(C) Absence of Action of Flagyl on Reproductive System in the Rat

As trichomonal infestation is common in pregnant women, it is of interest to know what effect, if any, Flagyl has on the reproductive system and offspring. Such animal studies are time-consuming, and they give us only partial information on what may happen in man, but they may serve as a pointer.

The work undertaken on this subject by those who carried out the early experiment with this compound is to be published at a later stage. The preliminary results obtained by Julou, Ganter, and Cosar (personal communication) are of considerable interest.

(a) Female rats received daily by mouth 50 or 100 mg./kg. Flagyl for 40 days. 10 days after starting treatment they were placed for 10 days along with untreated male rats, and for 20 days they were in individual cages. Each lot has the same proportion of pregnant rats as of untreated control animals. The average percentage increase in weight, and the average number in the litters were the same in all three groups.

(b) Male rats received daily by mouth 100 mg./kg. Flagyl for one month. At the end of that time they were placed for 10 days with untreated females. Thereafter they were killed and histological investigations were made of the genital system (to be reported later). Six out of nine females mated with treated males were impregnated, and among the controls six out of ten. It appears, therefore, that Flagyl has no effect on the fertility of rats, male or female.

(D) Blood Examinations

We continued, as a precaution, to check the blood picture in patients receiving Flagyl by mouth. We have already reported (Durel, Roiron, Siboulet, and Borel, 1960) the average counts before and after treatment in ten cases. Our observations now cover thirty patients, and no alteration has been noted.

Summary

(1) In two groups of women vaginal and oral administration have been compared. Given by mouth alone the drug is at least as active as when applied locally. Local treatment should probably be continued for more than 10 days.

(2) Flagyl (given orally) is recovered from the urine mostly in the free form. When the total daily dose is 500 mg., there is a tendency to accumulation which is not noted with lower dosages.

(3) In the rat the drug, given by mouth in high dosages, has had no effect on fecundity.

(4) No alteration of the blood picture, in either number or type of cell, was observed in a new group of patients who received the drug by mouth.

REFERENCE


Flagyl

Résumé

Le Flagyl (8823 R.P.) est efficace par voie générale comme ceci fut démontré, dès le début, par les succès observés chez l'homme. Chez la femme, le traitement mixte, oral et vaginal, donne les meilleurs résultats mais, pour comparer les deux modes d'administration, deux séries de femmes furent traitées: l'une par la seule voie locale, l'autre par la seule voie orale (500 mg. par jour pendant 10 jours, dans les deux cas).

Il y eut 13 échecs sur 40 (=32,5%) dans la première série, 6 sur 23 (=26%) dans la seconde; le traitement général est donc au moins aussi actif que le traitement local.

L'élimination urinaire du Flagyl, administré oralement, fut étudiée chez des volontaires. L'élimination est assez rapide et continue. La majeure partie du produit s'élimine à l'état nitré libre. Si les doses sont de 500 mg par jour, il y a une légère tendance à l'accumulation.

Des études sont en cours concernant un éventuel retentissement du traitement sur les fonctions génitales du rat. Jusqu'ici, on peut dire que le produit est sans action ni sur la gestation, ni sur l'embryogénèse de la rate, ni sur la fécondité du rat mâle.

Il n'a pas été noté d'altération de la numération ou des formules sanguines sur une nouvelle série de 20 malades soumis au traitement buccal.

DISCUSSION

Dr. G. W. Csonka (St. Mary's Hospital, London) said that his experience of Flagyl was the result of a double-blind controlled trial undertaken at the Central Middlesex Hospital and St. Mary's Hospital, Paddington, by Dr. Rosedale, Miss Bigby, and himself. The patients concerned were 66 females with clinical vaginitis in whom trichomonas vaginalis had been demonstrated by microscopy of a wet film of vaginal discharge. Pregnant women were excluded from the trial but otherwise the patients were unselected. Treatment consisted of 200-mg. tablets of Flagyl taken three times a day by mouth for 10 days. No local treatment was given. Dummy tablets (prepared by May & Baker
Ltd., through the courtesy of Dr. R. Forgan) in packets of thirty and similar packets of the drug were randomized and numbered. Until the end of the trial the key was known only to the Hospital Pharmacist. In some cases of clinical and microscopical evidence of failure the patients were re-treated with a 10-day course of Flagyl.

Results.—Of the 66 patients who started the trial, nine failed to return (13.6 per cent.). Seven of these defaulters had received dummy tablets. Of the remaining 57 patients, who were seen from 2 weeks to 5 months after the start of treatment, 27 had received Flagyl and thirty the dummy tablets. The two groups were closely comparable in age, social background, and duration of vaginitis before treatment. Of the 27 patients receiving the drug, only two were classed as failures. Of the thirty patients on control tablets, 28 failed to improve. Ten of the patients who had failed to respond after a 10-day course of the dummy tablets, were re-treated with a 10-day course of Flagyl, and nine responded rapidly to the drug. Adding this group to those originally treated with the active tablets, 37 patients received a course of Flagyl and all but three responded satisfactorily (91.9 per cent.). This was in contrast to 6.6 per cent. success in the control group.

Of the three failures after Flagyl treatment, one showed active trichomonads throughout the course and again one week after. In the second case there was temporary improvement with recurrence 6 weeks after treatment and the possibility of re-infection was admitted. In the third, the vaginitis cleared for almost 5 months and recurred after a menstrual period. In this case the possibility of re-infection was denied.

No side-effects were complained of by those taking the dummy tablets. Seven of the group receiving Flagyl, however, had epigastric discomfort, sometimes with nausea.

Total and differential white blood counts were carried out before and after treatment in 21 patients (ten on control tablets, eleven on Flagyl). There was a fall in total and polymorphonuclear neutrophils in four out of ten of the control group, and seven out of eleven of the drug-treated patients. This fall was usually of a minor degree except in two of the drug-treated patients in whom the polymorphonuclear neutrophils fell below 1,500 per c.mm. There were no clinical symptoms associated with this fall but clearly one must be watchful of the possibility of more serious bone-marrow depression.

Vaginal thrush was found for the first time in four patients after completion of Flagyl, but also in two patients after their course of control tablets. Even though Flagyl did not inhibit thrush, its effective use in trichomonas vaginitis had not led to any marked increase in its incidence in our patients.

In conclusion, this study seemed to show that at last we had a specifically-acting systemic drug for the treatment of trichomonas vaginitis.

Dr. M. Scott-Gray (Royal Infirmary, Edinburgh) gave a preliminary report on 67 patients, seven of whom were pregnant. The average age was 27½ years (range 14 to 56). The cases selected for the particular trial were all acute and showed active trichomonads. 43 (66 per cent.) had had previous treatment with varied preparations over a number of years; one woman "now thrilled with her cure" had been treated without relief for 21 years. There were eleven cases of combined urethral and vaginal infection (16 per cent.).

Treatment.—Three different regimes of treatment were tried:

(A) 21 patients received 21 tablets, one three times a day for 7 days.
(B) 27 patients received thirty tablets, one three times a day for 10 days.
(C) Nineteen patients received forty tablets, two four times a day for 5 days.

No local treatment was given to any patient. The clinical response was as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Tablets</th>
<th>No. of Cases</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>21</td>
<td>21</td>
<td>Excellent 18–86 per cent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Very Good 2–10 per cent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relapse 1</td>
</tr>
<tr>
<td>B</td>
<td>30</td>
<td>27</td>
<td>Excellent 18–67 per cent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Very Good 5–19 per cent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relapses 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failures 2</td>
</tr>
<tr>
<td>C</td>
<td>40</td>
<td>19</td>
<td>Excellent 16–82 per cent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Good 2–12 per cent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failure 1</td>
</tr>
</tbody>
</table>

Group B included five pregnant women. Two had a good response, one had an excellent response after a second course of thirty tablets, and one required three courses before her clinical condition was satisfactory.

Two of the good responses had urethral trichomonads. One of the relapses responded to a second course.

The two failures were suspected of "regular" intercourse, so that their relapses might easily have been re-infections.

Thirteen* of the "unsatisfactory" cases in this survey had or were having a further course of tablets and were still under review.

Side-Effects.—Two patients complained of taste in the mouth, and six of furred tongue (usually black), especially

* This number includes failures, relapses, and defaulters who returned.
if the tablet disintegrated or was crushed. In one of the six
the tongue gave a positive culture for yeast. Two com-
plained of drowsiness, and two of nausea, which was very
severe in one pregnant woman.

Results.—41 patients out of a possible 56 attending
showed no trichomonads at all after completing the
course of treatment; in others the immediate tests were
held up, either by menstruation (profuse in seven cases)
or by default. Three, however, still showed active
trichomonads.

The cases of clinical relapse occurred after about 6
weeks and here the possibility of re-infection arose, as
the patients had been told to abstain from intercourse for
at least 6 weeks. One failure responded to a second course
of tablets, and another had just started a second course.

Consorts.—Eight husbands were treated; six had been
found to have non-gonococcal urethritis (and T. vaginalis
were demonstrated in three cases) and two were treated
empirically. These male patients were given one tablet
times a day for 7 days (21 tablets). One husband with
urethritis thought it was a “wonder drug” as, apart from
clearing the penile condition, it also cured a chronic back-
ache of many years’ duration. The husband’s treatment
coincided with that of the wife, but two husbands flatly
refused examination or tablets and one of the wives
involved was having repeated “re-infections”.

Pregnancies.—Seven pregnant patients were treated.
Two received two tablets four times a day for 5 days
(40 tablets) and the results were excellent. Five received
one tablet three times a day for 10 days (30 tablets) and
three of them had excellent results. One relapsed patient
had three courses in all (110 tablets) but no side-effects
developed.

Only one patient had any side-effects; she had received
forty tablets, being 4 months pregnant and was very sick
indeed.

In consultation with Dr. R. Forgan, one woman was
treated throughout the whole of her labour (with two
tables 3–4 hourly), and blood samples were taken from
both mother and baby at the time of birth. The concen-
tration of the drug in the maternal serum was 9·5 μg. per
cent., and that in the baby’s serum 6·8 μg. per cent. This
was the first experiment of this type to be carried out. In
view of earlier reports regarding the toxicity of the drug,
it was wondered if such a concentration might be injurious
to the foetus, but the child showed no toxic reactions at
birth or subsequently.

The duration of pregnancy in these seven patients was
as follows: one at 2 months, two at 4 months, one at
5 months, one at 6 months, and two at 8 months.

Follow-up.—The longest observation period of cure was
5 months for five patients, 4 months for six, and 3 months
for thirty.

Yeast Infections.—It was noticed that some patients—
otherwise clear—were developing yeast infections. The
vaginal discharge in 28 patients was examined by film
and culture (4 per cent. glucose agar) and seven cultures
(25 per cent.) were found to be positive (not all of these
were due to Candida albicans).

A control series of 49 patients taken at random was also
examined and it was found that only five were infected
(10·2 per cent.).

These figures might be considered as statistically signif-
ificant, and it would be interesting to know whether the
appearance of yeast infections had been noted in other
clinics.

Dr. J. Chesney (Endell Street Clinic, London) said that
he fully agreed with the clinical and laboratory findings
of Mr. A. J. King and Dr. C. S. Nicol. He joined the
previous speakers in congratulating Dr. Durel and his
colleagues on their original work. Their pharmacological
and experimental data were convincing and their clinical
observations cautious and encouraging. The published
results indicated that Flagyl was a selective inhibitor of
Trichomonas vaginalis and did not seem to have any effect
on other organisms. In assessing therapeutic efficiency,
the clinician is always placed in a dilemma by the possi-
ibility of re-infections during the period of observation,
by the occurrence of resistant variations of species and
by the subsequent emergence of T. vaginalis from so-called
closed foci of infection which were inaccessible to the drug.
Congenital and acquired obstructive lesions in the urinary
and genital tract were also conducive to relapse.

The prerequisite of systemic therapy was effective
absorption, distribution, concentration, and elimination
of the drug by infected organs and tissues of the body,
and high blood levels were of only relative value.

Their main preoccupation was to trace and diagnose
the male carriers, especially the latent group, and to
achieve not only a temporary asymptomatic clinical effect
but a complete cure of patient and contact.

Examinations of urine gave only a limited number of
positive results, even after prostatic massages and culture
tests.

He would be interested to learn how often Mr. King,
Dr. Nicol, and Dr. Durel had obtained positive results in
cultures of semen before treatment and negative results
thereafter. Kuperberg (1955) considered this to be the
most reliable diagnostic procedure in trichomonad infec-
tions in the male.

With his colleagues he had treated 43 new cases, com-
prising 41 women and two men, at the Endell Street
Clinic, St. Peter’s and St. Paul’s Hospitals.

Eleven of the women had been under observation for
less than 4 weeks, but over 60 per cent. of the women had
been followed up by direct smears or cultures for 2 months
or more and had remained negative. There were a number
of defaulters, but as defaulters usually returned to the
Clinic if they noticed a recurrence of the discharge, those who failed to return could probably be considered as cured.

There were four relapses which had occurred 2 to 3 months after the termination of treatment, and these could be considered as probable fresh infections. Patients with a history of anaemia were not treated with Flagyl, though he felt that one course of treatment would have no permanent damaging effect on the blood picture. If fresh infections occurred with frequency in the same patient, a blood count would be carried out before recommencing treatment. He had found Flagyl far superior to other preparations for the systemic treatment of *T. vaginalis* infestations.

**DR. NEVILLE MASCALL (London)** said that he could confirm Dr. Chesney's findings from his own observations. He considered Flagyl far superior to any other preparation which had been submitted to the Endell Street Clinic for clinical trial in the treatment of *T. vaginalis* infestations.

**DR. E. REES (Liverpool Royal Infirmary)** said that 48 female patients with *T. vaginalis* infestation had been treated orally with 200 mg. Flagyl thrice daily, between December 17, 1959, and May 3, 1960. Ten had failed to return for any follow-up tests. Observations, including wet smear and culture tests (Feinberg and Whittington medium), were carried out for 3 to 5 months in five patients, 1 to 3 months in twenty patients, and under 1 month in thirteen patients.

Patients were asked to attend weekly for 4 weeks and then after two menstrual periods.

They were divided clinically into acute (fourteen), subacute (nineteen), and carrier (five).

Of the fourteen acute cases, within 2 weeks of treatment eleven became clinically normal and two showed no response. Symptomatically, nine were free from symptoms, two much improved, and two not improved. In one case the symptomatic and clinical response was not recorded. One patient in whom there was no response admitted erratic treatment, but the other did not, and both responded to a second course of treatment.

Of the nineteen subacute cases, within 2 weeks of treatment, eight were clinically normal, seven much improved, two showed no response, and two were not recorded. Symptomatically, fourteen were free from symptoms, two were much improved, and three were not recorded.

No clinical or symptomatic change followed the treatment of carrier cases.

Laboratory results showed a difference between the wet smear and culture tests. The wet smears were positive in only one of the 38 cases at the first test after treatment (this was a second course in two patients), and this one case was negative at the second smear test. In three cases however, a positive wet smear was reported during the follow-up period. One of these was a re-infection and in the other two no clinical or symptomatic relapse accompanied the positive smear, and subsequent tests were negative. The cultures were positive in seventeen cases at the first test after treatment, and most of these became negative in 2 to 3 weeks. In five cases an isolated positive culture unaccompanied by clinical or symptomatic relapse was reported during the follow-up period.

*C. albicans* was reported in cultures after treatment in nine of the 38 cases. This incidence was no higher than in diagnostic specimens from patients not treated with Flagyl.

Toxic symptoms were recorded in five cases: minor gastric discomfort in three, vomiting in one, and an irritable papulo-squamous rash of the forearms in one.

Fifteen male contacts received concurrent treatment. Ten were attending male clinics with non-specific urethritis and were examined for *T. vaginalis*, which was demonstrated in wet smears in three (two in the deposit from centrifuged urine and one in the prostatic bead). Cultures were not available.

**DR. R. R. WILLCOX (St. Mary's Hospital, London)** congratulated Mr. A. J. King and Dr. C. S. Nicol on their presentation—particularly for the comprehensive follow-up they had achieved, which was remarkable in a city such as London.

In many respects, it had been a noteworthy evening. He could not remember a previous occasion on which an effective new drug had been introduced for the treatment of venereal diseases when so many had been able to present first-hand evidence of their experiences. By and large, the reports had shown a large measure of agreement that 8823 R.P. (Flagyl) was an effective drug—although Dr. Rees had produced a cold douche with her cultural findings, which would require further investigation.

To date, he had treated forty women with vaginal trichomoniasis with 200 mg. Flagyl orally three times daily for one week, without other measures. Of these, 34 had been followed for periods of up to 3 months or more and there had been only two failures (5-9 per cent.). There had, however, been six recurrences (17-6 per cent.) and in two cases local treatment had subsequently had to be given for vaginal thrush.

**DR. R. D. CATTERALL (General Infirmary, Leeds)** reported results of the treatment of trichomonal vaginitis with Flagyl by mouth, which compared favourably with those obtained with S.V.C. pessaries.

**DR. A. C. C. DAVEY (Royal Infirmary, Manchester)** stated that with Dr. S. M. Laird he had treated 52 female patients who were found to have *T. vaginalis* on microscopic examination of the vaginal secretion with 200 mg. Flagyl three times daily for 7 days. Six patients failed to
return. Three attended after 7 days but, as they were menstruating, were not examined and thereafter defaulted.

Side-Effects.—Of the 46 who returned having completed the treatment, only two had had any adverse reactions. One complained of nausea and vomiting, and the other of acne and diarrhoea on the sixth day (this, however, was possibly due to food poisoning). Both patients finished the course of treatment and on follow-up were apparently cured.

Symptoms.—32 of the 46 had symptoms before therapy and all stated that these had ameliorated by the end of the week’s treatment. This improvement was most marked in patients presenting with an acute vulvo-vaginitis.

Tests of Cure.—To assess the effectiveness of the drug, tests of cure were carried out by microscopy and culture of the vaginal secretions.

Follow-up.—The aim was to follow up these cases for 3 months but, regrettably, many defaulted before that time. Fourteen were examined over a period of 60 days or more, six for 30–59 days, eight for 20–29 days, six for 10–19 days, and nine for 9 days or less. As already mentioned, three patients returned after 7 days but were not examined and thereafter defaulted.

Results.—There were no immediate failures out of the 43 and only three late failures, two of whom were almost certainly re-infections (one on the 48th and the other on the 100th day).

In this series no local therapy was given and no attempt was made to treat the male partner. Several of the patients had been treated previously with pessaries and some had had local reactions. One patient only was found to have vaginal thrush (Candida albicans) after Flagyl therapy.

Dr. J. S. McCann (Belfast) stated that trichomoniasis on the other side of the Irish Sea was responding to oral Flagyl as it was on this side of the Channel and in France. There had been only one failure in fifteen cases of trichomonal vaginitis treated with a dosage of 200 mg. three times a day for 10 days. There were no toxic reactions.

Dr. A. L. Hilton (Sheffield) stated that he had encountered three possible toxic reactions in pregnant women receiving Flagyl: one miscarried at 3 months, another complained at 5 months that foetal movements became less, and a third suffered from severe nausea.

Dr. W. Fowler (General Hospital, Birmingham) said that he had treated thirty patients, of whom five were males, with 200 mg. Flagyl three days daily for 7 days.

Females.—Three of the 25 females defaulted after the first attendance, seven were examined daily during the treatment period, and fourteen on the 3rd and 7th days. The 21 patients who were followed up showed no clinical evidence of a trichomonal infestation by the end of treatment. Trichomonads had disappeared from the discharge by the 3rd day of treatment at the latest, and by that time the vaginal discharge consisted almost entirely of epithelial cells. Twenty had shown no clinical or bacteriological evidence of relapse during a follow-up period of up to 5 weeks. One patient relapsed after 5 days, coitus was denied; treatment was repeated but the patient had not been seen since.

The remaining female patient had suffered from an intractable acute vaginitis for over 5 years. Unfortunately she could not attend the clinic while she was having treatment but she did attend 2 days after the course ended. She said that the discharge had cleared on the 4th day and that she felt comfortable for the first time in years. However, menstruation commenced 2 days later and the discharge and acute inflammation reappeared. She again presented a typical acute trichomonal vaginitis, and in accordance with Dr. Robert Forgan’s advice Flagyl 400 mg. and Temetil 5 mg. three times daily were prescribed for 7 days. The condition cleared again and she had remained well for 6 weeks.

Males.—Three of the male patients attended daily and the others on two occasions during the treatment period. In three cases all signs of urethritis had cleared by the 3rd day, and in another the discharge had cleared by the 3rd day, but a few threads persisted in the urine for another 3 days, although films and cultures from the urine contained no trichomonads.

The remaining male patient had been under treatment for 9 months; a slight urethral discharge was still present at the end of treatment, although trichomonads were not found in films. Rather than wait for the result of the culture test (which proved to be negative) he was given Flagyl 400 mg. and Temetil 5 mg. three times daily for a further 7 days, and at the end of this time there was no evidence of urethritis.

This man and two of the others had urethral strictures.

Side-Effects.—The female who was given the larger dosages developed mild diarrhoea during the second week of treatment. However, there was an outbreak of gastro-enteritis at the time and it is not certain if the diarrhoea was in fact due to the treatment. No other patient presented any signs of toxicity or intolerance.

Results.—In this small trial, 22 out of 25 cases appear to have been cured with one course of Flagyl, and one male case was probably cured although he was re-treated. These results are most impressive and very much better than anything previously achieved.

Mr. A. J. King, in replying, noted that there had been a fairly general agreement on the effectiveness of Flagyl.

He was interested to hear that Dr. Durel had been giving local treatment only, in one group of patients. He would have expected that the failure rate would be high through re-infection from the urethra.
Dr. Scott-Gray had stated that one of her patients had called Flagyl the “wonder drug”. He had been dismayed by this term which was likely to arouse false hopes, and trusted that it would not be generally used.

Dr. Chesney had asked about the taking of seminal fluid cultures. This had not been done because of moral objections to the method by which the specimens had to be obtained.

Dr. Willcox had asked about sexual intercourse during observation after treatment. Mr. King stated that Dr. Rodin had recorded that about one-third of patients successfully treated had admitted coitus during this period. In spite of improved methods of investigation it was difficult to exclude infestation in the male partner of a woman with trichomoniasis. He believed that such patients should be investigated fully, but now that effective and safe treatment was available, it seemed reasonable to treat the male consort even if the findings were negative.

The President concluded the discussion, thanking all those who had taken part and saying that the meeting had proved to be most interesting and stimulating, and an excellent example of the fruits of international co-operation. Flagyl was clearly a very useful addition to therapy.

Reference