

## SYSTEMIC TREATMENT OF TRICHOMONAS VAGINALIS INFESTATION IN WOMEN

### A PRELIMINARY REPORT

BY

ELISABETH REES, M.D. •

Department of Venereal Diseases, Liverpool Royal Infirmary

The combined oral and systemic treatment of *Trichomonas vaginalis* infestation in women by metronidazole 1- $\beta$ -hydroxyethyl-2-methyl-5-nitroimidazole (RP 8823; "flagyl"), a derivative of nitroimidazole, has been reported by Durel *et al.* (1959) and Sylvestre *et al.* (1959). At Liverpool Royal Infirmary a clinical trial of this preparation administered systemically without any concurrent local therapy was instigated in December, 1959. The preliminary results are reported.

The patients taking part were women who attended the female venereal disease department either at the special clinic or at the "non-specific" clinic which is held in the gynaecological out-patient department. Patients are referred to the former by their general practitioners or other hospital departments, or attend as contacts of male cases of gonorrhoea or on their own accord. Patients are referred to the latter, as contacts, by male cases of non-specific urethritis who are attending male venereal disease clinics.

In view of the variability in demonstrating trichomonads on examination of wet preparations in the carrier type of case, treatment was limited initially to cases showing an acute infestation, in order that an immediate clinical assessment could be made. In the first four cases treated the clinical and symptomatic response was prompt. Thereafter, all those who presented and in whom trichomonads were demonstrated in wet preparations received metronidazole. Culture methods of diagnosis were not available in the clinic or the hospital laboratory, but permission was given by Professor T. N. A. Jeffcoate for cultures to be supplied and examined by his department. These were used in the follow-up of all cases treated with metronidazole. The culture medium used was the Feinberg-Whittington liquid liver medium (Feinberg and Whittington, 1957). As the vaginal discharge became thick and often scanty after treatment, the specimen was collected on a swab stick, the end of which was broken off into the bottle containing the medium. This was incubated within five minutes of inoculation and examined after 24 hours. Negative cultures were re-examined after 72 hours. Centrifuging was not carried out. Trichomonads were reported present 1+, 2++, or 3+++, according to the number present. *Candida albicans* was reported when found. Diagnosis was by microscopical examination of fresh preparations in normal saline in the clinic within fifteen minutes of taking.

Clinically, cases were recorded as acute, subacute, or carrier according to the clinical signs present at the time of diagnosis. A full clinical examination was recorded at each attendance by the same clinician, except on a few occasions during absence on leave. In cases in which gonorrhoea was diagnosed, treatment for *T. vaginalis* infestation was withheld for one week after

completion of treatment for gonorrhoea in order that a more accurate clinical assessment could be made.

Patients were asked to attend for observation weekly for four weeks, and after the next two menstrual periods. Difficulty was experienced in persuading patients to continue observation when they were symptom-free and believed themselves cured.

The number of patients who received metronidazole was 48, of whom 9 failed to return for any follow-up tests. Of the 39 patients who did attend for observation 15 had gonorrhoea. Two of these patients received metronidazole before the diagnosis of gonorrhoea was made, as gonococci were demonstrated only in the second series of tests. 11 patients were married, 2 were married but separated, and 26 were single. All admitted sexual intercourse except one girl aged 16 who was not virgo intacta. Metronidazole was prescribed in a dosage of 200 mg. three times a day for seven days. Initially, no directions regarding pre- or post-prandial administration were given, but after complaints of nausea in some patients the directions were changed to three times a day after meals. So far as can be judged within the limits of the numbers treated, this led to a diminution in the proportion of patients complaining of gastric symptoms.

Except in those who had gonorrhoea, married women and women with a single regular consort were not asked to abstain from sexual intercourse, it being thought that a more reliable method of ensuring against reinfection was to treat the male partner concurrently, if possible. Metronidazole in similar dosage was given to the male partners who were attending the male venereal disease clinics, irrespective of whether trichomonads were demonstrated in them. Women, whose husbands or regular consorts were not attending a clinic, were given metronidazole for their partners to take concurrently. In all except one case the men were said to have co-operated.

Seven of the 39 patients were resident in approved schools; three of these absconded early in their period of observation.

#### Clinical Assessment at Time of Diagnosis

*Acute infestation* was recorded when the clinical signs of vulvitis, congestion of the urethra usually associated with purulent discharge, copious thin purulent vaginal discharge, and punctate erythema of the vaginal walls were present.

*Subacute infestation* was recorded when there was no vulvitis, little or no congestion of the urethra, mucoid or absent urethral discharge, moderate to much thin mucoid or muco-purulent discharge, and no punctate erythema of the vaginal walls.

*Carrier* type of infestation was recorded in the absence of any clinical signs of *T. vaginalis*.

The incidence of these clinical groups in the 39 cases was: acute, 14; subacute, 19; carrier, 6.

#### Results of Treatment

##### A: Acute Cases

*Clinical Results.*—The response to treatment was prompt and identical in the majority of cases. By the seventh day of treatment the vulva was dry, purulent urethral discharge had changed to mucoid or was absent, the vagina contained thickish mucoid discharge slightly excessive or normal in quantity, and residual

congestion of the vaginal walls was present but gradually decreased and disappeared during the ensuing week. Detailed results are given in Table I. The two cases in which there was no response to treatment were Nos. 4 and 6. Case 4 was that of a 16-year-old girl who finally admitted taking the tablets only

TABLE I.—Clinical Response Seven Days After One Course of Metronidazole

No. of Cases	Clinically Normal	No Response	Not Recorded
14	11	2	1

morning and evening when she remembered. A second course, given a week after the first course, was supervised by the mother and resulted in a complete clinical and symptomatic response. Case 6 was that of a 15-stone woman who denied irregular treatment. It was thought possible that the failure might be associated with her weight. However, a second identical course prescribed a week after the first course resulted in a prompt clinical and symptomatic response. The fact that this patient complained of nausea and vomited twice during the second course, while apparently suffering no toxic symptoms during the first course, suggests the possibility that she did not take the latter.

TABLE II.—Presenting Symptoms

T.V. and Gonorrhoea				T.V. Uncomplicated			
No. of Cases	Disch.	Disch. and Irritation	Not Rec.	No. of Cases	Disch.	Disch. and Irritation	Not Rec.
3	2	—	1	11	8	3	—

Not rec. = Not recorded.

TABLE III.—Symptomatic Response Seven Days After One Course of Metronidazole

No. of Cases	Symptom-free	Much Improved	No Response	Not Recorded
14	9	2	2	1

TABLE IV.—Laboratory Results

Case No.	Weeks from Beginning of Treatment							
	1	2	3	4	6	8	12	16
1 {S. C.	—	— +++	—	— +		— +	—	
2 {S. C.	—	— +						
3 {S. C.	— ++							
4 {S. C.	— +	— +++	— +	— —	— —	— —		
5 {S. C.	—	—	—	—				
6 {S. C.		— +++	— +	— —				
7 {S. C.		—	—	—	— +	—	—	—
8 {S. C.	— +	— +		— +				— —
9 {S. C.							—	—
10 {S. C.	—							
11 {S. C.	—		—	—		—		
12 {S. C.	—		—	—	—			
13 {S. C.		—	—	—		—		
14 {S. C.		—	—	—		—		

S. = wet smear. C. = culture. — = No trichomonads present. +++ = Numerous trichomonads present. + = A few trichomonads present.

Symptomatic Results.—The majority of patients seen at seven days were symptom-free (Tables II and III). One experienced and intelligent patient who had had three previous attacks of acute infestation stated that the “drying-up” began on the second day of treatment.

No response was recorded in Cases 4 and 6, described above. Both responded to a second course of treatment, one being symptom-free and one having a slight residual discharge.

Laboratory Results.—These results are tabulated in Table IV.

No clinical or symptomatic relapse was observed throughout the periods of observation recorded. No history of sexual intercourse with an untreated partner was obtained.

**B: Subacute Cases**

Clinical Results.—Clinically, results were less dramatic than in acute infestations. Mucoid urethral discharge usually cleared unless there was associated prolapse of the anterior vaginal wall, and mucopurulent

TABLE V.—Clinical Response Seven Days After One Course of Metronidazole

No. of Cases	Clinically Normal	Much Improved	No Response	Not Recorded
19	8	7	2	2

TABLE VI.—Correlation Between Symptoms and Clinical Signs in Eight Patients Judged to be Clinically Much Improved But Not Clinically Normal

No. of Patients	Asymptomatic 7 Days After Treatment	Asymptomatic Before Treatment	Symptomatically Much Improved	Not Recorded
8	3	2	2	

TABLE VII.—Presenting Symptoms

T.V. and Gonorrhoea					T.V. Uncomplicated			
No. of Cases	Disch.	Disch. and Irritation	Lower Abdominal Pain	Symptom-free	No. of Cases	Disch.	Disch. and Irritation	Symptom-free
9	6	1	1	1	10	6	2	2

TABLE VIII.—Symptomatic Response Seven Days After One Course of Metronidazole

No. of Cases	Symptom-free	Much Improved	No Response	Not Recorded
19	14	2	—	3

vaginal discharge changed to mucoid in character, becoming thick in most cases and normal in quantity. In a proportion of cases the residual discharge was judged clinically to be in excess of normal, although many of these patients regarded themselves as symptom-free (Tables V and VI).

Symptomatic Results.—Most patients were symptom-free at the end of the course of treatment (Tables VII and VIII). Two patients who were asymptomatic before treatment noticed a decrease in the amount of discharge, which they had previously regarded as normal.

Laboratory Results.—These results are tabulated in Table IX.

Case 16 defaulted for 12 weeks, and on her return had relapsed clinically and symptomatically. She admitted sexual intercourse, and gonococci and T.

TABLE IX.—Laboratory Results (Subacute Cases)

Case No.	Weeks from Start of Treatment								
	1	2	3	4	6	8	12	16	20
15 {S. C.	-	-	-	-	+	-	-	-	-
16 {S. C.	-	-	-	-	-	-	+	-	-
17 {S. C.	+	-	+	-	-	-	-	-	-
18 {S. C.	-	-	-	-	-	-	-	-	-
19 {S. C.	-	-	-	-	-	-	-	-	-
20 {S. C.	+++	-	-	+	-	-	-	-	+
21 {S. C.	+	-	-	-	-	-	-	-	-
22 {S. C.	+	-	-	-	-	-	-	-	-
23 {S. C.	++	-	-	-	-	-	-	-	-
24 {S. C.	+	-	-	-	-	-	-	-	-
25 {S. C.	++	-	+	-	-	-	-	-	-
26 {S. C.	-	-	-	-	-	+	-	-	-
27 {S. C.	+	-	-	-	-	-	-	-	-
28 {S. C.	-	-	-	-	-	++	-	-	-
29 {S. C.	+++	-	-	-	-	-	-	-	-
30 {S. C.	-	-	-	-	-	-	-	-	-
31 {S. C.	-	-	-	-	-	-	-	-	-
32 {S. C.	-	-	-	-	-	-	-	-	-
33 {S. C.	-	-	-	-	-	-	-	-	-

S.=Wet smear. C.=Culture. -=No trichomonads present. +++=Numerous trichomonads present. +=Few trichomonads present.

*vaginalis* were demonstrated in her cervical and vaginal secretions respectively. She was judged to be reinfected.

Case 24 reported reappearance of some discharge at six weeks. There was no irritation, but *C. albicans* had been found in a previous test. There were no clinical signs of *C. albicans*, but nystatin was prescribed and the symptoms resolved.

Case 21 reported the presence of some discharge at eight weeks, after being symptom-free from the end of treatment. Clinically very little mucoid discharge was found.

Case 28 presented with a moderate amount of thin mucoid vaginal discharge with gas bubbles. She complained only of vague lower abdominal pain. No clinical response to treatment was observed throughout the period of observation. Laboratory tests were nega-

TABLE X.—Laboratory Results (Carriers)

Case No.	Weeks from Start of Treatment						
	1	2	3	4	6	8	12
34 {S. C.	-	-	-	-	-	-	-
35 {S. C.	+	-	-	-	+	-	-
36 {S. C.	-	-	-	-	-	-	-
37 {S. C.	-	-	-	-	-	-	-
38 {S. C.	-	-	-	-	-	-	-
39 {S. C.	-	-	-	-	+	-	++

S.=Smear. C.=Culture. -=No trichomonads present. +++=Many trichomonads present. +=Few trichomonads present.

tive after treatment (Table IX), but a positive culture was obtained in the eighth week of observation. This patient is resident in an approved school.

In no other case was clinical or symptomatic relapse observed.

**C: Carrier Cases**

All six cases had no clinical signs of *T. vaginalis* infestation, and were asymptomatic. They attended for the following reasons: contacts of cases of non-specific urethritis, 2; contacts of cases of gonorrhoea, 3; routine tests in approved school, 1.

*Laboratory Results.*—These results are tabulated in Table X.

Case 39 was that of a single girl who in the sixth week of observation admitted sexual intercourse with an untreated male consort who had used a condom.

Case 35 was a contact of her husband, who had non-specific urethritis. Both were treated with metronidazole. No clinical signs of symptoms accompanied the positive laboratory tests in either case.

**Toxic Reactions**

Toxic reactions were reported by five patients. One complained of a bitter taste in the mouth, two complained of slight nausea, one complained of marked nausea resulting in vomiting on two occasions, and one complained of irritation of the skin of the forearms with "red scaling patches" which appeared on the second day of treatment. This patient continued treatment and the rash started to fade. Examination on the seventh day revealed fading irregular squamous papules on both forearms.

**Candida Albicans**

*C. albicans* grows luxuriantly in the Feinberg-Whittington medium. Its presence was reported in 9 of the 39 cases at some time during the follow-up period. No irritation was reported by any of the nine patients, one complained of slight discharge after being symptom-free for five weeks. A request was made to the department of obstetrics and gynaecology for an estimated comparison of the incidence of *C. albicans* in specimens from the special clinic and those from the gynaecological clinic where cultures were being used for diagnostic purposes and where no metronidazole had been given. No significant difference was reported. It was therefore concluded that metronidazole did not encourage or suppress the growth of *C. albicans* and that the culture medium merely supported the growth of a normal inhabitant.

**Treated Partners**

10 of the 39 patients attended as contacts of their husbands or consorts, who had non-specific urethritis. Of five males who attended the Seamen's Dispensary, *T. vaginalis* was demonstrated in three after recurrent relapse resulted in the attendance of the wife at the "non-specific" clinic and the diagnosis in her of *T. vaginalis* infestation. Wet smears of centrifuged urine were positive in two cases and the prostatic bead in one. Culture methods of diagnosis were not available. Metronidazole was given to all husbands and wives. Two of the three men remain symptom-free three months and six weeks respectively after treatment. One has defaulted.

All five males who attended the Liverpool Royal Infirmary clinical were given metronidazole after their

treatment for non-specific urethritis. Urine centrifuged on one occasion revealed no trichomonads in wet smears. Culture methods of diagnosis were not available.

In addition, on epidemiological grounds, treatment for husbands who were symptom-free and not attending a male clinic was given to five wives. The husbands were said to have co-operated.

### Summary of Results of Treatment

The clinical results of treatment were recorded within seven days of the end of treatment in 30 of the 33 patients in whom clinical signs of *T. vaginalis* were present (13 acute and 17 subacute infestations). The response in two patients (Cases 4 and 6) is after the second course of treatment (Table XI).

TABLE XI.—Total Clinical Results After Treatment in 30 Patients Showing Clinical Signs of *T. vaginalis* Infestation

	Clinically Normal	Much Improved	No Response
Number .. ..	20	8	2
Percentage ..	66.7	26.7	6.6

The symptomatic results were recorded within seven days of the end of treatment in 26 of the 30 patients who had symptoms (13 acute, 13 subacute). The response in two patients (Cases 4 and 6) followed the second course of treatment (Table XII).

TABLE XII.—Total Symptomatic Results After Treatment in 26 Patients With Symptoms

	Symptom-free	Much Improved	No Response
No. of patients ..	21	5	0
Percentage .. ..	80.8	19.2	0

The difference between the clinical and symptomatic results suggests that the clinical assessment erred on the cautious side. In all except two subacute cases (Cases 17 and 28), who regarded themselves as symptom-free and whose laboratory results were satisfactory, the clinical response to treatment was most pronounced, the residual symptoms or signs when present being of a minor character and possibly due to another cause.

Laboratory results after treatment showed some difference in pattern between wet smears and cultures (Table XIII).

TABLE XIII.—Laboratory Results at First Test After Treatment in 39 Cases

	Wet Smears		Cultures	
	Negative	Positive	Negative	Positive
Number .. ..	38	1	22	17
Percentage ..	97.4	2.6	56.4	43.6

In four cases, which were tested at four days, wet smears were already negative though cultures were positive +++ in three cases. It was thought that metronidazole immobilized the trichomonads, making them difficult to recognize microscopically.

No association between positive culture results and the clinical type of infestation was found. The 17 positive cultures were distributed as follows: acute, 6; subacute, 9; carrier, 2. No difference between the

clinical and symptomatic response of patients with positive cultures and those with negative cultures was observed.

Cultures usually became negative in the second or third week of observation (Tables VII, IX, X). In 10 cases a positive culture was reported in four weeks or later. In only one case (Case 16) was this associated with clinical or symptomatic relapse and a positive wet smear. This patient was judged to be reinfected.

### Conclusions

Metronidazole administered systemically in the absence of any local therapy is a most effective remedy in the treatment of *T. vaginalis* infestation in the female. Continued observation of treated cases is necessary to assess its long-term value, particularly in cases in which positive culture tests after treatment have been reported.

The possible hazards associated with its use should be recognized. The high incidence of *T. vaginalis* infestation in women suffering from gonorrhoea (in 1958, 66% in female patients attending Liverpool Royal Infirmary), together with the asymptomatic nature of gonococcal infections in approximately half the female patients seen in venereal disease clinics, demonstrates the danger present in its indiscriminate use in promiscuous women, or, indeed, in any woman who has sexual intercourse with a partner who may be promiscuous. In the absence of any bacteriological investigation the rapid disappearance of discharge after treatment with metronidazole will undoubtedly result in the delayed diagnosis or non-diagnosis of gonorrhoea in many women harbouring both gonococci and *T. vaginalis*.

I am indebted to Professor T. N. A. Jeffcoate, Professor of Obstetrics and Gynaecology in the University of Liverpool, for the provision and examination of cultures by his department; to Mr. H. H. Francis, Senior Lecturer in Obstetrics and Gynaecology, for his co-operation; and to Mrs. P. M. Thomas, senior laboratory technician in the department of obstetrics and gynaecology, who reported on the cultures.

I would like to thank Dr. E. E. Prebble and Dr. C. D. Alergant, at the Venereal Disease Department, Liverpool Royal Infirmary, and Dr. F. Lanceley, Dr. J. L. Fluker, and Dr. A. S. W. Egerton, at the Seamen's Dispensary, for their co-operation in treating male contacts at my request and for access to their records. I am also grateful to Miss E. R. Smith for her welfare work and secretarial assistance throughout the trial.

The supplies of metronidazole were provided by Messrs. May and Baker Ltd.

### REFERENCES

- Durel, P., Roiron, V., Siboulet, A., and Borel, L. J. (1959). *C.R. Soc. franç. Gynéc.*, **29**, 36.  
 Feinberg, J. G., and Whittington, M. J. (1957). *J. clin. Path.*, **10**, 327.  
 Sylvestre, L., Gallai, Z., and Ethier, S. (1959). *Premier symposium Canadien sur les U.N.G.* Montreal.

The National Association for Mental Health has recently published *Child Guidance at Home and Abroad* (price 3s. 6d.), the proceedings of the Sixteenth Inter-Clinic Conference for Staffs of Child Guidance Clinics held on April 22 and 23. Papers were read on: the efficacy of child-guidance clinics; some aspects of child guidance in Belgium; questions facing mental health workers with children in Italy; and the child psychiatric scene in Scotland and Israel—a study in contrast.