containing 14 ml. of nutrient agar and 1 ml. of a solution of antibiotic of such strength as to give the required concentration when uniformly diffused in the medium. Each plate was divided by diamond marking into 12 approximately equal sectors of just over 5 square cm. An 18-hour nutrient broth culture of each staphylococcus was used as the inoculum, a 1-mm. loopful of the undiluted culture being spread over each sector. (For streptomycin, tests were also made using this inoculum diluted 300 times.) The plates were incubated at 37° C. for 18 hours, and the end-point was determined by inspection of the surface of the medium.

Results

For *Staph. pyogenes*, resistance to penicillin is dependent on the production of penicillinase, and as this can be detected in primary culture no further examination was thought necessary. Of the 200 strains isolated, 43 produced penicillinase and were resistant. Sensitivity to the

Sensitivity of 200 Strains of Staph. pyogenes to Streptomycin, Oxytetracycline, Chloramphenicol, and Erythromycin

Minimum Inhibitory Concentration (μ g. per ml.)	Streptomycin		Oxytetra- cycline	Chlor- amphenicol	Erythro- mycin
	Undiluted Inoculum	1 in 300 Inoculum			
>64	1	—	—	—	—
64	1	—	—	1	—
32	26	—	—	1	—
16	87	—	—	186	—
8	67	1	—	12	—
4	17	4	—	—	—
2	1	103	38	—	—
1	—	90	119	—	13
0.5	—	2	42	—	187
0.25	—	—	1	—	—

other antibiotics is shown in the Table. With one exception strains found sensitive by the dilution method had already been so described on primary isolation.

We have deliberately used a heavy inoculum when testing sensitivity, partly to enable a comparison to be made with previous work, and partly in the belief that the results obtained may be more applicable to conditions in the body (Spink, 1951). In a small pilot experiment involving 12 strains it was found that for oxytetracycline, chloramphenicol, and erythromycin, the difference between an inoculum of undiluted culture or a 1 in 300 dilution of undiluted culture amounted to only one serial dilution of the antibiotic. For streptomycin the difference was greater, and the results are accordingly reported as those obtained with undiluted culture or its 1 in 300 dilution.

Discussion

Penicillin.—In the three years since the last survey much penicillin has been prescribed in general practice, and many members of the public have entered and left hospital wards. A considerable number of this last group of patients must have taken with them to the outer world penicillin-resistant hospital staphylococci, and it is gratifying and perhaps a little surprising that we have isolated only 43 resistant strains (21.5%), as compared with 16% three years ago. The spread of resistant staphylococci within hospitals has been so rapid that it might be thought that there is some special feature of the hospital environment which encourages them in preference to sensitive strains. Perhaps in the outer world sensitive staphylococci are better able to hold their own, and a 21.5% rate represents a state of equilibrium.

Streptomycin.—With the use of a heavy inoculum two of our strains were relatively resistant to streptomycin, but that this represents the selection of a few resistant variants is suggested by the finding that all the strains were sensitive when tested with a dilute inoculum. There are few indications for the use of streptomycin in the treatment of staphylococcal infections, and it was included as a matter of theoretical interest.

Other Antibiotics.—Resistance to oxytetracycline, chloramphenicol, erythromycin (and streptomycin) is the result of

exposure of staphylococci to these drugs, and resistance, once acquired, is permanent. This type of resistance is becoming an additional characteristic of hospital staphylococci, and its occurrence is related to the frequency with which the newer antibiotics are prescribed. That we have found only one staphylococcus to be resistant to chloramphenicol and none to be resistant to the other antibiotics presumably reflects the relatively restricted use of antibiotics in general practice, and the dilution among the general public of resistant hospital strains.

If *in vitro* sensitivity tests can be taken as a guide to the likely outcome of treatment—and for most infections and drugs there is general agreement that they can—our findings would suggest that some 80% of staphylococcal infections originating outside hospital will respond to treatment with penicillin, and almost all to treatment with oxytetracycline, chloramphenicol, and erythromycin.

Summary

Two hundred strains of *Staph. pyogenes* isolated from out-patients with acute staphylococcal infections of the skin and subcutaneous tissues have been tested for their sensitivity to penicillin, streptomycin, oxytetracycline, chloramphenicol, and erythromycin. Of the strains tested, 21.5% were resistant to penicillin. One strain was resistant to chloramphenicol, and none to the other antibiotics.

Comparison of these results with those of a similar investigation carried out three years ago has shown that there has been a slight increase in the proportion of strains resistant to penicillin, but virtually no increase in strains resistant to the other antibiotics.

We are indebted to Professor L. P. Garrod for advice, and to Miss M. Rhodes for technical assistance.

REFERENCES

- Birnstingl, M. A., Shooter, R. A., and Hunt, M. F. (1952). *British Medical Journal*, 2, 253.
Spink, W. W. (1951). *J. Lab. clin. Med.*, 37, 278.

TREATMENT OF THE PREMENSTRUAL SYNDROME VALUE OF ETHISTERONE, MEPHENESIN, AND A PLACEBO COMPARED

BY

G. I. M. SWYER, D.M., D.Phil., M.R.C.P.

Consultant Endocrinologist, Department of Obstetrics,
University College Hospital

In a recent penetrating contribution on the premenstrual syndrome Greene and Dalton (1953) reached the conclusion that the wide variety of distressing symptoms from which many women suffer during the final week or so of the menstrual cycle, and occasionally at other points of the cycle, are probably due to water-retention. This, in turn, they felt was very likely the result of an abnormal elevation of the oestradiol/progesterone ratio. Claims for the beneficial results of treatment aimed either at dehydration or at correcting the alleged hormonal disturbance have, they point out, been made by a number of writers. They themselves found treatment by a progestogen to be almost invariably successful, in mild cases relief usually being obtained by the oral administration of ethisterone in a dosage of 25 mg. twice daily during the second half of the menstrual cycle. Still more effective was the intramuscular injection of progesterone, 25 mg. on alternate days during

the same phase of the cycle, or the implantation of progesterone, which then remained available for many months.

My own experiences with ethisterone, used in much the same way as above, had been less convincing of its efficacy. Moreover, it has seemed probable that psychological factors, leading to the tension-pain syndrome, might constitute a not unimportant part of the premenstrual syndrome, so that the administration of a muscle-relaxing drug might be expected to have some value in the management of the condition. There have already been reports that mephenesin ("myanesin"; 3-(2-methylphenoxy)propane-1:2-diol) administered orally to patients with disturbed psychic functions manifested as anxiety could produce sedation without soporific effect (Schlan and Unna, 1949); and Ström-Olsen (1951) found this drug to be of value in combination with psychotherapy in relieving tension states. There seemed to be good reason, therefore, for submitting the use of mephenesin orally in the treatment of premenstrual symptoms to clinical trial, and at the same time to compare its value with that of ethisterone.

Plan of the Experiment

Since the assessment of the patients' symptoms could only be subjective, it was clearly necessary to adopt a plan which would eliminate, so far as possible, both patient and observer bias. The use of a placebo, indistinguishable from the active tablets, was a prime requirement, and ignorance of the nature of each set of tablets, both by the patient and, at least until after the result had been recorded, by the observer, was equally important. The scheme employed therefore consisted of four groups of treatments: placebo; ethisterone, 10 mg.; mephenesin, 0.5 g.; and ethisterone, 10 mg., + mephenesin, 0.5 g. All the tablets, of course, looked alike and were put up in numbered boxes, a complete set of the four treatments, in prearranged order, being contained within a larger numbered box. It was intended that each patient in the trial should have each of the four treatments in successive months, in random order, the actual order remaining unknown to the observer until the end of the trial. This therefore called for 24, that is 24, patients for a complete series.

The patients were women attending the Fertility and Endocrine Clinics of the Obstetric Hospital, University College Hospital, and employees of the Savings Bank division of the General Post Office (kindly referred by Dr. Mary Parkes). The nature of the trial was explained to them—namely, that they would be having four different treatments in successive months, and would be asked which seemed to be effective. A record was made of their age, parity, the duration of their premenstrual symptoms; whether the latter were mild or severe, and whether they were constant or inconstant from one cycle to another. They were entered into the trial in the order in which they presented themselves and were given the first box of tablets from the appropriate large container. They were told to take one tablet five times a day for 10 days, starting on the 15th day of the cycle, and to return a month later.

On their return the effect of treatment in the cycle just finished was scored as ++ if symptoms were completely abolished; + if there was some, but incomplete, improvement; 0 if the symptoms were unchanged; and — if the symptoms were worse, or additional symptoms, thought to have been caused by the treatment, were noticed. They were then given the second box of tablets, and so on until all four months of treatment had been accomplished. Naturally, in a trial of this kind, it is inevitable that, for one reason or another, not every patient completes the planned series of treatments.

Results

The clinical details of the patients, and their results with the individual treatments, are shown in Table I. From this it is at once clear that there is considerable variation in the severity and variability of the symptoms from patient to patient, and in the same patient from cycle to cycle. This naturally makes the assessment of the value of different treatments more difficult.

Table II shows the results of treatment for each successive month, regardless of the treatment actually used. It would

TABLE I.—Details of Patients and Their Individual Results

No.	Age	Parity	Duration of Symptoms	Symptoms		Months of Treatment				
						1	2	3	4	
1	24	0	3 yrs.	Severe	Constant	A+	Conceived in this cycle			
1a	37	0	>10 "	"	"	A0	B+			
2	30	2	>6 "	Mild	"	B0	A—	C—	D—	
3	34	2	3 "	Severe	Variable	B+	C+	A+	D0	
4	35	2	15 "	"	Constant	B0	C0	D0	A0	
5	33	0	>10 "	"	"	A—	D—	B0	C—	
6	40	0	>5 "	Mild	Variable	D—	A+	B0	C—	
7	31	0	3 "	Severe	Constant	C—	D—	A+	B+	
8	31	0	>5 "	"	Variable	C+	B0	D+	A++	
9	37	0	>5 "	"	Constant	A++	C0	D+	B+	
10	41	0	>5 "	"	Variable	C+	A++	D+	B—	
11	18	0	4 "	"	"	B0	C+	A0	D+	
12	34	1	5 "	"	Constant	C0	D0	B+	A++	
13	24	0	8 "	"	Variable	A+	B0	D+	C++	
14	21	0	>5 "	Mild	Constant	B++	A0	C+	D++	
15	18	0	3 "	Severe	"	B0				
16	30	0	3 "	"	"	B—	D+	C+	A++	
17	33	0	20 "	"	Variable	A++	C0	B+	D++	
18	20	0	6 "	Mild	Constant	C+	A++	B++	Pregnant	
19	34	0	20 "	"	"	D—	C++	A++	B+	
20	18	0	1 "	Severe	"	A+	B++	C+	D0	
21	16	0	1 "	Mild	"	A—	D0	C+	B+	
22	37	0	10 "	Severe	"	D0	A—	C++	B+	
23	32	0	5 "	"	Variable	"	"	"	"	
24	17	0	1 "	Mild	"	D—	C+	B+	A0	

A = Mephenesin. B = Ethisterone. C = Mephenesin + ethisterone. D = Placebo. ++ = Very good. + = Good. 0 = No effect. — = Side-effects.

TABLE II.—Results of Treatment by Months Irrespective of Actual Treatment

Month	Very Good	Good	Total	No Effect	Side-effects	Total
1	3	7	10	7	7	14
2	4	6	10	8	4	12
3	4	12	16	4	1	5
4	5	7	12	4	4	8

TABLE III.—Comparison of Results in First and Second Months with those in Third and Fourth

Months	Good	No Good
1+2	20	26
3+4	28	13

TABLE IV.—Results of Treatment by Different Treatments, Irrespective of Months

Treatment	Very Good	Good	Total	No Effects	Side-effects	Total
Mephenesin	8	6	14	5	4	9
Mephenesin + ethisterone	3	10	13	4	4	8
Ethisterone	3	10	13	8	2	10
Placebo	2	6	8	6	6	12

TABLE V.—Comparison of Mephenesin versus the Rest

Treatment	Good	No Good
Mephenesin + (mephenesin + ethisterone)	27	17
Ethisterone + placebo	21	22

TABLE VI.—Comparison of Ethisterone versus the Rest

Treatment	Good	No Good
Ethisterone + (ethisterone + mephenesin)	26	18
Mephenesin + placebo	22	21

appear that fewer good results were obtained during months 1 + 2 than during months 3 + 4; this is more apparent in Table III. The difference is not significant ($\chi^2=1.302$); nevertheless it seems possible that the suggestibility of the patients may have been heightened towards the latter part of the trial, so that those who had not yet experienced relief from the treatments they had had so far presumably thought that some of the later treatments ought to be effective.

Table IV sets out the results of the different treatments, irrespective of months. It will be seen that complete relief of symptoms occurred most often with mephenesin, but that when the "very good" and "good" results combined were compared with the poor results, there was not much to choose between mephenesin, ethisterone, or mephenesin + ethisterone. The placebo, though less effective than the above, was by no means devoid of apparent value.

Tables V and VI compare mephenesin with the rest and ethisterone with the rest. The similarity in these groups of figures will be noticed. None of these differences is statistically significant.

Discussion

The results of this limited trial suggest that both ethisterone and mephenesin have some value in the treatment of the premenstrual syndrome, but that neither can be expected to help more than about 60% of patients. The combination of mephenesin and ethisterone appears to be no better than either substance alone. Mephenesin alone completely relieved eight patients, whereas ethisterone and ethisterone + mephenesin had this effect on only three each, and the placebo did as well in two patients. Table I shows that of the 21 patients who had all four treatments, only 3 had no relief from any treatment, 10 benefited from either ethisterone or mephenesin, and 8 appeared to be helped by both.

The incidence of side-effects was notably low both with mephenesin and with ethisterone; in point of fact, more complaints of these were recorded for the placebo than for the other tablets.

Since in this trial either ethisterone or mephenesin alone helped some 60% of patients, and one or the other was of some value to about 90% of the patients, it is apparent that hormonal imbalance may not be the sole cause of the symptoms in at least some of the patients. The evidence suggests that psychological factors, manifesting themselves in tension states, may be an important part of the premenstrual syndrome in some cases, and where successful treatment does not follow from ethisterone therapy the use of mephenesin might well be considered.

Summary

A clinical trial of ethisterone and of mephenesin, alone and in combination, for the treatment of premenstrual symptoms has been carried out by means of a random block design, whereby the effects of the various treatments could be compared with each other and with those due to a placebo.

While mephenesin produced complete relief more often than ethisterone, an overall analysis suggests that there is little to choose between them. Either substance alone helped only some 60% of patients, and a combination of the two was no more effective; but one or the other was of some value to about 90% of the patients.

My thanks are due to Dr. Mary Parkes for referring the majority of the patients to me for the purposes of this trial; and to Dr. B. M. Merriman, of British Drug Houses Ltd., for supplying the sets of tablets.

REFERENCES

- Greene, R., and Dalton, K. (1953). *British Medical Journal*, 1, 1007.
Schlan, L. S., and Unna, K. R. (1949). *J. Amer. med. Ass.*, 140, 672.
Ström-Olsen, R. (1951). *Practitioner*, 167, 140.

ANTERIOR TIBIAL SYNDROME FOLLOWING ARTERIAL EMBOLISM

BY

D. C. WATSON, M.C., M.D., M.R.C.P.

Senior Medical Registrar, United Liverpool Hospitals

(From the Liverpool Royal Infirmary)

Carter *et al.* (1949) described a syndrome consisting of ischaemic necrosis of the muscles of the anterior tibial compartment of the leg, with a lesion of the anterior tibial nerve. Their 10 patients were fit young men, in eight of whom the onset was clearly related to strenuous unaccustomed exercise involving the use of the leg muscles. The condition developed in their two remaining cases after transfusion into the affected limb. The main clinical features were pain, swelling, redness, and tenderness in the front of the leg. There was inability to dorsiflex the foot and toes. The peroneal muscles were not affected. Involvement of the anterior tibial nerve produced paralysis of the extensor digitorum brevis muscle and sensory loss on the dorsum of the foot. The degree of residual foot-drop was lessened by the development of contracture in the affected muscles.

Vogt (1943) described the first similar case. Sirbu *et al.* (1944) described one case in which both legs were affected after marching, and another which followed repair of a small muscle hernia through the anterior crural fascia. Horn (1945) reported two cases in young soldiers after marching, and Phalen (1948) described the case of a young man who developed the syndrome after walking half a mile. The case of a young Greek who showed the same condition in both legs after long-jumping on a concrete pavement was recorded by Pearson *et al.* (1948). Hughes (1948) described three cases of "ischaemic necrosis of the anterior tibial muscles due to fatigue." Two were in healthy men who played football before the onset of their symptoms, and the third case occurred in a young man suffering from a febrile systemic illness, possibly polyarteritis nodosa. Tillotson and Coventry (1950) described a case in a hiker following his first walk of the season. Horn and Sevvitt (1951) reported a case in which the syndrome was included in the sequelae of a traumatic rupture of the popliteal artery. Similar symptoms were noted by Psaki and Schields (1952) in a soldier who sustained a twisted ankle.

Below, two cases are described in which the syndrome followed arterial embolism.

Case 1

A woman aged 51, who had chronic rheumatic heart disease, with aortic incompetence, mitral stenosis, and controlled auricular fibrillation, was admitted to hospital on May 25, 1954. There was a moderate degree of peripheral arteriosclerosis. She complained of severe pain, of sudden onset, in the right calf. The right lower limb was found to be cold and pale up to a handbreadth below the knee; the toes were deeply cyanosed, and gangrene appeared likely. The right popliteal pulsation was much weaker than the left and no pulsations could be felt at the right ankle. The right femoral pulsation and all pulses in the left lower limb were normal. A diagnosis of arterial embolism was made and treatment begun with analgesics and oral vasodilators (nicotinic acid, 100 mg., and tolazoline hydrochloride, 25 mg., both thrice daily). The affected leg was exposed and the foot supported in a right-angled splint.