been negative after three subsequent periods. This patient was therefore regarded as cured.

Summary and Conclusions

A series of 42 patients were given metronidazole for trichomoniasis; there were two failures (4.7%). This compares favourably with the results of local treatment and with the results of previous oral preparations. Side-effects were infrequent: only one patient developed nausea of sufficient severity to stop the drug.

Metronidazole has no effect on candida; with the reduction of their rivals, however, candida may be encouraged.

Durel *et al.* concluded that systemic treatment may be an adjunct to local treatment, but our experience suggests that systemic treatment alone is sufficient for vaginal and urinary infections. With the possibility of treating the husband or consort simultaneously a fruitful source of relapse is overcome.

Results have hitherto been such that caution is necessary until findings can be assessed over a longer period, but our evidence in this series seems to justify a more extensive trial of the drug.

We gratefully acknowledge the help and co-operation of Dr. Jean Young, of the Glasgow Public Health Department, in carrying out the laboratory investigations in this trial; also of the laboratory of Falkirk and District Royal Infirmary, especially Mr. W. Bertram, who contributed to this part of the work. We are also grateful to Dr. Robert Forgan for his encouragement and help, and to May & Baker Ltd. for generous supplies of metronidazole.

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PHENMETRAZINE HYDROCHLORIDE IN TREATMENT OF OBESITY

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Phenmetrazine hydrochloride is the approved name of the compound 2-phenyl-3-methyl-tetrahydroxazine hydrochloride, marketed under the trade name of "preludin." It is related to ephedrine and has chemical and pharmacological similarities to amphetamine. In reviewing this pharmacological relationship, Thomä and Wick (1954) infer that drugs of the amphetamine group suppress the appetite by their action on hypothalamic nuclei; according to Natenshon (1956) phenmetrazine has less tendency to raise the blood-pressure or to stimulate the cerebral cortex than amphetamine, the administration of which is sometimes accompanied by such side-effects as insomnia, anxiety, and palpitations.

Anand and Brobeck (1951) have shown that experimentally produced hypothalamic lesions may lead to anorexia or a voracious appetite, according to which nuclei are affected, and that appetite and satiation are opposing sensations that are under hypothalamic control. Berneike (1955) has suggested that the action of phenmetrazine is to induce the feeling of satiation earlier than it would normally occur. Fazekas *et al.* (1958) studied the effect of phenmetrazine and of placebo tablets in a series of adult patients attending a weight-reduction clinic, but these were given an "individualized diet" of unspecified calorie value. Moreover, the results were not standardized for the patients' initial percentage overweight. Rendle-Short (1960) has described the effect of phenmetrazine on the weight of obese children who were on an unrestricted food intake, and showed that the drug was effective in producing a loss of weight in these circumstances.

The object of the present investigation was to study the effect of phenmetrazine given to obese adults on a restricted diet by comparing the effect with that produced by a placebo.

Method and Material

Women between the ages of 20 and 66, and at least 15% overweight (Levine, 1923) but otherwise healthy, who attended the endocrine department for the treatment of obesity, were asked to take part in the trial. Sixty consented to do so, but only 32 completed it, possibly because of a widespread bus strike at that time. Of these 32, 16 were in each group. Of the 28 patients who defaulted, 19 failed to attend after the first visit, and, of these, 12 had been given the active drug. At the first visit an attempt was made by one of us (P. M. N.) to assess the daily calorie intake from the patient's own description of her diet, although this can be a notoriously unreliable procedure.

The patients were divided randomly into two groups irrespective of the degree of obesity and age, and all were instructed to take one tablet three times a day half an hour before meals. One group of patients were given phenmetrazine 25 mg. thrice daily for four weeks, followed by placebo tablets of identical apearance for the next four weeks. The placebo tablets were administered for the first four weeks to the other group, and then these patients were placed on phenmetrazine. The tablets were dispensed by one of us (J. H. B.), who was aware of their nature; the patients were unaware that some of the tablets were inert. No patient received any other drug treatment to suppress appetite during the trial or three months before it started. All patients were given a 1,000-calorie diet sheet and told to carry out the instructions on it or to continue on their present dietary regime if they were consuming less than 1,000 calories.

Each patient was weighed in indoor clothes without shoes on scales the accuracy of which was checked every two weeks.

Results

The results of treatment with phenmetrazine and diet restriction are summarized in the Table. It will be seen that there is a comparable mean loss of weight during the month on phenmetrazine, whether it was given during the first month (6.5 lb.) or the second (6.4 lb.). However, the mean loss of weight during the month on placebo was much greater when the placebo was given first—3.3 lb.; when placebo was given after phenmetrazine there was a mean *gain* in weight during that month—0.73 lb. Consequently, the group which received placebo followed by phenmetrazine had a mean

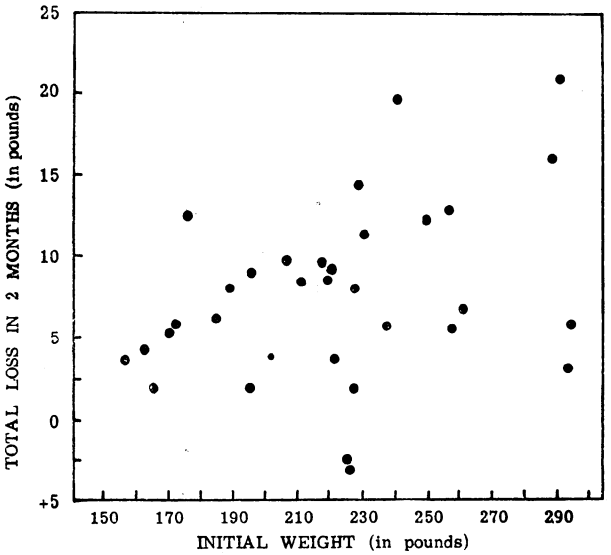
Analysis of Weight Changes (in Pounds) in Each Month on Phenmetrazine and Placebo

Order of Treatment	No. of Patients	Mean Weight Changes ±S.D. During Month on		Overall Loss ±S.D.
		Phen-metrazine	Placebo	
1st month phenmetrazine 2nd ,, placebo	16	−6·5±1·1	+0·73±0·7	2·9±0·9
1st ,, placebo 2nd ,, phenmetrazine	16	−6·4±0·8	−3·3 ±0·8	4·8±0·7
Overall mean loss±S.D. ..	32	6·4±0·7	1·3 ±0·7	

loss of weight of 4.8 lb., whereas the group which received the phenmetrazine before placebo had a mean loss of weight of 2.9 lb.

Inspection of the results suggests that those patients who were initially most overweight were those who lost most weight, and this trend is shown in the Chart, though the coefficient of correlation, $r=0.22$, is below the level of significance, $r=0.35$. To exclude this factor as a possible source of bias the loss of weight was expressed as a percentage of the initial weight:

$$\text{Percentage loss} = \frac{\text{Weight loss}}{\text{Initial weight}} \times 100.$$



Relationship between loss of weight and initial weight. Although suggestive this did not attain the level of significance.

The correlation coefficient between the percentage loss and the initial weight is not significant, and when the percentage loss was substituted for the observed loss the level of significance was of a lower order—$r=0.11$.

A statistical analysis shows that the effect of the drug compared with that of the placebo is of a high degree of significance ($P<0.001$) and that the order of treatment —that is, whether the placebo or phenmetrazine was given first—is also significant: $0.05>P>0.02$.

Side-effects.—Forty-six women received phenmetrazine in doses of 25 mg. thrice daily, and only one was unable to tolerate it; she said, "It made me feel ill." Of the 32 patients who received both types of tablets one said that phenmetrazine did not help her, whereas 15 experienced no suppression of appetite when taking the placebo. While taking the drug two patients complained of sleeplessness, two of mild "depression," and three of headache or dizziness, but these symptoms were not severe enough to make the patients abandon the treatment. Four patients complained of similar symptoms when they were taking the placebo. In no case was there any psychotic manifestation.

Discussion

It is not easy to design an ideal clinical trial that involves keeping patients on a constant calorie intake. If the trial period is too long the patients are apt to break their diet; if the period is too short the drug that is being studied may not have been given a fair chance to show its appetite-suppressing properties. For these reasons four-week periods on the drug and on the placebo were chosen. Such short periods, however, cannot demonstrate any long-term effects on phenmetrazine.

There is clearly no significant difference between the loss of weight in the two groups in the phenmetrazine month—6.5 lb. against 6.4 lb. It is evident that patients who received the placebo followed by phenmetrazine showed a more satisfactory loss of weight than those who received the phenmetrazine in the first month. The patients who received the placebo in the second month actually showed a mean gain in weight during the period of treatment, though they were unaware of the nature of the tablet. We have the impression that obese patients lose weight more satisfactorily if they have been submitted to the discipline of dieting before being given phenmetrazine.

Patients did not complain of insomnia, which sometimes occurs during treatment with drugs of the amphetamine group, in spite of the fact that phenmetrazine was given three times a day. We are of the opinion that this is a safe and effective drug, provided that the dose is not excessive.

Summary

An account is given of a controlled trial in which 32 obese patients were given phenmetrazine and placebo tablets and who completed the trial period. The patients, all of whom were at least 15% overweight, were observed for a period of two months.

25-mg. phenmetrazine tablets were given thrice daily, and in this dosage side-effects were insignificant and there was no interference with sleep.

Attention is drawn to the fact that during the second month patients on phenmetrazine lost weight whereas patients receiving the placebo in the second month gained weight. The influence of initial weight on loss of weight is considered, and there is some evidence to indicate that those who were most overweight lost more weight on treatment.

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