A STUDY OF PREMENSTRUAL TENSION IN GENERAL PRACTICE

BY

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Premenstrual tension is the term commonly applied to a syndrome occurring in a proportion of women in the days immediately preceding the menstrual cycle. The symptoms are partly psychological, such as irritability and depression, and partly somatic, such as swelling of the breasts and abdomen. Headache, a symptom which defies classification into either group, is also present in most cases.

The incidence of premenstrual tension varies a great deal between different series, as Pennington (1957) states that it occurs to some degree in 95% of women in the child-bearing years, while Bickers and Woods (1951) report an incidence of only 36% in a population of female factory workers. Differences in criteria for making the diagnosis undoubtedly play a part in these variations, but the type of patient being studied also contributes to the variation, as it has been pointed out (Fortin *et al.*, 1958) that the incidence in a prison population was 33% while among student nurses 73% were sufferers. In my own practice approximately 55% of the female patients between the menarche and the menopause have some degree of premenstrual tension, and in about 29% of these it is severe enough to require treatment.

Many theories have been advanced to explain this syndrome, the most popular of which are hormonal imbalance, especially a relative lack of progesterone with secondary water retention (Morton, 1950; Greene and Dalton, 1953; and Hauser *et al.*, 1959), and psychological upset (Stieglitz and Kimble, 1949; Pennington, 1957; Fortin *et al.*, 1958). It is difficult to understand how one disturbance of the type mentioned above could allow for the varied symptoms, and it seems more probable that the somatic changes are found to some degree in all women and that in these patients they are more severe or emotional imbalance makes the sufferers more aware of them (Davis, 1958). It is clear that a number of factors play a part, but the important point is that in most cases no definite cause can be established (Hauser *et al.*, 1959), and this is particularly true in general practice.

Recommendations for treatment have been similarly varied. Progesterone supplements in some form have been recommended by Greene and Dalton (1953), Rees (1953), and Hauser *et al.* (1959); dehydration has been used successfully by Greenhill and Freed (1941), Stieglitz and Kimble (1949), Bickers (1958), and Argonz and Abinzano (1959); psychotherapy by Davis (1958); and Fortin *et al.* (1958); and sedatives or tranquillizers by Phillips (1956), Nixon (1956), and Pennington (1957). The different results with these treatments may be partly caused by different criteria for cure, but there have been some comparative trials, including those of Rees (1953) and Swyer (1955). Rees treated 30 patients with psychotherapy, dehydration, progesterone, and androgens. Psychotherapy was of no value when given alone, though it was a useful adjunct: dehydration gave slight improvement; while both progesterone and androgens produced benefit in

85% of patients. Swyer found that both progesterone and mephenesin improved about two-thirds of his patients, though complete relief was more often obtained with the mephenesin. These trials did not include sedatives or the tranquillizers which have come into use since that time, and it was therefore decided to carry out a trial under the conditions of general practice, comparing a diuretic, a tranquillizer, two types of oral progesterone, and a placebo. No attempt was made to measure objective parameters when assessing results, as the complaints of the patients are subjective, and subjective improvement or relief of symptoms must indicate successful therapy.

Material and Methods

Thirty-two unselected consecutive patients with moderate or severe premenstrual tension who had suffered from symptoms for at least six months without change were included in the trial. One of these left the trial because of side-effects while on dimethisterone, and another became pregnant, reducing the final trial population to 30. The average age was 28.1 years; the average duration of symptoms 5½ years; 22 were married, one was widowed, and seven were single; six of the married women were nulliparous. The majority were housewives or had clerical work. Symptoms occurred with the following frequency: irritability in 24 patients, depression in 23, headache in 15, listlessness in 5, vertigo in 3, and nausea in 1.

It was thought that treatment with each preparation for at least three months was necessary to give a true picture of the response to that preparation and to eliminate chance fluctuations in the patients' condition. After initial interview and assessment the patients were therefore seen at three-monthly intervals, and tablets for the next period of treatment given, with instructions to start taking them nine days before the expected day of each period and to continue until menstruation started. The drugs were given in a random order. At the same time the results of the previous three months' treatment were noted. In order to eliminate personal views in assessing the results, the patients were requested to fill in a card, putting their response in one of the following categories: worse, no change, slight improvement, marked improvement, or complete relief of symptoms. When the cards were presented, the patients were asked if the tablets had affected them in any other way. In this manner side-effects were recorded. The medicaments given were as follows: chlorothiazide, 0.5 g. b.d.; meprobamate, 400 mg. t.d.s.; tablets of ethisterone, 25 mg. b.d.; dimethisterone, 5 mg. t.d.s.; placebo (lactose), one tablet b.d. As every patient had three months' treatment with each of the drugs they all took part in the trial for 15 months.

Results

A description of the cases and the results obtained are shown in Table I. In addition to the details given, the length and regularity of the periods, the presence of dysmenorrhoea, the degree of menstrual loss, and pre- and post-menstrual body weights were noted. None of these bore any relation to the severity of the symptoms of premenstrual tension or to the results of treatment, and have been excluded.

A summary of the results is shown in Table II. It can be clearly seen that meprobamate was the most effective treatment, giving total or marked relief to over half of

TABLE I

Case No.	Occupation	Age	Children	Age at Menarche	Years of Premen. tension	Symptoms	Chlorothiazide	Mepro- bamate	Tab. Ethisterone	Dimethi- sterone	Lactose (Placebo)
1	Typist	19	—	12	1	I	+++	+	—	++	++
2	Housewife	28	2	13	6	IDV	—	+	++	+	—
3	Machinist	26	—	16	3	IN	+	++	—	—	—
4	Typist	29	1	10	1	IDH	+	+++	—	—	—
5	Checker	36	1	10	1	IDHV	—	+++	—	+	+
6	Housewife	41	3	13	18	ID	—	—	—	—	—
7	Student	13	—	11	1	ID	—	+	—	—	—
8	Housewife	38	1	12	5	IDH	++	+	+	—	—
9	Student	17	—	13	2	ID	+	+++	—	—	—
10	Housewife	32	1	14	12	IDH	—	+++	+	—	—
11	"	26	2	10	9	ID	+++	+++	—	—	—
12	Typist	21	—	12	1	ID	—	+++	—	—	—
13	Housewife	26	4	13	1	IDHL	++	+++	+	—	—
14	Café owner	43	3	14	2½	HL	++	++	—	—	—
15	Typist	25	—	13	9	ID	+++	—	—	—	—
16	Packer	43	—	11	2	IDH	+++	+	—	—	—
17	Housewife	24	2	12	2½	D	—	+	—	—	—
18	Clerk	29	—	13	1	DH	—	++	—	—	—
19	Housewife	39	3	16	23	DL	—	+	—	—	—
20	"	28	2	12	2	DHL	—	+++	—	—	—
21	Clerk	25	—	13	12	IH	+	++	—	—	—
22	Typist	20	—	12	1½	I	++	+++	++	—	—
23	"	21	—	12	1	ID	+	—	+	—	—
24	Student	15	—	12	1	HV	+	+	—	—	—
25	Panel-wirer	23	—	14	9	ID	—	++	—	—	—
26	Clerk	36	2	14	10	IDH	—	++	—	—	—
27	Housewife	41	2	13	10	IDH	—	++	+++	—	—
28	"	27	2	14	2½	IDL	+++	—	—	—	—
29	"	26	4	14	2	IDH	+	+	—	++	—
30	"	26	2	13	7	IH	++	+++	—	+	—

I = Irritability. D = Depression. H = Headaches. L = Lassitude. V = Vertigo. N = Nausea.

Scoring: — Worse. + — No change. + Slight improvement. ++ Marked improvement. +++ Complete relief of symptoms.

the patients, while chlorothiazide had a similar effect in only one-third and the progesterone derivatives in about one-fifth. The results given are the average of the three months on each treatment, but in fact there was remarkably little variation in response between different months on the same drug.

It is an interesting feature of the above results that patients rarely responded well to more than one agent. Out of the 30 patients, 11 derived marked or complete relief from meprobamate but not from chlorothiazide, five derived similar benefit from chlorothiazide but not

forward the next period, menstruation starting significantly earlier than anticipated in six patients. This drug also caused frequency in one patient and increased libido in another. No untoward effects were noted with meprobamate.

Discussion

Premenstrual tension is a relatively common condition which, in common with the other similar syndromes of dysmenorrhoea and "menopausal misery," causes a great deal of distress and suffering in the patients and yet has received scant attention by the medical profession as a whole. There are probably three main reasons for this: the first is that all are benign subjective conditions, so that no obvious harm will come to the patients even if untreated; the second is that women have come to accept these symptoms as inevitable ills; and the third is that the majority of the profession are male and, never having suffered personally from these complaints do not really take them seriously.

Premenstrual tension is undoubtedly connected with some form of hormonal imbalance and water retention in a large number of cases, but there is, in addition, a marked functional element, which overshadowed the somatic symptoms in this series. It has been shown (Sweeny, 1934) that one-third of normal women gain 3 lb. (1.4 kg.) or over in body weight premenstrually, but these women do not necessarily suffer from premenstrual tension, so that if the emotional upset can be overcome patients may become symptom-free even though they will continue to retain fluid before the periods. Bickers (1958), on the other hand, related the amount of gain in weight to the severity of the symptoms and found that patients who experienced a marked loss of weight with chlorothiazide were improved. This has not been my experience, as premenstrual gain in weight and symptoms of swelling of breasts and abdomen were as common in normal women as in patients suffering from the irritability and depression of pre-menstrual tension. In addition there was no correlation between loss of weight with

TABLE II

	Chloro- thiazide	Mepro- bamate	Tab. Ethi- sterone	Dimethi- sterone	Lactose (Placebo)
Complete relief of symptoms	5	10	1	1	0
Marked improvement	5	6	2	2	2
Slight " "	7	7	6	8	4
No change " "	8	6	17	14	24
Worse	5	1	4	5	0
Patients with some degree of improvement	57%	77%	30%	37%	20%
Patients with complete relief or marked improvement	33%	53%	10%	10%	7%

from meprobamate, and five obtained marked or complete relief from both drugs. Out of the remaining nine patients, who did not benefit greatly from either meprobamate or chlorothiazide, only two showed marked improvement with either of the progesterone derivatives.

Patients therefore seem to fall into three main groups: (a) those responding to meprobamate, (b) those responding to chlorothiazide, and (c) those not responding to either.

Side-effects.—There were no serious side-effects, but four patients complained of increased dysmenorrhoea while on ethisterone treatment, and dimethisterone caused nausea in one patient and very severe dysmenorrhoea in another, so that she had to withdraw from the trial. Chlorothiazide appeared to bring

chlorothiazide and relief of these symptoms. The symptoms of swelling were decreased, but this decrease was of little value, as the patients were not troubled by these symptoms and did not consider themselves improved until the irritability, depression, and headache had been relieved.

From a practitioner's point of view the only object is the relief of symptoms whatever their precise aetiology, and once this has been achieved the patient is cured. Organic disease must therefore be excluded and then an attempt made to provide symptomatic relief. Other workers have obtained high rates of cure with drugs of the progesterone type and with diuretics. In this present series of unselected patients the majority were much improved by meprobamate and a third by chlorothiazide.

The division of patients into those responding to one drug and those responding to another suggests various types of the premenstrual syndrome differing in aetiology and optimum treatment. The results of this study suggest that psychological factors are responsible for the symptoms in a large number of cases. Hormonal imbalance and water retention are probably of major importance in others. It is, however, impossible to differentiate one group from another on present evidence, and it therefore seems reasonable to start treatment with meprobamate, and if that is not effective to give chlorothiazide, progesterone, or a combination of drugs.

Summary

Earlier studies on the aetiology and treatment of premenstrual tension are reviewed, and a study of 30 consecutive patients in general practice is reported. All of these patients received treatment with chlorothiazide, meprobamate, ethisterone, dimethisterone, and a placebo. Over half of the patients obtained complete relief or marked improvement with meprobamate, one-third with chlorothiazide, and one-fifth with progesterone derivatives.

Possible conclusions to be drawn from the results of this series are discussed.

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TOXIC COMPLICATIONS OF TREATMENT WITH 6-MERCAPTOPURINE

TWO CASES WITH HEPATIC NECROSIS AND INTESTINAL ULCERATION

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6-Mercaptopurine (6-M.P.) in a dose of 2.5 mg./kg. body weight is an established treatment for acute leukaemia which, if successful, produces a remission in four to eight weeks. It is generally agreed to be innocuous though slow-acting (Bernard and Seligmann, 1954), toxic effects other than marrow aplasia being rare (Bodley Scott, 1958).

6-M.P. causes hepatic necrosis and intestinal ulceration in experimental animals (Clarke *et al.*, 1953; Philips *et al.*, 1954). In leukaemic patients the complication of liver damage ascribed to treatment with 6-M.P. rather than to the disease process itself has been reported (Burchenal *et al.*, 1953; Gaffney and Cooper, 1954; Frei *et al.*, 1958; McIlvanie and MacCarthy, 1959), but intestinal ulceration has not been specifically described as a complication of this treatment.

From a series of 34 cases of acute leukaemia treated at Lewisham Hospital with 6-M.P. since 1955, we now report two consecutive cases in which the patients died with hepatic necrosis and intestinal ulceration prior to any remission.

Case 1

A boy aged 5 years, weight 36½ lb. (16.6 kg.), was admitted to hospital on April 30, 1959, with a history of spontaneous bruising for one month, and bleeding from the gums for one week. His mother stated that she was twice x-rayed during pregnancy.

On examination he was found to have a palpable spleen but no enlarged lymph nodes. His haemoglobin was 48% (7.1 g./100 ml.), white-cell count 4,400/c.mm. (polymorphonuclear leucocytes 308, lymphocytes 2,068, myelocytes 44, promyelocytes 1,056, myeloblasts 704, Türk cells 176, unclassified cells 44/c.mm.). The platelet count was less than 10,000/c.mm. A diagnosis of acute myeloid leukaemia was confirmed by sternal marrow biopsy.

Treatment was started on April 30, but in view of his poor clinical condition it was thought unlikely that he would survive long enough to obtain a remission on 6-M.P. alone, and so he was given methotrexate (amethopterin) 1.25 mg. daily in addition to 50 mg. daily of 6-M.P. Methotrexate was withheld between May 20 and 27 because of gastro-intestinal bleeding, and was finally discontinued on June 3; 6-M.P. was continued at the same dose throughout until June 16. Fresh blood transfusions and antibiotics were given as indicated.

Minimal jaundice was first noticed on June 15, towards the end of his seventh week on 6-M.P., becoming obvious by the next day. The liver-function tests on June 16 showed: alkaline phosphatase 6 K.-A. units, direct bilirubin ++, indirect bilirubin 6.6 mg./100 ml., thymol turbidity