LONG-TERM ASPECT OF TREATMENT WITH METRONIDAZOLE (FLAGYL) IN TRICHOMONAL VAGINITIS*

BY

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This study began in January, 1960, as a double-blind controlled therapeutic trial to determine the short-term value of metronidazole (Flagyl) in symptomatic trichomoniasis of women; 3 months later, when the results were analysed and found to be excellent, it was decided to continue the investigation and to arrive at a long-term assessment of the drug.

Material and Results

The patients were seen at the V.D. Clinic of the Central Middlesex Hospital. Prostitutes and women known to be very promiscuous were excluded from the trial as it was thought that the re-infection rate might make the interpretation of results difficult. Flagyl (200 mg. three times daily for 10 days) and dummy tablets were dispensed in identical packets which were randomized and numbered. The key to the numbers was kept by the hospital pharmacist until the end of the trial 3 months later. In cases of treatment failure, the patient was given a 10-day course of Flagyl; this ensured that all who failed to respond had at least one course of the drug.

In this controlled part of the trial, there were 67 women, 10 of whom defaulted after their first attendance; of the remaining 57 patients, 28 had received Flagyl and 29 a course of dummy tablets. It was of interest to find that of the ten early defaulters, seven had received dummy tablets, which suggests in the light of the trial results that early defaulting does not necessarily indicate successful treatment.

Table I gives the results of the controlled trial; there were three (10.3 per cent.) failures after Flagyl against 27 (93.1 per cent.) failures in the controls. The results of re-treating the failures are shown in Table II. There thus remained four treatment failures after Flagyl: two after two courses, and two after one course of the drug.

* The failures were re-treated with Flagyl.

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* Paper read at the M.S.S.V.D. meeting in Copenhagen on June 7, 1963.
The consolidated results of the two groups of patients are given in Table III. Of the 21 pregnant women, twenty were observed for from one month to one year after treatment and seventeen responded promptly to treatment. Seven of the infants born to these women were examined in due course and no abnormality was apparent. It is proposed to extend this part of the study in the future.

Among the 101 patients followed for a reasonable period there were eleven treatment failures; four responded to a second course of Flagyl, five did not, and the remaining two had only a single course of the drug. The possibility of re-infection was admitted by seven patients classified as treatment failures but for various reasons the consorts of these women could not be examined and this added to our uncertainty whether any of them had a re-infection rather than a relapse. In three patients active trichomonads were found at the end of treatment and these are clearly treatment failures.

The result as a whole is gratifying with 92 per cent. seemingly cured. Experience suggests that, in patients who fail after the standard 7-day course of Flagyl, it is worth repeating the drug before resorting to other measures. The fact that a few primary treatment failures did occur in this series might be due to poor absorption of the compound, as shown by Kane, McFadzean, and Squires (1961), or to the existence or development of Flagyl-resistant *Trichomonas vaginalis*, as found by Robinson (1962).

Eight patients complained of a bitter taste in the mouth, epigastric discomfort, and sometimes nausea whilst taking Flagyl, but it was not necessary to discontinue the drug. No side-effects were complained of by those taking dummy tablets. As Flagyl is a nitro-derivative, special attention was paid during the controlled trial to the blood picture, and total and differential white blood counts were carried out before and after treatment in forty patients, eighteen of whom were on dummy tablets and 22 on Flagyl. There was a fall in total and polymorphonuclear neutrophils in six of the control group and twelve of the drug-treated patients. This fall was of a minor degree except in two of the cases receiving Flagyl where the polymorphonuclear neutrophil count fell from 4,500 and 6,000/cmm. before treatment to 1,500/cmm. after treatment in both cases. The counts recovered their pre-treatment level a week later and there were no clinical symptoms associated with the fall, but clearly one must remain watchful for the possibility of more serious bone-marrow depression.

The incidence of fungi seen on direct microscopy of vaginal secretions before and after treatment with Flagyl is shown in Table IV. There is a significant increase in fungi after successful treatment of trichomonal vaginitis with Flagyl though some of these cases remained asymptomatic. The increase may be more apparent than real because of the unmasking of fungi when *T. vaginalis* was no longer present. As only one out of ten cases treated with Flagyl had some vaginitis afterwards which could have been due to fungi, prophylactic therapy against fungi when administering Flagyl is not advocated.

### Table III
**Consolidated Results of Treatment with Flagyl in 101 Patients with Trichomoniasis**

<table>
<thead>
<tr>
<th>Period of Observation (mths)</th>
<th>Number of Patients</th>
<th>Result of Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Success</td>
<td>Failure</td>
</tr>
<tr>
<td>None</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>67</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>Over 12</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Total Patients Followed</td>
<td>101</td>
<td>93 (92.1 per cent.)</td>
<td>8 (7.9 per cent.)</td>
</tr>
</tbody>
</table>

Among the 101 patients followed for a reasonable period there were eleven treatment failures; four responded to a second course of Flagyl, five did not, and the remaining two had only a single course of the drug. The possibility of re-infection was admitted by seven patients classified as treatment failures but for various reasons the consorts of these women could not be examined and this added to our uncertainty whether any of them had a re-infection rather than a relapse. In three patients active trichomonads were found at the end of treatment and these are clearly treatment failures.

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The incidence of fungi seen on direct microscopy of vaginal secretions before and after treatment with Flagyl is shown in Table IV. There is a significant increase in fungi after successful treatment of trichomonal vaginitis with Flagyl though some of these cases remained asymptomatic. The increase may be more apparent than real because of the unmasking of fungi when *T. vaginalis* was no longer present. As only one out of ten cases treated with Flagyl had some vaginitis afterwards which could have been due to fungi, prophylactic therapy against fungi when administering Flagyl is not advocated.

### Table IV
**Incidence of Vaginal Fungi in 101 Patients Treated with Flagyl**

<table>
<thead>
<tr>
<th>Fungi Found</th>
<th>No. of Patients</th>
<th>Symptoms probably Due to Fungal Vaginitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Only Before treatment with Flagyl</td>
<td>2</td>
<td>?</td>
</tr>
<tr>
<td>Only After treatment with Flagyl</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Before and After Treatment with Flagyl</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

### Summary and Conclusions

1. 122 women with symptomatic trichomonal vaginitis were treated with Flagyl; 21 (20.8 per cent.) defaulted immediately after treatment, but the rest could be re-examined for various periods, the majority for one year. Over 92 per cent. responded favourably to the drug.

2. The early part of the investigation was in the nature of a double-blind therapeutic trial, and the results in 57 patients showed that only 6.7 per cent. were clinically and microscopically clear after a course of dummy tablets as against 89.9 per cent. after a single course of Flagyl.
(3) In a few patients who did not respond to a 7-day course of Flagyl, a second course was successful.

(4) 21 patients were pregnant and twenty attended follow-up clinics; no abnormality in mother or child has so far been noted. This part of the study is to be extended.

(5) The clinical side-effects of Flagyl were of a minor nature and did not necessitate withdrawal of the drug. The results are given of a controlled total and differential white blood count in forty patients.

(6) There was an increase in the incidence of fungi seen in vaginal secretions after the successful eradication of *T. vaginalis* with Flagyl, but this may be due to the unmasking of these organisms rather than to a real increase. As only 10 per cent. of patients complained of symptoms which might be associated with fungal vaginitis, routine prophylactic measures against fungi are not advocated.

My thanks are due to Miss M. A. M. Bigby of the Central Middlesex Hospital for her interest and for referring patients to take part in the trial. I am also grateful to May and Baker Ltd., for supplying Flagyl and the dummy tablets.

REFERENCES

Résultats lointains du traitement de la trichomoniasi vaginale par le Flagyl (métronidazole)

**Résumé**

(1) Sur 122 femmes atteintes de trichomoniasi manifeste traitées par le Flagyl, 21 (20,8%) ne sont pas revenues à la clinique, mais on put suivre les autres pendant quelques mois, la plupart pendant un an. Plus de 92% furent guéries.

(2) Cette enquête fut d’abord “aveugle”; c’est à dire que ni le médecin ni la malade ne savait si la dose était du Flagyl véritable ou un remède factice. Sur 57 femmes 6,7% guéirent après avoir pris le remède factice, et 89,9% après un seul traitement de Flagyl.

(3) Quelques-unes ne guéirent pas après un traitement régulier hebdomadaire, mais un second traitement réussit.

(4) Sur 21 femmes enceintes, 20 furent suivies jusqu’à la parturition; aucune abnormalité ne fut constatée ni chez la mère ni chez l’enfant. Cette partie de l’enquête sera poursuivie.

(5) Les effets secondaires furent minimes et il ne fut jamais nécessaire de suspendre l’administration de Flagyl. On étudia aussi les globules blancs du sang chez 40 sujets.

(6) On observa des fongi dans les sécrétions vaginales plus souvent après l’éradication de *T. vaginalis*, mais ceci peut bien indiquer non pas l’augmentation mais la découverte de ces organismes. Puisque seulement 10% des malades accusèrent des signes d’infection vaginale fongueuse, on ne croit pas que la prophylaxie anti-fongueuse soit nécessaire.