

The prematurity rate was similar to the general rate. The abortion rate was not much greater than that estimated for spontaneous abortion. The ectopic rate was very high, being no less than eight times the general incidence.

An attempt has been made to relate possible causal factors of the infertility to the outcome of the pregnancy. There is inevitably a lack of precision in assessing causal factors, especially when factors in both husband and wife have to be considered together. Generally speaking, however, the outcome is surprisingly good once pregnancy has been achieved, and labour is no more difficult in these cases. There is no increased risk of a deformed child.

The results suggest that routine hospital investigation of primary infertility, followed in some cases by treat-

ment of specific abnormalities, increases the chance of pregnancy quite considerably.

I should like to thank Professor Sir Dugald Baird for his helpful advice and criticism.

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METRONIDAZOLE TREATMENT OF TRICHOMONIASIS IN THE FEMALE

REPORT OF AN EXTENDED TRIAL

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The cautious initial claims (Durel *et al.*, 1959) of the efficacy of metronidazole (1- β -hydroxyethyl-2-methyl-5-nitroimidazole) in the treatment of trichomoniasis in both sexes have been confirmed. In France, Durel *et al.* (1960) still favour combined local and oral metronidazole in the treatment of females, but in Britain it has been stressed that coincident local application is unnecessary (Nicol *et al.*, 1960; Rodin *et al.*, 1960; Watt and Jennison, 1960a; Willcox, 1960). Table I combines the results obtained by these British workers in the treatment of females and shows that 219 (84.9%) of 258 patients were cured and 39 (15.1%) showed post-treatment recurrence.

TABLE I.—*Results of Treatment (Various Workers)*

| Reports | No. of Cases | Successful Treatment | | Treatment Failure | | | | | |
|----------------------------|--------------|----------------------|------|-------------------|-----|------|------|-------|------|
| | | No. | % | Primary | | Late | | Total | |
| | | | | No. | % | No. | % | No. | % |
| Nicol <i>et al.</i> (1960) | 122 | 105 | 86 | 5 | 4.1 | 12 | 9.8 | 17 | 13.9 |
| Rodin <i>et al.</i> (1960) | 52 | 43 | 83 | 3 | 5.8 | 6 | 11.5 | 9 | 17.3 |
| Watt and Jennison (1960a) | 50 | 44 | 88 | 2 | 4 | 4 | 8 | 6 | 12 |
| Willcox (1960) | 34 | 27 | 79.5 | 2 | 5.8 | 5 | 14.7 | 7 | 20.5 |
| Total .. | 258 | 219 | 84.9 | 12 | 4.6 | 27 | 10.5 | 39 | 15.1 |

Primary failure of response to the drug occurred in 12 (4.6%) of these and 27 (10.5%) showed recurrence after initial apparent cure. In males with trichomoniasis 100% response to treatment is reported in 11 patients (Nicol *et al.*, 1960), 20 patients (Rodin *et al.*, 1960), and 32 patients (Sylvestre *et al.*, 1960).

Only minor side-effects have so far been reported and no evidence of any haemopoietic or hepatic damage has been noted (Jennison *et al.*, 1961).

Present Investigation

The present study was undertaken in St. Mary's Hospital for Women, Manchester, to gain further experience of the treatment of trichomonal vaginitis with metronidazole and to investigate some possible causes of

treatment failure and recurrence. During the investigation no restriction was placed on coitus, and the possibility of sexual reinfection (Watt and Jennison, 1960b) received particular attention.

The clinical material, methods of examination, and criteria of cure were as described previously (Watt and Jennison, 1960a). The ages of the patients varied widely, the extremes being a virgin of 15 and a woman of 74 with coincident diabetic vulvitis. All were given a standard course of 600 mg. of metronidazole daily for one week and were regarded as cured if clinically and bacteriologically free from infection for three months. Some who showed recurrence were re-treated with 1,200 mg. daily for seven days or 600 mg. daily for 14 days. Patients discharged cured were instructed to return if symptoms recurred.

Efforts were made to examine the male consorts of all women who suffered late recurrence after initial apparent cure. The methods of examination of males were as described previously (Watt and Jennison, 1960b), reliance being placed on cultural examination of specimens obtained from the urethra, prostate, and post-massage urine. If *Trichomonas vaginalis* was found in the male both partners were treated simultaneously with a standard course. If *T. vaginalis* was not found in the male the female alone was re-treated. In each case a further three months' observation for the female was instituted. Because of the difficulty in persuading males to attend, absence of further signs of infection in the female was taken as presumptive evidence of cure of the male.

Results

Including the 50 reported previously (Watt and Jennison, 1960a) 200 consecutive female patients with trichomonal vaginitis have been treated, and 8 (4%) of these defaulted without post-treatment observation and 1 (0.5%) was unable to tolerate the drug in the standard dosage. Of the 191 followed, 142 (74.3%) remained free from clinical or laboratory evidence of infection during

the period under observation and 49 (25.6%) showed primary failure or late recurrence. Of the 142 who remained well after initial treatment 123 (86.6%) completed full observation, but 19 (13.4%) defaulted before completion. Of the 123 patients completing observation, 7 (5.6%) reattended later with recurrence of symptoms, only two of whom again had trichomonal vaginitis; both returned 20 weeks after original treatment.

Primary Failure

Thirteen patients (6.8%) showed no response to a standard course at the end of the treatment week and were classified as primary failures. Three responded to increased dosage and completed observation and five failed to respond. Five defaulted, one being unable to tolerate higher dosage. One patient (0.5%) responded initially but showed primary failure of re-treatment after recurrence. She was pregnant when originally treated and recurrence occurred after delivery. Her consort was infected and simultaneous treatment of both partners on two occasions and re-treatment of the female with higher dosage failed. The consort refused to come for re-examination.

Late Recurrence

After initial response, recurrence was shown by 38 (19.8%) patients, 36 during the observation period and two after completing observation (Table II). The male consorts of 30 were examined and 16 (53.3%) harboured *T. vaginalis*. Eight consorts (21%) did not attend.

One uncooperative pair defaulted and simultaneous treatment was impossible, but 37 patients were re-treated (Table III). Simultaneous treatment of both partners was successful in 13 (86.6%) of the 15 instances where the male was also infected. One female defaulted apparently well and one showed primary failure of re-treatment. Simultaneous treatment was also successful in one patient where repeated recurrence implied sexual reinfection but *T. vaginalis* was not found in the male. Trichomonads were not demonstrated in

the male consorts of 14 patients and re-treatment of the female alone was successful in 11 (78.5%), though three responded only to higher dosage after further recurrence. Five of the eight females whose consorts failed to attend were cured by re-treatment, one after suffering three recurrences. Two admitted regular coitus, two denied coitus because of the consort's absence, and the patient showing three recurrences was cured after her husband returned to sea.

Pregnancy

Of the 23 (11.5%) patients who were pregnant, 19 continued under observation. Eight did not complete observation, but nine responded to treatment or re-treatment and were cured (Table IV). Two showed primary failure of response — one to repeated re-treatment. Six had late recurrence, three after delivery, of whom one, whose consort was infected, showed primary failure of re-treatment.

TABLE IV.—Treatment of 19 Pregnant Patients

| | Cured | | Defaulted | | | | Failed | |
|------------------------------------|----------|-------------|-----------|-------------|-----------|-------------|----------|-------------|
| | | | T.V. Neg. | | T.V. Pos. | | | |
| | No. | % | No. | % | No. | % | No. | % |
| Standard treatment | 7 | 36.8 | 4 | 21.0 | 1* | 5.2 | | |
| Re-treatment after primary failure | — | — | — | — | — | — | 2‡ | 10.5 |
| Re-treatment after late recurrence | 2† | 10.5 | 2† | 10.5 | 1 | 5.2 | — | — |
| Total | 9 | 47.3 | 6 | 31.5 | 2 | 10.5 | 2 | 10.5 |

* Primary failure. † *T. vaginalis* not found in one consort. ‡ *T. vaginalis* found in one consort.

The outcome of four pregnancies is unknown. Sixteen normal infants were delivered and one anencephalic monster. There were two abortions—one surgical in a schizophrenic patient.

During post-treatment observation another 7 (3.6%) patients became pregnant, one of whom had had apareunia for over a year because of trichomonal vaginitis.

TABLE II.—Time of Late Recurrence

| | Post-treatment Week | | | | | | | | | | | Total | |
|---------------------|---------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|-----------|------------|
| | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | >12 | No. | % |
| Consort: | | | | | | | | | | | | | |
| T.V. positive | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 2† | 1 | 4 | 16 | 42.1 |
| T.V. negative | 2 | 2* | 1 | 2 | — | 1 | — | — | 3* | — | — | 14 | 36.8 |
| Not seen | 2* | 1* | — | — | — | — | — | — | 1 | — | 3† | 8 | 21.0 |
| Total | 5 | 4 | 5 | 3 | 1 | 2 | 2 | 2 | 6 | 1 | 7 | 38 | 100 |
| Cumulative % | 13.1 | 23.6 | 36.8 | 44.7 | 47.3 | 52.6 | 55.2 | 63.1 | 78.9 | 81.5 | 100 | | |

* One pregnant. † One post-delivery.

TABLE III.—Re-treatment of 37 Patients with Late Recurrence

| No. | First Re-treatment | | | | | | | Subsequent Re-treatment | | | | | | | Ultimate Result | | | | | | |
|----------------------|--------------------|-----------|-------------|-----------|-------------|----------|------------|-------------------------|-------------|-----------|-------------|----------|------------|----------|-----------------|-----------|-------------|----------|-------------|--|--|
| | Cured | | Defaulted | | | Failed | Cured | | Defaulted | | | Failed | Cured | | Defaulted | | | Failed | | | |
| | | | T.V. Neg. | T.V. Pos. | T.V. Neg. | | | | T.V. Pos. | T.V. Neg. | T.V. Pos. | | | | | | | | | | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | | | |
| <i>Female Only</i> | | | | | | | | | | | | | | | | | | | | | |
| Consort: | | | | | | | | | | | | | | | | | | | | | |
| T.V. neg. | 14 | 8 | 57.1 | 1 | 7.1 | — | 5 | 35.7 | 3 | 21.4 | 1 | 7.1 | — | — | — | 11 | 78.5 | 2 | 14.2 | | |
| Not seen | 8 | 4 | 50.0 | 2 | 25.0 | 1 | 12.5 | 1 | 12.5 | — | — | — | — | — | — | 5 | 62.5 | 2 | 25.0 | | |
| Total | 22 | 12 | 54.5 | 3 | 13.6 | 1 | 4.5 | 6 | 27.2 | 4 | 18.2 | 1 | 4.5 | — | — | 16 | 72.7 | 4 | 18.1 | | |
| <i>Both Partners</i> | | | | | | | | | | | | | | | | | | | | | |
| Consort: | | | | | | | | | | | | | | | | | | | | | |
| T.V. neg. | — | 15 | 86.6 | — | 6.6 | — | — | — | — | — | — | — | — | — | — | 1 | 7.1 | — | — | | |
| T.V. pos. | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | | |
| Grand total | 37 | 25 | 67.5 | 4 | 10.8 | 1 | 2.7 | 7 | 18.9 | 5 | 13.5 | 1 | 2.7 | — | — | 30 | 81.0 | 5 | 13.5 | | |

Side-effects of Treatment

Minor gastro-intestinal upset was noted by 20 (10.5%) patients, but only 1 (0.5%) was unable to tolerate the drug in standard dosage. With increased dosage, gastro-intestinal upset was common, especially with 1,200 mg. daily, but again only one patient failed to complete treatment. A bad taste in the mouth caused concern to 6 (3.1%) patients and 2 (1%) showed well-marked brown furring of the tongue. Headache was mentioned by 7 (3.6%) patients and there were isolated reports of dizziness, depression, drowsiness, and agitation. One patient noted itching of the skin without rash. One developed a typical drug eruption of the face and neck which cleared spontaneously and did not recur some weeks later when she had to be re-treated. One pregnant patient suffered increased irritation of an existing herpes gestationis and one with psoriasis had a very acute exacerbation during treatment. Tolerance for metronidazole was not reduced during pregnancy.

Laboratory Investigations

The technical methods have been described previously (Jennison *et al.*, 1961). The minimum inhibitory concentration of metronidazole for 139 strains of *T. vaginalis* was estimated (Table V). The sensitivity ranged from 0.075 to 1 $\mu\text{g./ml.}$, with 91% between 0.1 and 0.5 $\mu\text{g./ml.}$ Serial testing of trichomonads from 11 patients with primary failure of treatment or

TABLE V.—Sensitivity of Strains of *T. vaginalis* to Metronidazole

| | No. | Concentration of Metronidazole ($\mu\text{g./ml.}$) | | | | | |
|------------------|-----|---|-----|-------|------|-----|-----|
| | | 0.075 | 0.1 | 0.125 | 0.25 | 0.5 | 1.0 |
| Before treatment | 71 | 1 | 11 | 19 | 25 | 10 | 5 |
| After | 68 | 2 | 8 | 11 | 28 | 16 | 3 |
| Total | 139 | 3 | 19 | 30 | 53 | 26 | 8 |

re-treatment showed sensitivities between 0.1 and 1 $\mu\text{g./ml.}$ The organisms obtained from 29 patients with post-treatment recurrence had sensitivities ranging from 0.075 to 1 $\mu\text{g./ml.}$ Some strains from patients with multiple recurrence were retested on each occasion. The sensitivity of seven of these organisms had been estimated before initial treatment and no decrease was noted except in one where the minimum inhibitory concentration had risen from 0.5 to 1 $\mu\text{g./ml.}$, which is within the limits of experimental error. After repeated re-treatment of eight patients with primary failure or multiple recurrence the causative organisms showed no decrease in sensitivity.

Serum levels at the end of the treatment week varied between 1.25 and 25 $\mu\text{g./ml.}$ in 23 patients who responded. The time since ingestion of the last tablet varied between 1 and 21 hours. Serum levels in nine patients with primary failure varied between 2.5 and 10 $\mu\text{g./ml.}$ and in 1 was <2.5 $\mu\text{g./ml.}$ The time since ingestion of the last tablet varied between one and a half and five and a half hours, but there was considerable doubt about the time interval in the patient with the low level. Serum levels of 14 patients after treatment of late recurrence varied between 1.25 and 25 $\mu\text{g./ml.}$ The time since ingestion of the last tablet varied between one and eight hours, with the lowest level occurring after the longest time.

Direct phase-contrast examination of specimens obtained from 30 male consorts demonstrated

T. vaginalis in 7 (23.3%)—six in prostatic fluid and one in post-massage urine. Culture confirmed these findings in the five instances where it was undertaken. Culture also demonstrated *T. vaginalis* in 9 (30%) specimens when direct examination failed.

Discussion

A summary of the results of the investigation (Table VI) shows that 154 (80.6%) of the 191 patients who remained on observation were ultimately cured and 25 (13%) defaulted apparently cured. Treatment and re-treatment were known to have failed in 6 (3.1%),

TABLE VI.—Final Results of Treatment of 191 Patients

| | Cured | | Defaulted | | | | Failed | |
|------------------------------------|-------|------|-----------|------|-----------|-----|--------|-----|
| | No. | % | T.V. Neg. | | T.V. Pos. | | No. | % |
| | | | No. | % | No. | % | | |
| <i>Female Only</i> | | | | | | | | |
| Standard treatment | 121 | 63.3 | 19 | 9.9 | — | — | — | — |
| Re-treatment after primary failure | 3 | 1.5 | 1 | 0.5 | 4 | 2.0 | 5 | 2.6 |
| Re-treatment after late recurrence | 16 | 8.3 | 4 | 2.0 | 1 | 0.5 | — | — |
| Total | 140 | 73.2 | 24 | 12.5 | 5 | 2.6 | 5 | 2.6 |
| <i>Both Partners</i> | | | | | | | | |
| Re-treatment after late recurrence | 14 | 7.3 | 1 | 0.5 | 1 | 0.5 | 1 | 0.5 |
| Grand total | 154 | 80.6 | 25 | 13.0 | 6 | 3.1 | 6 | 3.1 |

and 6 (3.1%) defaulted still harbouring trichomonads. Only 1 (0.5%) patient was unable to tolerate the drug. Treatment of the female alone ultimately resulted in cure of 140 (90.9%) of the 154 patients who were discharged cured, and simultaneous treatment of both partners was effective in the other 14 (9%). No serious side-effects were noted apart from exacerbation of an existing psoriasis in one patient. These results confirm previous reports and indicate that metronidazole, in the vast majority of cases, has rendered obsolete other methods of treatment of trichomoniasis in the female.

Primary failure of response to treatment occurred in 14 (7.3%) patients, one of whom had responded during pregnancy but showed primary failure of treatment of recurrence after delivery. Three responded to increased dosage and completed observation. Possible causes of primary failure are lack of strain sensitivity of the infecting organism or failure to absorb the drug if in fact the patient took the prescribed dosage—a hazard inherent in treatment necessitating unsupervised patient co-operation. The organisms from 11 of these patients were tested for sensitivity to metronidazole and all were within the normal range. Further testing of six of these strains showed no evidence of resistance developing after repeated treatment of the patients. Serum levels at the end of the treatment week were within expected limits in nine patients and low (<2.5 $\mu\text{g./ml.}$) in one where doubt existed about the time of ingestion of the last tablet. These findings suggest that in this series, neither lack of strain sensitivity nor failure to absorb the drug was responsible for primary failure of response. There was no reason to suspect, except in the one case, that the prescribed dosage schedule was not being followed.

Of the 38 (19.8%) patients showing recurrence after initial response, two had been discharged cured eight weeks previously. Late recurrence may be due to reinfection or persistence of a nidus of infection. Recently, attention has been focused on sexual

reinfection (Whittington, 1957; Catterall and Nicol, 1960; Watt and Jennison, 1960b). Coitus is possibly not the only means of infection or reinfection, and evidence to support this view has been produced by Whittington (1957) and Burch *et al.* (1959), who demonstrated survival of *T. vaginalis* on inanimate objects. Four (2%) of the 200 patients in the present series were virgins and denied coitus.

A previous report (Watt and Jennison, 1960b) indicated that the husbands of 60% of women with recurrent trichomonal vaginitis harboured the organism. In the present study the parasite was found in 16 (53.3%) of the 30 male consorts examined after post-treatment recurrence in the female. Simultaneous administration of metronidazole to 15 of these couples resulted in known cure of 13 (86.6%) females. This suggests that recurrence in these females was due to sexual reinfection and that simultaneous treatment had eradicated the conjugal infection.

Re-treatment of the female alone was ultimately successful in 16 of the 23 patients with late recurrence whose consorts were not proved to be infected or not examined. Regular coitus was admitted by 12 but denied by four. One negative examination of the male does not preclude the possibility of infection. In those patients who admitted coitus, infection in the male, if present, may have undergone spontaneous cure, possibly during abstinence enforced by vaginitis in the female or recurrence may not have been due to sexual reinfection.

Local complicating factors with persistence of a nidus of infection are possible causes of primary failure or recurrence. Of the 191 patients observed, 19 (9.9%) were pregnant when treated, 5 (2.5%) had recently been delivered, and 1 (0.5%) had recently aborted. Eight (32%) of these 25 patients showed primary failure or recurrence. This number included five in pregnancy and three recently delivered, and suggests that pregnancy and recent delivery may influence response to metronidazole.

Coincident symptomatic gynaecological abnormalities were present in 40 patients in the series. Primary failure or recurrence occurred in only 6 (15%) of these, suggesting that the abnormalities had no effect on response. It may be significant that two of three patients with condylomata acuminata showed primary failure of response.

It has been suggested that male sexual partners should be given metronidazole routinely when females are treated for trichomonal vaginitis. Table VI shows that treatment of the female alone has been ultimately effective in 140 (90.9%) of the 154 patients who co-operated fully and were discharged cured. This represents 73.2% of the total of 191 patients under observation. Treatment of the female alone also resulted in apparent cure of 24 (12.5%) patients who did not complete the period of observation. These findings indicate that it is unnecessary as a routine to administer coincidental metronidazole to the male sexual partner.

Recurrence suggesting sexual reinfection occurred in 20 (10.4%) patients. Trichomonads were demonstrated in 16 consorts; simultaneous treatment effected cure in one female where the history implied sexual reinfection though no trichomonads were found in the male; three females whose consorts were not examined responded to re-treatment during the absence of their partners. Thus sexual reinfection may be responsible for over half of late post-treatment recurrences in females. Because of

the difficulty in persuading consorts to attend for examination and the undoubted difficulty with present techniques of demonstrating *T. vaginalis* in males, it seems justifiable, when faced with late recurrence in the female, to treat both partners simultaneously. Since trichomoniasis in the male is in most instances asymptomatic (Watt and Jennison, 1960b), detailed explanation of the condition is often necessary before treatment is accepted. No evidence of absolute or acquired resistance of *T. vaginalis* to metronidazole has been demonstrated (Jennison *et al.*, 1961), but the acquisition of resistance is a theoretical possibility. The story of sulphonamides in gonorrhoea could well be repeated with metronidazole in trichomoniasis by the failure of asymptomatic often unwilling patients to follow prescribed dosage schedules.

Summary

An extended trial of metronidazole in the treatment of trichomoniasis in 200 females is reported. Post-treatment observation of 191 was possible. According to the criteria adopted, ultimate cure resulted in 154 (80.6%) patients, while 25 (13%) defaulted apparently cured. Six (3.1%) showed treatment failure and 6 (3.1%) defaulted still infected.

Primary failure of response to the drug occurred in 14 (7.3%), of whom three were later cured by higher dosage.

Late recurrence after initial response occurred in 38 (19.8%) patients. Sexual reinfection was proved in 16 and suspected in four of these patients and is the possible cause of approximately half such recurrences.

Treatment of the female alone ultimately cured 140 (73.2%) patients. After recurrence suggestive of sexual reinfection simultaneous treatment of both partners was effective in a further 14 (7.3%) cases.

Routine administration of metronidazole to the male sexual partner appears to be unnecessary but is justifiable after late recurrence in the female.

Neither lack of strain sensitivity of *T. vaginalis* to metronidazole nor poor absorption of the drug appears to cause failure of treatment. Pregnancy and recent delivery may influence the response to metronidazole.

Metronidazole has so far proved non-toxic and has rendered obsolete other methods of treatment in most cases of trichomoniasis in the female. Evidence of acquired resistance is lacking, but such resistance is a theoretical possibility and may be fostered by inadequate dosage.

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