

# Trichomoniasis

## Clinical Trial of Metronidazole (Flagyl®)

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RECOGNIZING trichomoniasis as a common cause of distressing vaginitis not amenable to cure by topical therapy, we welcomed the opportunity to evaluate metronidazole, a trichomonacide developed for oral administration. Encouraging results, reported in 1959, of comparative pharmacologic studies showing superior trichomonacidal activity for metronidazole soon were followed by reports of clinical studies<sup>6,9</sup> showing that trichomonacidal concentrations are achieved in serum and urine by oral administration of metronidazole in therapeutic dosages. Reports of early therapeutic trials of this drug were equally encouraging, and now have been confirmed by numerous clinical investigators who have reported consistently high cure rates with minimal side effects.<sup>1-4,6-18</sup>

### METHODS AND MATERIALS

Metronidazole was given to 138 patients drawn from those attending a small medical group in a city of southern California having a population of 37,000. Of these, 41 were lost to follow-up, leaving a series of 97 for evaluation of results. Ages ranged from 14 years to 52 years, 73 being between ages 21 and 40. Seventy-one were married; 24 were divorced, separated or widowed; and five were single. Duration of trichomonal infection, shown in Table 1, varied from a few days to 35 years. Of the 97 patients, 22 were asymptomatic, the other 75 accounting for the 104 complaints shown in Table 2. Twenty-five patients were pregnant when treated, ten in the first trimester, five in the second and ten in the third.

Diagnosis of trichomoniasis was confirmed microscopically in all cases. The immediate examination of wet smear (secured by using a cotton-tipped applicator, which when well filled with exudate is agitated in a small amount of normal saline solution in a test tube) has proved efficient. When motile, the trichomonads are seen readily under low power magnification.

After recent douching it may not be possible to find motile trichomonads, making culture necessary.

Flagyl®, a brand of metronidazole, was supplied for this study by G. D. Searle & Co.  
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• Metronidazole was given in various dosage regimens to 97 patients having microscopically diagnosed trichomoniasis.

At the first examination after treatment all 97, including 76 to whom metronidazole had been given orally only, were found by culture and wet smear to be free of trichomonads.

Reexamination of the 65 patients followed up for periods ranging from two weeks to 14 months revealed reappearance of trichomonads in eight cases.

Nineteen husbands were treated. No patient had a recurrence after treatment of the husband.

No effect of metronidazole on pregnancy or on fetal development was seen. Side effects, noted in 19 cases (20 per cent), generally were mild and transient and in no case were severe enough to terminate therapy before cure was effected.

TABLE 1.—Duration of Trichomoniasis\* at Beginning of Treatment with Metronidazole.

	No. Patients
0-1 month .....	7
1-6 months .....	9
7-12 months .....	7
2-5 years .....	20
6-10 years .....	11
11-20 years .....	6
21-30 years .....	1
31-40 years .....	1
Unknown .....	35
	97

\*From onset of symptoms.

TABLE 2.—Symptoms Associated with Trichomoniasis in 97 Patients.

	No. Patients
No complaints .....	22
Complaints .....	75
Leukorrhea .....	66
Pruritus .....	15
Scalding discharge .....	7
Vaginal irritation .....	6
Urinary frequency .....	3
Burning on micturition .....	2
Pelvic discomfort .....	1
Serosanguineous discharge .....	1
Urethritis .....	1
Dyspareunia .....	1
Pain on douching.....	1

**TABLE 3.—Results of Treatment with Metronidazole in 97 Patients with Microscopically Confirmed Trichomoniasis**

Daily Dosage	Number of Patients	Microscopic Findings at First Examination After Treatment		Patients Lost to Follow-up	Microscopic Findings at Subsequent Follow-up Examinations	
		Neg.	Pos.		Neg.	Pos.
100 mg orally for 10 days.....	67	67	0	23	39	5
1000 mg orally + 1000 mg vaginally for 10 days.....	19	19	0	4	12	3
500 mg orally for 10 days.....	7	7	0	4	3	0
1000 mg orally for 7 days.....	2	2	0	1	1	0
1000 mg orally + 1000 mg vaginally for 10 days.....	1	1	0	0	1	0
1000 mg vaginally for 10 days.....	1	1	0	0	1	0
Total.....	97	97	0	32	57	8

Our present practice is to culture in Kufferberg Trichosel broth. Cultures are examined at 48 to 96 hours. The following staining method has worked best in our laboratory: An air-dried smear is stained immediately with Giemsa tissue stain, Wolbach modification. The undiluted stain is left on the slide about one minute and then an equal amount of phosphate buffer at pH 7.2 is added. Staining is continued for two to three minutes.

Various dosage regimens were prescribed, including oral therapy alone in 76 cases, vaginal therapy alone in one case, and combinations of oral and vaginal therapy in 20 cases. Both tablets and suppositories were given in divided doses, twice daily. (See Table 3.)

All patients were asked to return within a week following the end of treatment and an attempt was made to see them several times subsequently at monthly intervals. A few patients have been followed for more than a year. The first examination after treatment included culture in 73 cases and wet smear in 96. Follow-up examination of 65 patients included culture in 52 cases and wet smear in 65.

**RESULTS**

As shown in Table 3, there were no failures as judged by wet smears and cultures at the first examination after treatment. Among the 75 symptomatic patients, all reported alleviation of symptoms within 48 to 72 hours after start of treatment.

Reexamination of the 65 patients followed up after apparent cure revealed reappearance of trichomonads in eight. Except for two lost to follow-up, these patients were retreated as often as indicated by reappearance of trichomonads. One of these eight patients now has had a total of four courses of metronidazole. Each of her first two repeat courses resulted again in apparent cure, but again follow-up examinations disclosed trichomonads. After the third such recurrence the husband's urine was cultured and found positive for trichomonads. He was then given a course of oral metronidazole at the same time as the wife was given her fourth course. At

**TABLE 4.—History of Ten Cases of Previously "Intractable" Trichomoniasis and Length of Follow-up After Apparent Cure with Metronidazole**

Case No.	Duration	
	Infection*	Follow-up
19.....	10 years	3 months
53.....	10 years	14 months
95.....	over 10 years	2 weeks
1.....	12 years	1 month
15.....	12 years	5 months
2.....	14 years	5½ months
16.....	15 years	2½ weeks
82.....	20 years	1 month
76.....	30 years	9 months
85.....	35 years	2½ months

\*From onset of symptoms.

**TABLE 5.—Relative Incidence of Side Effects Attributed to Metronidazole by 19 of 97 Patients (19.6 Per Cent)**

Complaint	No. Patients
Nausea .....	5
Vomiting .....	2
Gastric upset .....	3
Abdominal cramps .....	2
Malaise .....	1
Iron taste .....	2
Burning tongue .....	1
Generalized itching .....	2
Itching and burning of vagina.....	2
Dry mouth .....	1
Dizziness .....	1
Grogginess .....	1
Back pain .....	1

the time of this report she had remained negative for trichomonads for five weeks.

A total of 19 husbands now have been treated. No patient has had a recurrence after treatment of the husband.

Because all patients in the series were negative for trichomonads at the first examination after treatment, any influence that pregnancy may have on the responsiveness of trichomoniasis to metronidazole was not discernible. Of the eight recurrences, however, two were pregnant patients. Careful observation in the 25 cases in which metronidazole was administered during pregnancy revealed no deleterious effect on pregnancy or fetal development.

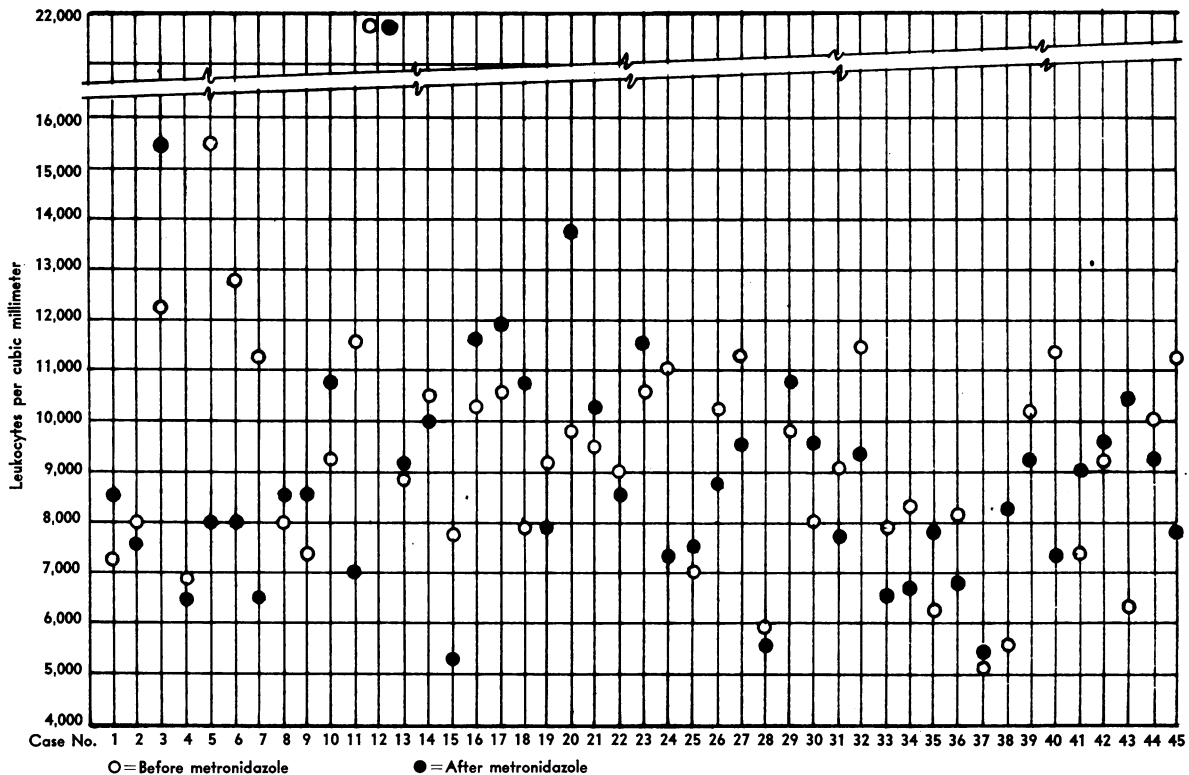


Chart 1.—Leukocyte counts in 45 patients immediately before and after treatment with metronidazole.

### Rapidity of Action

To determine how rapidly metronidazole would eliminate trichomonads, a special study was made of 24 patients in the series. It was found that two patients became negative within 48 hours after start of therapy, three in 96 hours, four in four days, six in five days, two in six days and one in seven days, the remaining six being found negative in eight to fourteen days.

### “Intractable” Cases

Ten patients had had trichomoniasis for ten years or more, and one had been given a variety of treatments during 35 years without a cure. (See Table 4.) Each of these ten was relieved of symptoms promptly and was proved free of trichomonads as judged by culture and wet smear. These patients were among the most grateful, as they had practically given up hope of permanent relief.

### SIDE EFFECTS

The 24 complaints of side effects (listed in Table 5) were made by 19 patients. The two who complained of vaginal symptoms were using metronidazole suppositories. Although several investigators have found that concentrated specimens of urine from patients taking metronidazole may have a red-

dish-brown color, no patient in our series remarked about any change in the urine.

With reassurance and instruction to take the tablets immediately after meals, all patients were able to continue therapy until cure was effected. For one patient a side effect was severe enough to necessitate discontinuing therapy. This patient, who because of nausea took only 26 of her 40 tablets, nevertheless was free of trichomonads when examined after her shortened course of therapy.

Leukocyte counts were done at the start and after conclusion of treatment in 45 cases. No significant changes were noted. See Chart 1.

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