TREATMENT OF TRICHOMONIASIS WITH METRONIDAZOLE

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It is generally agreed that vaginitis due to *Trichomonas vaginalis* is easy to treat and difficult to cure. Substances for local use have so far offered only a limited prospect of eliminating the organism ; symptoms are relieved but relapse is frequent. The solution of this problem seemed to be a preparation which would be effective systemically, but the results with " trichomycin " and acinitrazole were disappointing. The continued search for a more effective substance led to experimental work on metronidazole (1-β-hydroxyethyl-2-methyl-5-nitroimidazole ; " flagyl " or 8823 R.P.) by Cosar and Julou (1959), and the clinical study of Durel, Roiron, Siboulet, and Borel (1960) has opened up a new line of investigation.

Present Investigation

The patients in this series were women who were attending out-patient clinics for the treatment of venereal diseases. In the course of a routine investigation they were all examined for the presence of the gonococcus and of *T. vaginalis*. Specimens from the urethra and vagina were conveyed to the Glasgow Public Health Laboratory in Stuart's transport medium, which preserves the vitality of the trichomonads, although it was produced primarily to keep the gonococcus alive in transit. At the laboratory a wet film was examined, and if trichomonads were not found a culture was made.

The drug was given to those patients who, by film or culture, were found to harbour the protozoon. The degree of infection varied from heavy, with profuse discharge, to light, with few parasites and only slightly increased secretion. No selection was made, other than exclusion from the trial of those women who were assessed as almost certain to default. Even with this reservation 5 out of the 42 patients to whom the drug was given failed to return. Four patients in the series were post-menopausal, six were pregnant, and three suffered from a concurrent vaginal mycosis.

The first 14 patients were treated with one 200-mg. tablet orally thrice daily for 10 days, and one 0.5-g. vaginal pessary each night during that period. The next 24 patients were given the same oral dosage but no local treatment. The most recently treated cases, four to date, were given the same daily dosage, but for seven days only.

Of the 42 patients treated, 26 had a concurrent trichomonal and gonococcal infection, and these women were instructed to attend for the surveillance usual in the latter disease. Routine tests of cure were made at the same time for the trichomonal infection: it was hoped to persuade *all* patients to attend for these tests after three successive menstrual periods, but this proved to be a more perfectionist pattern than they were disposed to follow. Most of them did attend during the first two weeks after treatment, and after the first period ; some returned after the second period, and some completed the full three months. Tests of cure consisted in every case of direct examination of wet films and cultures from urethra and cervix, the culture medium being that advocated by Feinberg and Whittington (1957).

Table I shows the extent to which it was possible to assess the cure rate, and the duration of surveillance for each case.

TABLE I.—*Results of Tests of Cure*

Result	Duration of Surveillance after Treatment						Total No. of Patients
	4 Days	1 Week	2 Weeks	1 Month	2 Months	3 Months	
Successful ..	2	2	1	9	12	14	40
Failed ..	0	0	0	2	0	0	2

Where it was possible to examine the patients on the third day after the start of treatment it was found that the trichomonads in all these cases had disappeared and symptoms had subsided. This was not our experience with an earlier preparation said to be active by mouth, but the problem in the past has not been the immediate control of trichomonal vaginitis but its permanent elimination. Metronidazole appeared to be effective in pregnant women and without additional hazard ; it was also successful in three out of the four post-menopausal patients. The presence of a cervical erosion, which formerly seemed to make the cure of trichomonal vaginitis even more difficult, did not interfere with the response to metronidazole.

In three patients found to harbour *Candida albicans* the presence of this infection had not been apparent before metronidazole was given ; the effect of the drug was to play up the mycosis. One of these patients suffered so severely from pruritus vulvae that she stopped taking the drug after three days, but, in spite of this truncated dosage, trichomonads did not reappear ; in the second patient symptoms were of moderate degree and the full course of the drug was given ; the third had no symptoms due to candida.

The results of treatment are shown in Table II.

TABLE II.—*Results with Different Schedules of Treatment*

Result	Metronidazole		
	200 mg. Orally t.i.d. and 0·5-g. Pessary Daily for 10 Days	200 mg. Orally t.i.d.	
		For 10 Days	For 7 Days
Cured ..	13	24	3
Relapsed ..	1	0	1

Patients Who Failed to Respond

Case 1.—This patient, aged 50, was treated by oral and vaginal routes for 10 days. Trichomonads were found after the first and second months, and she was again treated systemically for 10 days. Trichomonal vaginitis was again present. This patient must therefore be regarded as resistant to metronidazole.

Case 2.—This patient, aged 19, had a very profuse discharge with numerous trichomonads. She was given seven days' oral treatment and relapsed after the first period. There has not yet been time for re-treatment ; the result shows that a course of treatment lasting seven days was not sufficient for this patient, and suggests that a heavily infected patient may require longer treatment.

A third patient, aged 19, who had oral treatment only for 10 days, had negative tests after one week, two weeks, and after the first period. Trichomonads were found after the second period, but without further treatment tests have

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.

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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