OBSERVATIONS ON VAGINAL TRICHOMONIASIS II. TREATMENT WITH METRONIDAZOLE*

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IN PART I of these communications[1] describing the studies on *Trichomonas vaginalis* infestation that are being conducted at Dalhousie University, the following observations were reported:

1. In pregnant women, the presence or absence of *T. vaginalis* appears to be unrelated to the various other bacteria and fungi which may be present in the vagina; that is, there is no "favourable" or "unfavourable" underlying vaginal flora.
2. Untreated, the parasite remains in the vagina throughout pregnancy and delivery, and can be cultured from the lochia.
3. There appears to be no "favourable" pH range.
4. The presence of *T. vaginalis* in the mother's vagina has no ill effect on her infant.
5. Though "symptomatic" cases are less frequent (8%) than asymptomatic cases, the organism can be obtained by culture from about 50% of the women attending the Dalhousie University Prenatal Clinic.

PROBLEMS IN TREATMENT

Because this organism is harboured by many asymptomatic women—about 40% in our series, which now includes over 1000 pregnant women—and apparently does not harm the child, the question arises "Who should be treated?" At the present time, we know of no means whereby we can predict which patients will develop symptoms. Leukorrhea of itself is such an "indefinite" condition that only the most severe examples can be classified as "symptomatic". The woman who complains of irritation—if she has trichomoniasis—is obviously a candidate for treatment, and those with associated urinary symptoms attributable to this infection may be relieved by treatment.

Heretofore our practice has been to treat those who carry a heavy infection—as determined by the ease with which the motile flagellates are identified on direct microscopic examination of the wet preparation. This policy has resulted in moderately satisfactory results except for those "resistant" or "recurrent" cases which have led to trichomoniasis being called a stubborn disease. In the light of our present limited knowledge, these criteria may be satisfactory.

Previous methods of treatment are innumerable. *In vitro* activity of any particular agent is not necessarily related to its *in vivo* effectiveness. Trussell's[2] extensive list of preparations tested for *in vitro* activity and *in vivo* effectiveness indicates the magnitude of the search being carried on for the ideal therapeutic agent; and it points clearly to the fact that no ideal agent was available at the time that these studies were reported in 1947. The difficulty of dispersing any trichomonicidal agent thoroughly and continuously throughout the vagina is great. Tablets, jellies, douches, paints, powders, pledgets and ointments all have had their advocates. Furthermore, the parasite may be harboured in the cervix, in Bartholin's glands and in the urinary tract and probably in other sites which are less accessible. However, there is no reason to believe that it survives in the blood stream or lymphatics.[3]

Our lack of factual knowledge of the epidemiology of this disease makes it almost impossible to institute prophylaxis. It is quite apparent that promiscuous venereal spread cannot explain many of the cases encountered. For the present, we must be satisfied with improved methods for treating known cases.

Criteria for a Satisfactory Drug

A suitable antitrichomonal agent should show the following characteristics:

1. It must be safe—to both the adult and the fetus.
2. It must have greater than 90% effectiveness.
3. It must be administered easily.
4. It must be stable, package easily, and be comparatively economical.
5. It must not be unpleasant to use or have undesirable side effects.
6. The treatment course should not be prolonged, and symptoms must be promptly relieved.
7. It must disperse well and have a potent, rapid local effect.
8. It must be effective in tissue fluids so that it may reach otherwise inaccessible sites.
9. It must be effective in the urinary tract as well.

METRONIDAZOLE

Metronidazole became available to us in 1959 after preliminary clinical studies by Darel *et al.*[3] in Paris and Sylvestre, Gallai and Ethier[4] and Fortier[5] in Canada. We carried out an independent pharmacological assessment of this substance as follows.

1. Serial dilutions of metronidazole were made and added to actively growing cultures of *T. vaginalis*. Duplicate experiments were carried out and suitable controls maintained; 1 c.c. of 1/10,000 dilution (0.0001 mg. of metronidazole) killed the organism growing in simplified trypticase medium (Kupferberg) in 24 hours, and 1 c.c. of 1/100,000 (0.00001 mg.) was effective in 36 hours. Stronger solutions were more rapid in their action; weaker solutions were ineffective. Therefore, metronidazole is trichomonicidal in concentrations which can be attained in the tissues of the human ingesting

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250 mg. twice daily, if that concentration is maintained for several days.

2. Serum drawn from patients taking 250 mg. of metronidazole twice daily by mouth and control serum were added in decreasing amounts to cultures of *T. vaginalis* of a 10 c.c. volume. The organisms were killed by 0.5 c.c. or more of the serum from treated patients but not by that from controls. It appears that therapeutically effective concentrations of metronidazole are achieved in human serum when the recommended dose schedule is maintained.

3. Urine from treated cases and controls was similarly tested; 1 c.c. added to active cultures killed the parasites in four hours; 0.5 c.c. did not kill all the parasites, and the urine from controls had no effect. It appears that effective concentrations of the drug occur in the urine of patients on therapy with this agent.

Biochemical, pharmacological and experimental biological features of metronidazole have been reported by Cosar and Julou,[6] who developed the drug.

No serious toxic effects have been reported in adults in the accumulating literature on this substance, but some toxic effects were noted in animal fetuses where large doses were administered to the parent animal.[7] A small proportion of fetuses died *in utero*, presumably as a result of the huge doses of the drug administered to the pregnant animals; no deaths occurred in the control animals. No problems of this kind have been reported in the human subject.

Most of the criteria which we have established for a suitable trichomonicidal drug were therefore satisfied.

CLINICAL TRIALS

A. Thirty non-pregnant women, all of whom had trichomonads in vaginal culture, were treated, using 250 mg. tablets which were taken orally twice daily for 10 days; no topical therapy was used. Twenty-seven of these patients did not have the organism on subsequent vaginal culture; three patients required one additional course of therapy before the cultures became negative. No intolerance or dyscrasias were noted in the women who were treated, but long-term follow-up was not possible. Because our culture technique is highly accurate[1] and the mechanism of infestation is not known, there does not appear to be any value in long-term follow-up if the individual cannot be isolated. This drug appears to be highly trichomonicidal when given by mouth only. Although this was a small preliminary study, the cure rate, 90% on a 10-day course, is similar to that found in a number of other reported series, most of which are also based on small numbers of patients.

B. One hundred women at the Dalhousie Prenatal Clinic were found to have vaginal trichomoniasis, by smear and/or culture. These were all treated as follows: They were given 20 250-mg. tablets and instructed to take one tablet by mouth each night and morning for 10 days. They were also given 10 500-mg. tablets and instructed to insert one tablet into the vagina each night for 10 days.

Married women were also provided with sufficient tablets so that their husbands could have a similar course of oral treatment. No other treatment was prescribed. The women were at various stages of gestation when they were treated.

None of the women or their husbands complained of intolerance to or symptoms from the drug, although each was specifically questioned in this regard. Twenty-seven women had symptoms, possibly due to trichomoniasis, such as itching, profuse discharge, or both. In each case, the itching was fully relieved and the discharge disappeared or was greatly diminished.

TABLE I.

Cases treated	*Negative smear and culture*		
	1 month	*2 months*	*3 months*
100	93 (of 100)	41 (of 46) (3 previously negative) (2 previously positive)	11 (of 14) (1 previously negative) (1 positive 1st month) (1 positive 1st and 2nd month)

Gross cure rate (1 month): 93%

The gross cure rate at one month was 93%. Further tests were made on some of the women at two and three months (Table I). Obviously, the possibility of re-infection in some cases cannot be excluded. No attempts at further treatment were made and it was impossible to follow up all the women for an extended period. This was not regarded as an important defect in our investigation, as the gross cure rate, based on an accurate testing method, was highly satisfactory. In 21 cases, the leukocyte count was checked before and one to three weeks after treatment. No significant alteration or abnormality was recorded.

C. The babies of 92 women, including one set of twins, were studied; eight women have not yet been delivered or have left the clinic and their babies are not available for study. These women were delivered in the Grace Maternity Hospital, Halifax, under the supervision of the resident or attending staff. Initial observations of the babies were made by the resident, and a complete physical examination of the infant was carried out at birth and before discharge at one week. During the neonatal period, the infants were examined by the pediatric attending or resident staff. The observations on the babies are recorded in Table II. It is unlikely that any of the few abnormalities noted can be attributed to the absorption of metronidazole by the mother.

TABLE II.—BABIES

Total number	93 (1 set twins)
Apgar rating (1 minute):	
Score of 8 or higher	89
Score of 7	1
Score of 6	2
Score of 5	1 (breech)
"Congenital" defects	
None	90
Umbilical hernia	1
Hydrocephalus	1
Two small skin tags on right ear	1
Birth weight	
>6 lb.	84
<6 lb.	9 (including 1 twin)
Capillary hemoglobin at birth	
> 17 g.%	82
16 - 17 g.%	7
15 - 16 g.%	3
14 - 15 g.%	0
13 - 14 g.%	1
Neonatal disease (during the first seven days)	
Severe vomiting	1 (recovered)
Pneumonia	2 (recovered)
Upper respiratory infection	1 (recovered)

DISCUSSION

Since metronidazole was first described in 1959, there have been a number of reports of its use; these are summarized in Table III. All these studies indicate that the drug is more than 90% effective both when taken alone orally, and when taken in combination with topical therapy. In general, our observations agree with those of others regarding the therapeutic effectiveness of this agent. The fact that this substance, when taken orally, reaches concentrations in tissue fluids and urine which are trichomonicidal is of primary importance. We are not aware of any other drug which has shown this property and believe that this quality represents a genuine advance in the treatment of this infection. The drug, by and large, fulfils the other desirable criteria, emunerated above, for a suitable trichomonicidal agent and has replaced the arsenicals as the treatment of choice in this prenatal clinic.

In our experience with the drug, no contraindications to its use have been discovered.

TABLE III.—RESULTS IN WOMEN TREATED WITH METRONIDAZOLE.

	Oral therapy		*Combined therapy*	
Author	*Number*	*Cure*	*Number*	*Cure*
Fortier	8	4	31	28
	—	—	65	65
Darel	—	—	19	17
Watt and Jennison	50	44	—	—
Moffet	28	27	14	13
Robinson and Johnston	30	27	100	93
	116	102 (87.9%)	229	216 (94.3%)

SUMMARY

Thirty women with *T. vaginalis* infestation were treated with metronidazole, a new trichomonicidal substance taken orally; 90% were cured with a single 10-day course; 10% required a second course of therapy.

One hundred prenatal clinic patients who harboured the same flagellate were treated orally and topically; the husbands of these women were treated orally with the same drug; 93% of the women were free of the infection one month later.

No complications from treatment were recognized and the babies born to these women were not adversely affected.

Metronidazole appears to be the treatment of choice for *T. vaginalis* infections at the present time.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Regret is often expressed that common sense is not more generally used in the propagation of the human species, and we are familiar with attempts at legislation aimed at the control of marriage, the sterilization of degenerates, etc. Sentiment, however, is generally against such measures, and doubtless, also, there are better reasons than mere sentiment for opposing them. Something may be done in dealing with the more reasonable sort, by the gentle art of persuasion, the objections to marriage and especially to procreation being set forth tactfully, as one has opportunity in dealing with those in any way predisposed to psychic disturbance. Such instruction might well be undertaken early in life, before any suspicion of a "love" entanglement has to be combatted. When there is evident defect, particularly if any tendency to eroticism is manifest, the safety of the community, as well as of the unfortunate individual, demands segregation in a suitable institution. This costs more than sterilization or the lethal chamber, but does less violence to sentiment. Some authorities, as Archibald R. Douglas, of the Royal Albert Institution, assert that the imbecile is a much more potent agent in producing racial deterioration than the lunatic. I doubt if we have any more pressing need in Canada to-day than the proper provision for the feeble-minded members of our country, particularly those who are still sexually competent.

At best, we shall, for many years at least, be able to control the production of potential lunatics to only a very small extent.—W. H. Hattie, *Canad. M. A. J.*, 1: 1021, 1911.