 1946; Freed, 1945, 1946; Chiray *et al.*, 1940). Androgens, such as testosterone propionate, which must be administered by injection, are no longer worthy of serious consideration. Methyltestosterone, administered by mouth, is sometimes effective, especially in those patients in whom mastalgia is a prominent symptom. It is less generally successful than progesterone in relieving other symptoms of the syndrome. Its chief disadvantage is the danger of virilization. It occasionally happens that the dose needed to relieve symptoms is high enough to cause acne, the growth of a slight moustache, and lowering of the voice. Menstruation may be suppressed.

Vitamins.—M. S. Biskind (1943) was influenced in his views by the occurrence of glossitis in the syndrome and obtained relief by the administration of vitamin B. He quoted G. R. Biskind and Mark (1939), who had shown that in vitamin-B deficiency the liver's ability to inactivate oestrogens may be impaired. With G. R. Biskind and L. H. Biskind (1944) he published 11 cases, all relieved by this therapy. In a small series treated by one of us (R. G.) before the present one was begun no success was achieved. Bickers and Woods (1951) were also unsuccessful. The effectiveness of vitamin A has been vouched for by Argonz and Abinzano (1950). Vitamin A has not been tried by us. If, as is suggested, its efficacy depends on its diuretic properties, it can hardly be expected to compete with mersalyl, urea, or the newer diuretic drugs.

Oophorectomy and X-ray Treatment of Ovaries.—These have been used successfully by Frank (1931). They are measures obviously too drastic for the present day.

Treatment with Progestogens

Progesterone has been used successfully by Gray (1941), Puech (1942), and Albeaux-Fernet and Loublie (1946). These workers administered the hormone by intramuscular injection. No report has so far appeared of the use of ethisterone, or of progesterone other than by intramuscular injection.

All patients in this series were treated by means of progestogens. The results of the treatment of 84 patients are presented. All were treated between January, 1948, and June, 1952, some of those included in the analysis of symptoms being excluded from consideration here for lack of a sufficiently long period of observation.

Cases of mild and moderate severity were treated at first by means of ethisterone, given in oral doses of 30 to 150 mg. daily for twelve days from the fourteenth day of the cycle. If at the end of the cycle a patient remained symptom-free, she was observed at monthly intervals. If she improved without becoming symptom-free, treatment was continued

TABLE X.—*Results of Treatment*

No.	Symptoms	Ethisterone	Progesterone	Final Treatment	Side-effects
1	Asthma	—	Free	Implant 10.52	—
2	Migraine	No relief	,,	,, 10.52	—
3	,,	—	,,	Observation 3/12	Dysmenorrhoea
4	,,	Improved	,,	Implant 10.52	—
5	,,	—	,,	,, 6.51	—
7	,,	Free	—	Observation 4/12	—
8	Oedema	,,	—	Implant 10.49	Heavy periods with clots
9	Acne	Improved	—	Observation 4/12	Dysmenorrhoea
10	Rheumatism	—	Free	Implant 11.52	—
11	Acrocyanosis	Improved	Improved	,, 10.52	—
12	Migraine	Free	Free	,, 4.51	—
13	,,	—	,,	,, 2.52	Amenorrhoea 8/52
14	,,	No relief	,,	,, 6.48	—
15	Asthma	—	,,	,, 1·49	—
16	Migraine	—	,,	Observation 7/12	Erythema at injection site
17	,,	—	,,	Implant 2.50	Shorter cycle, heavier loss
22	,,	—	,,	,, 2.49	Hyperchromic anaemia. Hb 49%
23	Vertigo	—	,,	Observation 5/12	—
24	Styes	Free	,,	,, 5/12	Nausea with each injection
25	Migraine	,,	—	,, 3/12	—
26	,,	,,	Free	,, 3½ years	—
27	Acne	Improved	Improved	,, 3/12	—
28	Asthma	—	Free	Implant 12.48	—
29	Migraine	Free	,,	Observation 2/12	—
31	Rheumatism	—	,,	,, 4/12	—
32	,,	—	,,	Implant 11.49	—
33	Migraine	Postponed attack	,,	Observation 3/12	—
34	,,	No relief	Not known	Did not return	—
35	Petit mal	Free	—	Ethisterone	—
36	Migraine	,,	Free	Implant 2.51	—
37	Petit mal	No relief	No relief	Improved on testosterone	—
38	Migraine	Free	Free	Implant 7.52	—
39	,,	—	,,	,, 6.50	—
40	,,	—	,,	Observation 6/12	—
41	Rheumatism	—	,,	,, 10/12	—
42	Migraine	No relief	,,	Implant 11.51	—
43	,,	Free	—	,, 7.52	—
44	Erythema multiforme	No relief	Free	Progesterone injections	—
45	Migraine	—	,,	Observation 7/12	—
46	,,	—	,,	,, 14/12	—
47	Migraine and seborrhoeic dermatitis	Improved	,,	,, 7/12	Erythema at injection site
48	Migraine	—	,,	Implant 4.52	—
49	,,	—	,,	Observation 5/12	—
50	Asthma	—	,,	Implant 9.52	—
51	Eczema	—	Improved	Observation 5/12	—
52	Irritability	—	Free	Implant 12.48	—
53	Migraine	No relief	No relief	Free on testosterone	—
54	Acne	Improved	—	Observation 4/12	—
55	Migraine	No relief	Free	Progesterone injections	Sl. ovulatory bleeding
56	,,	,, ,,	Not known	Did not return	—
57	,,	Improved	Free	Observation 5/12	—
58	Glossitis	Free	—	,, 3 years	—
59	Glossitis and petit mal	,,	—	,, 3 ,,	
60	Migraine	—	Free	,, 8/12	—
61	Nausea	—	,,	Implant 2.49	—
62	Migraine	Free	—	Continuing ethisterone	—
63	,,	,,	—	Observation 5/12	Longer period
64	,,	,,	—	,, 5/12	—
65	Rheumatism	—	Free	,, 3/12	—
67	Migraine	—	,,	,, 3/12	Erythema at injection site
68	,,	Free	—	,, 3/12	—
69	,,	Not known	No relief	No report after ethisterone	Headache with each injection
70	,,	No relief	Free	Awaiting implant	—
71	Irritability	Free	,,	Continuing ethisterone	—
72	Rheumatism	—	,,	Observation 3/12	—
73	Migraine	—	,,	Implant 11.52	—
74	,,	No relief	,,	Observation 2/12	—
75	,,	Free	—	,, 5/12	—
76*	,,	,,	—	Continuing ethisterone	—
77	,,	No relief	Improved	Progesterone injections	Sl. ovulatory bleeding
78	,,	Free	—	Continuing ethisterone	—
79	,,	Improved	Free	,, ,,	—

TABLE X.—*(Continued)*

No.	Symptoms	Ethisterone	Progesterone	Final Treatment	Side-effects
80	Rheumatism	—	Free	Observation 2½ years	—
81	Nausea	—	,,	Observation 2½ years	—
82	Migraine	—	No relief	Artificial menopause; migraine now worse	—
84	,,	Free	—	Continuing ethisterone	—
85	Styes	No relief	Free	Awaiting implant	—
86	Migraine	,, ,,	,,	Implant 10.52	—

Cases 6, 18, 19, 20, 21, 30, 66, and 83 did not report back after treatment.
Cases 85 and 86 not included in previous analysis owing to insufficient history.

until she became symptom-free. If no improvement occurred she was given intramuscular injections of progesterone instead, in doses at first of 10 mg. daily during the second half of the cycle. Later it was found that an injection of 25 mg. on alternate days was equally effective. Severe cases were treated by this method from the outset. Patients who responded to this treatment were kept under observation: if they were only improved, treatment was continued until they were symptom-free. Those who became symptom-free but afterwards relapsed for lack of treatment were selected for treatment by means of implantation, doses from 200 to 500 mg. being employed. In a few cases in which treatment with oral ethisterone or intramuscular progesterone was used, the symptoms instead of being completely relieved were postponed until the later days of menstruation or even until the post-menstrual phase. Such patients were subsequently treated with ethisterone or progesterone throughout the entire month, and were ultimately treated by implantation.

Tables X and XI show the results obtained. The oral administration of ethisterone gave complete relief in 22 cases (47.9%) and partial relief in a further 8 cases (17.4%).

TABLE XI.—*Comparison of Results of Treatment with Ethisterone and Progesterone Injections*

Result	Ethisterone		Progesterone		Total After Final Treatment	
	No.	%	No.	%	No.	%
Symptom-free ..	22	47·9	51	83·5	66	84·7
Improved ..	8	17·4	4	6·6	6	7·7
Postponed attack	1	2·1	—	—	—	—
No relief ..	14	30·5	4	6·6	3	3·8
Not known ..	1	2·1	2	3·3	3	3·8
Total ..	46	100	61	100	78	100

Of the 14 cases unsuccessfully treated 9 had complete relief and 1 partial relief when treated with intramuscular progesterone, 2 obtained no relief from intramuscular progesterone, and 2 patients did not report the result. The results with intramuscular progesterone in 61 cases were more satisfactory—51 (83.5%) became free from symptoms, 4 (6.6%) improved, and 4 (6.6%) obtained no relief. Of the 4 patients unsuccessfully treated with progesterone 2 were treated with methyltestosterone, 5 mg. twice daily, from which one obtained complete relief and one partial relief. One patient unsuccessfully treated failed to report the result of treatment with ethisterone. The remaining unsuccessfully treated woman, aged 45, had suffered from toxaemia in all her five pregnancies and had been sterilized in 1942. In 1949, after the unsuccessful trial of progesterone, she was given an artificial menopause by means of radiotherapy. After this her migraine, which had previously been premenstrual, became weekly, and had remained so when last seen in March, 1952.

Table XII summarizes the final treatment of 78 patients: thirty are symptom-free without regular medication and 4 so much improved that regular medication is unnecessary; 28 were treated with progesterone implants, and, of these, 27 had complete relief and one partial relief of symptoms.

TABLE XII.—*Final Treatment in 78 Cases*

Final Treatment	Total Cases	Total %	Free		Improved		No Relief
			No.	%	No.	%	
Observation	34	43·6	30	44·7	4	57·1	—
Progesterone implant ..	28	35·8	27	40·5	1	14·3	—
Continuing ethisterone	7	8·9	7	10·4	—	—	—
,, progesterone	3	3·9	2	2·9	1	14·3	—
Testosterone	2	2·6	1	1·5	1	14·3	—
Artificial menopause ..	1	1·3	—	—	—	—	1*
Not completed	3	3·9					
	78	100	67	100	7	100	1

In three cases "not completed," patients did not report after change of treatment.
* Migraine worse after artificial menopause.

Summary

A large proportion of women, estimated by one author as 40%, suffer a variety of distressing symptoms during the final week or so of the menstrual cycle. In occasional cases, similar symptoms may occur at monthly intervals at other points of the cycle. They are probably produced by water-retention, and the evidence at present available suggests that this in its turn is due to abnormal elevation of the oestradiol/progesterone ratio.

Various treatments aimed at either dehydration or a correction of the disturbed hormonal ratio have proved partially effective. Treatment with a progestogen is almost invariably successful. In mild cases relief is usually obtained by the oral administration of ethisterone in a dosage of 25 mg. twice daily during the second half of the menstrual cycle. A larger proportion of patients can be relieved by the intramuscular injection of progesterone, 25 mg. on alternate days during the same phase of the cycle. Such cases are more effectively treated, with less labour for the patient, by the implantation of progesterone, which remains effective for many months.

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THE PREMENSTRUAL TENSION SYNDROME AND ITS TREATMENT

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Premenstrual tension is a syndrome occurring during the second half of the menstrual cycle and consisting of a number of mental and physical symptoms. The syndrome is composed of marked general tension and irritability, together with one or more of the following symptoms: anxiety, depression, bloated abdominal feelings, swelling of subcutaneous tissues, nausea, fatigue, painful swelling of the breasts, headaches, dizziness, and palpitations. Less frequently there may be increased sex desire, excessive thirst, increased appetite, and hypersomnia. The symptoms usually start about seven to fourteen days before menstruation and pass off soon after the onset of the menses, although some patients continue to have symptoms throughout the period. The syndrome must not be confused with the premenstrual discomfort experienced by many women. The premenstrual tension syndrome may seriously interfere with work and social activities, and can be incapacitating. The condition is by no means as uncommon as suggested in some reports.

Literature

The aetiology of the condition is still obscure. Frank (1931), who introduced the term "premenstrual tension," considered it to be due to excess of circulating oestrogen. Israel (1938) believed the syndrome not to be due to excess oestrogen itself, but rather to the action of unantagonized oestrogen resulting from faulty luteinization. Gillman (1942) and Hamblen (1945), in contrast, implicate progesterone as the responsible hormone. Convincing evidence in support of the hypothesis of faulty luteinization permitting the action of unantagonized oestrogen as the primary cause of premenstrual tension is, however, given by Morton (1950).

Water retention is postulated by Greenhill and Freed (1941) as the immediate cause of premenstrual tension symptoms. Hoffman (1944) considered that an unstable nervous system was an important factor, and a number of authors have expressed the opinion that the condition seems to be more frequent in unstable women.

Rees (1953), in a psychosomatic study of 145 subjects, including normal and psychiatric patients, found that marked premenstrual tension could exist in normal women of stable personality and that many severely neurotic women were free from it. In neurotic patients with premenstrual tension there was a positive correlation between degree of premenstrual tension and degree of personality instability and severity of neurosis. Rees, while in general supporting the theory that the condition was primarily physiogenic and due to changes resulting from defective progesterone secretion, stressed that the syndrome was of complex causation in which personality and constitutional and emotional factors operate in addition to the primary physiogenic changes.

There is now considerable evidence to suggest that the bodily changes of the premenstrual tension syndrome are primarily due to a lack of progesterone, which allows the unopposed action of oestrogens during the second half of the menstrual cycle. It is known that oestrogens cause sodium and water retention. Hydration is a common feature of the premenstrual tension state, and many patients put on from 2 to 9 lb. (0.45 to 4.1 kg.) in weight during the premenstrual phase and lose a corresponding amount with the diuresis following the onset of the menses. Oestrogens stimulate growth of the epithelia of the breast, vagina, and endometrium, and this together with hydration may account for painful swelling of the breasts. Hypoglycaemia and hyperinsulism have been noted to occur during premenstrual tension states (Billig and Spaulding, 1947; Morton, 1950) and may be the cause of increased appetite and fatigue noted in some patients. These changes in the internal environment cause a number of specific symptoms and also may result in autonomic lability, causing such symptoms as palpitations and dizziness. The patient's reaction to these changes can be influenced by such factors as personality type and stability, emotions, attitudes, and degree of autonomic instability.

The treatment of premenstrual tension can therefore be directed at different aetiological levels. (1) Psychotherapy, including explanation and re-education to improve attitudes, relieve symptoms, and minimize degree of incapacity. (2) Dehydration by means of diuretics to relieve symptoms due to hydration and possibly to facilitate elimination of the noxic agent. (3) Administration of progestogens to compensate for any lack of progesterone and to antagonize action of oestrogens. (4) Administration of androgens to antagonize action of oestrogens as suggested by Greenblatt (1940), Geist (1941), and Freed (1945).

Gonadotrophins are generally considered to be ineffective (Bowes, 1950), and as oestrogens tend to intensify symptoms (Morton, 1950) they are contraindicated.

Present Investigation

The following therapeutic methods have been studied in a group of 30 patients suffering from severe premenstrual tension: psychotherapy; dehydration therapy using ammonium chloride; administration of progestogens, including progesterone by injection and ethisterone by mouth; and administration of androgens in the form of methyltestosterone by mouth. The patients have been observed for from six months to four years, giving a total of 207 cycles.

The assessment of premenstrual tension was made from data obtained during clinical interview and from special daily records of symptoms. Detailed instructions were given to patients regarding the daily recording of symptoms, so that scoring was, so far as possible, kept standardized. The day-to-day records were kept for some months before starting treatment, and the data so provided permitted a detailed assessment of the premenstrual tension and provided a baseline for measuring the effects of treatment.

Clinical Data.—The age distribution of the group was 15–24 years, 8%; 25–34, 56%; 35–44, 36%. Most patients had developed premenstrual tension before 35 and about one-fifth before the age of 20. Two developed premenstrual tension after childbirth, and three just before the menopause. 80% of the group were married. The mean age of menarche was 14.7 years and the frequency distribution of menarchial ages was similar to that described by Ellis (1947) for normal British women. The symptoms of premenstrual