Discussion

The proportion of staphylococci resistant to penicillin responsible for sepsis in out-patients attending this hospital is still increasing. The increase presumably reflects the continued use of penicillin in hospital and general practice, and while this continues there is little reason to expect that the proportion of resistant staphylococci will fall. For infections of the skin and subcutaneous tissues this may not be of great importance, as there is evidence that these conditions perhaps respond to treatment with penicillin, even if caused by penicillin-resistant staphylococci (Burn *et al.*, 1957). More serious infections, however, do not react in this way. A penicillin-resistance rate of 39% implies that penicillin should not be used for the treatment of dangerous staphylococcal infections initially until the results of sensitivity tests are known.

Within hospital, patients who are nasal carriers of staphylococci seem to be more prone to sepsis than those who are not carriers, and the staphylococci responsible can frequently be isolated from the patient's nose before the onset of sepsis (Williams *et al.*, 1959). In our patients, 71% of those with sepsis were nasal carriers as compared with 34% of those without sepsis. That the nasal and septic staphylococci may in most cases have been the same was perhaps suggested by the observation that only 13 (8%) of the patients had a sensitive organism in the nose and a resistant one in the lesion, or *vice versa.* These figures suggest that, outside hospital, sepsis occurs more often in carriers than in non-carriers; but to establish this hypothesis would need a survey of a different kind.

As our survey was conducted on somewhat different lines from those of Galbraith (1960) and McDonald *et al.* (1960), a direct comparison cannot be made. Our results agree in that for staphylococci isolated from patients with sepsis and for staphylococci carried by patients without sepsis the penicillin-resistance rates were considerably higher for the staphylococci belonging to patients with direct or indirect hospital contacts.

Rycroft and Williams (1960) described the high carriage rates of penicillin-resistant staphylococci in children under 6 months who had been born in hospital, an increase which continued at a lower level up to 4 years. They concluded that their results drew attention once more to the part that hospital infection may play in seeding the population with antibiotic-resistant staphylococci. We believe that our results do the same.

Summary

One hundred and seventy strains of *Staph. aureus* have been isolated from out-patients with sepsis. Of these, 39% were found to be resistant to penicillin, the highest figure yet recorded at this hospital and nearly double that reported in 1955.

Patients with a history of hospital contacts or treatment with an antibiotic were more often infected with or carried staphylococci resistant to penicillin than those with no such history. It is suggested that this is a further illustration of the part played by hospital infections in seeding the population with antibiotic-resistant staphylococci.

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CLINICAL EVALUATION OF METRONIDAZOLE

A NEW SYSTEMIC TRICHOMONACIDE

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Infestation with *Trichomonas vaginalis* causes much distress to many women of all ages. The incidence of the condition in the population as a whole is difficult if not impossible to determine. In this country, in recent years, *T. vaginalis* was found in 5.3% of 562 women attending a birth-control clinic (Whittington, 1951), in 12.8% of 400 women attending a gynaecological department, and in 21.3% of 400 women attending a venereal disease clinic (Whittington, 1957). These figures represent the incidence in highly selected groups of patients and do not take into account the women who are treated by their own practitioners and those who, for reasons of modesty or fear, prefer to suffer in silence rather than seek advice. Apart from the often considerable physical discomfort, much psychological upset occurs in many cases because of the offensive nature of the discharge and the marital disharmony consequent on vaginismus and dyspareunia.

It now seems clear that *T. vaginalis* is a pathogen and not a harmless inhabitant of the genital tract, though it may be seen occasionally in the absence of clinical signs of infection. Recently, since improved laboratory methods of demonstrating the organism have made diagnosis easier, the protozoon has been shown to be present in the male genito-urinary tract with increasing frequency. Whittington (1957), using cultural techniques, showed the organism to be present in 15.3% of 325 men with non-gonococcal urethritis, and in 8 (33%) of 24 symptomless male consorts of women with chronic trichomonal vaginitis. In a group of 30 husbands of women with chronic trichomonal vaginitis we found that 18 (60%) harboured the organism, most commonly in the prostate (Watt and Jennison, 1960). Male trichomoniasis is in many cases completely silent and may represent a carrier state.

Treatment of human trichomoniasis has until now been very unsatisfactory and at best could often be only palliative. Local pessaries of various kinds in the female produced symptomatic relief in a proportion of cases, but the incidence of recurrence was always high and the incidence of chemical vaginitis by no means negligible. Treatment of the male, especially if a prostatic focus

was present, in many instances presented an insuperable problem, though, as in the case of the female, spontaneous remissions apparently occurred. Among the reasons suggested for failure of local treatment in the female, the existence of a focus of infection elsewhere than in the vagina and repeated reinfestation by male consorts are most likely. The organism has been demonstrated in the urinary tract by Kean (1955) and Whittington (1957), and has been seen on a number of occasions in this hospital. Recurrent vaginitis in virgins, and women who, for one reason or another, are not indulging in coitus, is a well-known entity, so that, though both factors may play a part, extravaginal foci of infection are probably the most important single cause of failure of treatment. The ideal treatment, therefore, is obviously one which is administered systemically, and which can, if necessary, be given to both partners simultaneously.

Various systemic drugs have been used in the treatment of human trichomoniasis but have been abandoned as useless. The most recent of these was acinitrazole (2-acetylamino-5-nitrothiazole), which was considered by Plentl *et al.* (1956) to be effective; but their findings have not been confirmed (Catterall and Nicol, 1957; Willcox, 1957; Jennison, 1957; Dunlop, *et al.*, 1958).

A new derivative of imidazole, metronidazole (1-β-hydroxyethyl-2-methyl-5-nitroimidazole; "flagyl"), was studied by Cosar and Julou (1959) in France, and its antitrichomonal activity and toxicity in both experimental animals and humans have been reported by Durel *et al.* (1960). The original investigations showed definite antitrichomonal activity both *in vitro* and *in vivo*, and significant levels of the drug were found in the blood and urine after ingestion. No severe toxic effects were noted.

Durel *et al.* (1960) report the successful treatment of all of 13 males with urethritis due to *T. vaginalis*. They were given 500 mg. of the drug by mouth in two equal doses daily for 10 days; one patient failed to respond but was cured after a further identical course of treatment. The period of observation varied from 1 to 12 months. Six women were treated with a similar oral course, 21 were treated orally and with vaginal tablets of 500 mg. daily, and four were treated with the drug locally only. One failure (16.6%) occurred in the first group, four failures (19%) in the second group, and one (25%) in the group with local treatment only. The length of the observation period is not recorded.

Present Investigation

In an attempt to determine the clinical efficacy of metronidazole a trial was arranged in St. Mary's Hospital for Women, Manchester, where there exists a special clinic for the treatment of non-specific vaginal infections. Patients are referred to this clinic through the co-operation of the consultant staff, and the investigations and treatment are carried out by the venereologist. It should be pointed out that this clinic is entirely separate from the venereal disease clinic.

Fifty consecutive patients suffering from vaginitis due to *T. vaginalis* were included in the trial (48 white and 2 coloured). Their ages ranged from 17 to 58 years. All were complaining of offensive vaginal discharge of varying duration, some with irritation and others with dyspareunia as a symptom. Before inclusion all patients were shown, by examination of vaginal secretion by direct phase-contrast microscopy, to harbour *T. vaginalis*. Table I shows the duration of symptoms. Since many of the patients were attending the clinic before the commencement of the trial, a high proportion had had symptoms for more than one year (64%) and had had previous ineffective local treatment (66%). One patient was known to have had treatment intermittently for 13 years.

TABLE I.—*Duration of Symptoms in 50 Patients*

	Duration of Symptoms (Months)				Previous Local Treatment
	-3	-6	-12	>12	
Number ..	8	6	4	32	33
Percentage ..	16	12	8	64	66

Monilial infection, atrophic vaginitis, condylomata acuminata, and various gynaecological abnormalities were noted in some patients. One patient was approximately six weeks pregnant at the time of treatment. One suffered from chronic bronchitis and asthma, one from bronchiectasis, one had an active duodenal ulcer, and one was under treatment for mild thyrotoxicosis. Multiple skin sensitivity to antibiotics, sulphonamides, and various pessaries was recorded in one patient, sensitivity to penicillin in another, and sensitivity to acetarsol in two.

Durel *et al.* (1960) favoured combined local and systemic use of metronidazole. In the present series the drug was given by mouth only, 200 mg. t.d.s. for one week. Patients were not advised to avoid coitus.

In the earlier stages of the trial, in an attempt to preclude the possibility of error in assessing symptomatic or clinical improvement, inactive tablets were issued to unselected patients by the hospital pharmacist. He alone knew which patients had the active drug. This was abandoned after 30 patients had been treated, six with inactive tablets. In each of the six cases the lack of clinical response was immediately apparent, and was confirmed by laboratory examination.

Results of Treatment

All patients were asked to report for observation at the end of the first week of treatment, then at weekly intervals, and then at longer intervals when the response to treatment was satisfactory. An arbitrary period of three months' post-treatment observation was fixed as being adequate to assess cure. At each visit a clinical examination was made and specimens of vaginal secretion were obtained by pipette. Specimens were examined immediately by phase-contrast microscopy. All specimens negative by direct examination were inoculated into the medium described by Stenton (1957) and incubated for three days. Patients were regarded as cured only if both direct and cultural examinations were negative.

On examination at the end of treatment and subsequently, 44 patients (88%) showed no clinical or laboratory evidence of infection. The length of observation after treatment is shown in Table II. More than half (56.8%) have completed three months' observation

TABLE II.—*Length of Observation in 44 Cases Treated Successfully*

	Post-treatment Week											
	12+	11	10	9	8	7	6	5	4	3	2	1
Number	25	1	0	1	2	1	3	4	2	4	0	1
Cumulative %	56·8	59	59	61·3	65·9	68·1	75·9	84	88·6	97·7	97·7	100

and have been discharged, and 84% have been observed for more than one month. The average number of post-treatment examinations was four per patient.

In the successful cases symptomatic improvement was apparent during the first few days of treatment, the most notable feature being the rapid relief of irritation. The first post-treatment examination usually showed improvement in the vaginitis, most pronounced in relatively acute vulvovaginitis of recent onset. Vaginal tenderness and vaginismus resolved rapidly in most instances, as, in the absence of complicating factors, did vaginal discharge of recent origin. Patients who had more chronic infections showed improvement over a number of weeks, with gradual lessening of vaginal discharge and slow return to normal of the vaginal wall. In three out of four patients with cervical erosion healing took place coincident with the subsidence of other signs. Four patients with atrophic vaginitis, in addition to trichomonal infection, were made much more comfortable after the disappearance of the flagellate, but the atrophic vaginitis persisted. Coincident monilial infection in six patients and condylomata acuminata in two were unaffected by treatment.

One striking effect of treatment was noticed in the mental attitude of patients who responded. Many had become depressed at the failure of previous treatment, some who had taken part in previous abortive clinical trials approached yet another with considerable scepticism, yet within a week their attitude changed and depression and anxiety lessened with continuing relief of symptoms.

At the first post-treatment examination *T. vaginalis* was not found in the specimens obtained from any patient who responded to treatment. At the time of this examination, in most cases the course of treatment had just finished and presumably active serum levels of the drug were still present. At subsequent examinations *T. vaginalis* was not recovered from any of this group.

Failure to Respond to Initial Course

Six patients did not respond to the initial course of treatment. Table III summarizes the results of the laboratory examinations in these. Five were white and one was coloured. Four were married and two were single but cohabiting.

TABLE III.—*Results of Laboratory Examination in Patients not Responding to Treatment. (Positive Implies T. Vaginalis seen or cultured)*

Case	Marital Status	Age	Duration of Symptoms	Initial Treatment (600 mg. Daily)				Re-treatment (1,200 mg. Daily)			
				Post-treatment Week							
				1	2	3	4	1	2	3	4
1	M	39	3 months	Neg.	Pos.			Neg.		Neg.	Neg.
27	M	34	5 years	Neg.		Neg.	Pos.	Neg.		Neg.	Neg.
28	M	27	2 months	Pos.							
35	M	28	6 ,,	Pos.				Neg.		Neg.	
39	S	24	6 ,,		Neg.		Pos.				
46	S	42	6 ,,		Pos.						

Case 1.—Married. Vaginitis for three months. Clinical improvement on first post-treatment visit was maintained on second visit, but direct examination revealed *T. vaginalis*. Admitted coitus since treatment. Husband clinically, and on culture, free from infection. Patient re-treated with similar course. Clinical improvement maintained, but at first post-treatment visit again showed *T. vaginalis* on direct examination. Probable treatment failure. Re-treated with 1,200 mg. daily, and has apparently responded. Husband not treated.

Case 27.—Married. Chronic relapsing vaginitis under treatment for five years. Stated no improvement at first post-treatment visit and clinically still showed vaginitis though *T. vaginalis* not found. Examined two and three weeks later. Still complained of discharge and irritation, and clinically unchanged. *T. vaginalis* not found on second examination. Direct microscopy on third examination was negative, but culture showed *T. vaginalis*. Denied coitus. Husband examined on previous occasion and found negative. Probable treatment failure. Has apparently responded to higher dosage and is clinically improved. Husband not treated.

Case 28.—Married. Vaginitis with *T. vaginalis* and candida. Complained of increase of irritation whilst on treatment. Clinically not improved on first post-treatment visit, and direct examination showed *T. vaginalis*. Denied coitus. Husband not examined. Probable treatment failure. Unable to tolerate higher dosage.

Case 35.—Married. Vaginitis for six months. Stated no improvement on first post-treatment visit and still showed vaginitis. Direct examination revealed *T. vaginalis*. Defaulted and returned after one month with acute trichomonal vaginitis. Admitted coitus on this occasion. Husband not examined. Probable treatment failure. Has apparently responded to higher dosage. Husband not treated.

Case 39.—Single. Cohabiting. Delivered of child six months previously. First post-treatment examination showed clinical improvement and no *T. vaginalis*. Second post-treatment visit after two weeks showed no vaginitis, but direct examination revealed *T. vaginalis*. Defaulted. No further information available. Reinfection cannot be excluded.

Case 46.—Single. Jamaican. Cohabiting. First post-treatment visit after two weeks showed clinical improvement. Direct examination negative but culture grew *T. vaginalis*. Defaulted. No further information available. Reinfection cannot be excluded.

Of the six patients who failed to respond to the initial course of treatment, three showed clinical improvement at the first post-treatment examination. This was maintained on subsequent examination, though direct microscopy in two cases and culture in one case revealed *T. vaginalis*. Three patients failed to show clinical response to treatment on the first visit and two showed *T. vaginalis* on direct examination. One was followed for four weeks without clinical improvement, culture finally demonstrating the organism when direct examination was negative. Three of these patients have apparently responded to increased dosage.

Side-effects of Treatment

All 50 patients reported for at least one post-treatment examination. The possible side-effects encountered by those treated with a daily dosage of 600 mg. and by four who were re-treated with 1,200 mg. are summarized in Table IV. No side-effects were reported by 39 (78%) patients treated with 600 mg. daily, but all four on the higher dosage complained, one having to stop treatment

TABLE IV.—*Side-effects of Treatment*

Side-effects	Total Daily Dose 600 mg. (50 Patients)		Total Daily Dose 1,200 mg. (4 Patients*)	
	No.	%	No.	%
Bad taste	1	2	—	
Anorexia	2	4	1	
Flatulence	3	6	—	
Nausea	2	4	—	
,, +Dizziness	1	2	2	
,, +Vomiting	—	—	1	
Headache	2	4	2	
Agitation	—	—	2	
Total No. of patients	11	22	4	100

* All patients reported multiple symptoms.

because of vomiting. Most of the side-effects were minor and associated with the gastro-intestinal tract, but two patients on the lower dosage reported headache and two on the higher dosage noted headache in association with dizziness and agitation and with dizziness and nausea. Dizziness of severe degree was mentioned by one patient on the lower dosage and by one on the higher dosage—neither had nystagmus, but one showed definite Rombergism. Two patients on the higher dosage reported agitation and a feeling of tension. The patient who was pregnant reported nausea but no vomiting. All side-effects ceased on stopping the drug. None of the patients who suffered from other ailments noted any worsening of their condition, and no evidence of skin sensitivity was observed in any patient.

Discussion

A long observation period is necessary before claims regarding the efficacy of any antitrichomonal agent are substantiated. In the present series of 50 consecutive patients treated with metronidazole, 44 (88%) have responded to treatment, and 25 (56.8%) of these have remained free from infection on clinical and laboratory examination for three months or longer, 29 (65.9%) for two months, and 39 (88.6%) for one month. This indicates that the drug shows considerable promise in the chemotherapy of trichomonal infections. Clinical response appeared to be dramatic, especially in acute vulvovaginitis of recent onset. Irritation, vaginismus, and inflammation disappeared within a week. Symptomatic response in chronic cases was equally dramatic, especially the relief of irritation, but clinical examination of such cases revealed a slow process of resolution. Dyspareunia was relieved in three out of four patients in whom it was a presenting symptom.

Reactions to treatment occurred in 11 patients (22%) treated with 600 mg. daily, and in all four patients treated with 1,200 mg. daily. The side-effects were not incapacitating in most cases, and only one patient, on the higher dosage, was unable to continue treatment. Durel *et al.* (1960) found no evidence of damage to the haemopoietic system, and in 10 patients we have examined after treatment the red-cell, white-cell, and platelet counts were normal.

Treatment failed in 6 (12%) patients. Three have been re-treated with the higher dosage (1,200 mg. daily) and have apparently responded, though the observation period is as yet too short to draw final conclusions.

Failure of treatment may be due to insensitivity of certain strains of *T. vaginalis*, to poor absorption of the drug, or to reinfection.

Fourteen strains of *T. vaginalis* have been tested for sensitivity to metronidazole by culturing in media containing the drug and incubating for three days. This method differs from that of Bushby and Copp (1955), but we believe our technique to represent more closely the conditions *in vivo*. With our technique the majority (nine) of the strains tested were killed by dilutions of 1 in 4 million or greater. Of the five strains growing in concentrations of 1 in 2 million or stronger, three came from patients who had not responded to the initial course of treatment.

The concentration of the drug in patients' serum and urine is being estimated, but it is as yet too early to draw conclusions on the relationship of serum levels and resistance to treatment.

Both these aspects of the investigation of metronidazole will be reported in full later.

Although patients were not advised to avoid coitus, only two have possibly been reinfected during the period of observation. In this series, and within the limits imposed by the period of observation, reinfection from sexual partners would not appear to be a common cause of failure of treatment. In fact, reinfection would seem to be most unlikely in those patients who still showed *T. vaginalis* at the first post-treatment visit—that is, just having completed treatment—because such patients, if they absorb the drug, should still have a trichomonacidal level in the blood which would act prophylactically. Reinfection cannot, however, be excluded in any patient who failed to respond to treatment, unless there is proof of inadequate absorption or the presence of a resistant strain of *T. vaginalis*.

In many patients who responded to treatment, especially those with chronic vaginitis, marked and understandable psychological benefit was very apparent.

Summary

A new derivative of imidazole, metronidazole (1-β-hydroxyethyl-2-methyl-5-nitroimidazole; "flagyl"), was investigated in the treatment of trichomonal vaginitis in 50 consecutive patients. Dosage was 600 mg. given by mouth daily for seven days. No local treatment was used. Test of cure included laboratory examination by direct and cultural methods.

Of 44 (88%) women responding to the initial course of treatment, 25 (56.8%) have remained free from infection on clinical and laboratory examination for three months or longer, 29 (65.9%) for two months, and 39 (88.6%) for one month. Six patients (12%) were regarded as treatment failures or as reinfections; three of these have apparently responded to re-treatment with 1,200 mg. daily for one week.

Side-effects occurred in 11 patients (22%) treated with the lower dose and in all four patients on the higher dose. One patient could not tolerate the drug in higher dosage.

In this series reinfection would not appear to be a common cause of failure of treatment during the period the patients were under observation. Such failure may possibly be due to the existence of relatively less sensitive strains of *T. vaginalis* or to inadequate absorption of the drug.

This preliminary investigation indicates that metronidazole appears to be an effective trichomonacide when taken orally. Local treatment is apparently unnecessary.

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