TREATMENT OF NON-GONOCOCCAL URETHRITIS*

BY

J. OLIVER DOYLE, A. J. GILL, AND S. M. LAIRD

From St. Luke's Clinic, Manchester, 3

With the increasing incidence of non-gonococcal urethritis (NGU), its treatment has assumed greater importance. The aetiology of NGU is far from clear but probably includes different factors; hence, it is not surprising that the response to treatment is so variable. The clinical picture in NGU also varies widely in severity. The mildest cases are sometimes difficult to distinguish from gonophobia and examination early in the morning, before urination, may be the only time at which any physical abnormality can be noted. In a significant number of patients, symptoms predominate and may appear out of proportion to the objective findings. In these circumstances, the assessment of cure is often not easy. The difficulties of diagnosis and assessment of cure are increased by the high default rate and make comparison of the results of different treatment schedules a hard task. In spite of these objections, however, it seemed desirable to attempt such a study in view of the wide variation in reported results: Lyall (1953) obtained good results from a combination of streptomycin and sulphonamide; both Harkness (1953) and Willcox (1953) considered oxytetracycline the most effective antibiotic; Gartman and Leibovitz (1955), studying cases in U.S. Air Force personnel in Korea, found that more than half the cases cleared up within 8 weeks without treatment. Recently, Fowler (1957) has also suggested that NGU is often a self-limiting condition which undergoes spontaneous cure, and Prebble (1957) has found that urethral irrigations were at least as effective as erythromycin (Ilotycin) 200 mg. 6-hourly for 5 days (total 4 g.), or streptomycin 1 gm. combined with sulphathiazole 1 g. four times daily for 5 days (total 20 g.).

In a recent paper on NGU, Willcox (1957) has contrasted the poor response to novobiocin and chloramphenicol with the reasonably good response to the wider spectrum antibiotics tetracycline, oxytetracycline, chlortetracycline, spiramycin, and erythromycin, and has suggested that this may be of significance in the search for the causal agents.

Present Investigation

It was decided to study the response of cases of NGU seen at St. Luke's Clinic, Manchester, to one of six treatment schedules. There was no selection, cases being allotted to one of the six schedules according to the order in which they attended the clinic.

Diagnosis.—All previously untreated male cases of urethral discharge, in which a smear stained by Gram's method contained pus cells but no gonococci, were included in the study. Between November 28, 1955, and October 15, 1956, 302 such cases have been treated. In 207 of these 302 cases a wet smear was examined for *Trichomonas vaginalis* with negative results in all except one case. Wassermann reactions (WR) and Kahn tests for syphilis were carried out as a matter of routine.

Clinical Material.—The mean age of these 302 cases of NGU was 31 years, the youngest being eighteen and the oldest 66 years. 164 patients were single and, of the 138 married patients, 116 admitted extra-marital exposure to infection; all 302 patients admitted heterosexual intercourse. The group included 201 whites born in the United Kingdom, seventeen whites from Eire, 29 other whites of various nationalities, 23 West Africans, and 32 West Indians (Table I).

Treatment.—The six treatment schedules were as follows:

- (1) A potassium citrate mixture† thrice daily.
- (2) Sulphatriad 1 g. thrice daily for 5 days.
- (3) Streptomycin 1 g. daily for 3 days.
- (4) Schedules (2) and (3) combined.
- (5) Oxytetracycline 250 mg. 6-hourly for 2 days (total 2 g.).
- (6) Oxytetracycline 250 mg. 6-hourly for 4 days (total 4 g.).

With both schedules (5) and (6) the vitamin B complex was given concurrently.

Follow-up.—All patients were told to abstain from alcohol and intercourse and to report back in one week. If, at this examination, there was no urethral discharge and the urine was clear without threads, clinical cure was assumed: the case was classified as a failure if urethral discharge, hazy urine, or threads in the urine were present. Patients were asked to attend again 14 and

* Received for publication January 3, 1957.

† Potassium citrate 20 gr. Ext. hyoscyamus liq. 2 mg. Chloroform 0.5 mg. Aq. ad ½ oz.

TABLE I
AGE, MARITAL STATUS, AND RACE OF 302 PATIENTS WITH NGU BY TREATMENT SCHEDULES

Treatment		Potassium Citrate		Sulphatriad only		Streptomycin only		Sulphatriad + Streptomycin		Oxytetracycline (lg. × 2)		Oxytetracycline (lg. × 4)		Totals
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
Average Age (yrs)		33		30		30		33		25		33		31
Marital Status	Married	18	52	23	45	26	46	19	38	20	40	32	52	138
	Single	17	48	28	55	30	54	30	62	30	60	29	48	164
Race	United Kingdom	20	59	39	76	35	63	30	61	32	64	45	73	201
	Eire	3	8	3	6	2	3	4	8	2	4	3	5	17
	Other Whites . .	4	11	3	6	4	7	6	12	4	8	8	13	29
	West Africans . .	4	11	0		7	12	4	8	5	10	3	5	23
	West Indians . .	4	11	6	12	8	14	5	10	7	14	2	3	32
	Totals	35		51		56		49		50		61		302
Total Whites			78		88		73		81		76		91	
Total Coloured			22		12		26		18		24		8	

21 days after starting treatment; at the 21st day the prostatic secretion was examined and, if this was normal and clinical cure as defined above was maintained, "presumptive cure" was recorded. In practice, observation for 3 months, concluding with further serological tests for syphilis, was recommended in all patients, but the present study was confined to the findings at 7 and 21 days from the beginning of treatment.

Results

These are shown in Table II. Some 67 (22 per cent.) patients failed to return after 7 days (Item 3).

In the 235 cases available for follow-up (Item 2), the effectiveness of the six treatment schedules based on the assessment of clinical cure 7 days after commencing treatment (Item 4) in ascending order of success was potassium citrate, Sulphatriad alone, oxytetracycline 2 g., streptomycin alone, oxytetracycline 4 g., and the combination of streptomycin and Sulphatriad. Only 41 patients (14 per cent.) were available for assessment of presumptive cure at 21 days, and it is unwise to draw any conclusion from these figures (Item 5). The cases classified as failures at 7 days are shown in Item 6. Here again, oxytetracycline

TABLE II
RESULTS IN 302 PATIENTS WITH NGU BY TREATMENT SCHEDULES

Item	Potassium Citrate only		Sulphatriad only		Streptomycin only		Sulphatriad + Streptomycin		Oxytetracycline (lg. × 2)		Oxytetracycline (lg. × 4)		Totals
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
(1) Total Cases Treated	35		51		56		49		50		61		302
(2) Cases Followed-up	27	77	46	90	47	84	37	75	36	72	42	70	235
(3) Cases not Returning	8	22	5	9	9	16	12	24	14	28	19	31	67
(4) Defaulted after Clinical Cure at 7 days	3	11*	8	17*	19	40*	22	60*	14	39*	23	55*	89
(5) Presumptive Cure at 21 days, including Prostatic Smear	1	3	2	4	10	21	6	16	7	19	15	36	41
(6) Failure at 7 days	23	85†	36	78†	18	38†	9	24†	15	41†	4	9†	105
(7) Adding Items 3 and 4	11	31	13	25	28	50	34	69	28	56	42	69	156
(8) Adding Items 3, 4, and 5	12	34	15	29	38	67	40	81	35	70	57	93	197

* Percentages in Item 4 calculated from number of patients showing clinical cure among those returning 7 days after commencing treatment, not among the total number treated.

† Percentages in Item 6 calculated from the number of failures observed among the patients returning 7 days after starting treatment, not among the total number treated.

4 g. and the combination of streptomycin and Sulphatriad are superior to the other schedules. There is no difference in the success achieved by oxytetracycline 2 g. and streptomycin alone, while the results with the potassium citrate schedule and Sulphatriad alone were especially disappointing.

Complications.—No patient presented complications at the time treatment was commenced. Subsequently, three patients developed epididymitis and four showed signs of Reiter's syndrome (Table III). Of the 35 patients treated with potassium citrate, one case of epididymitis and one case of Reiter's syndrome occurred; of the 51 patients treated with Sulphatriad, epididymitis occurred in one; of the fifty patients treated with oxytetracycline (2 g.), two developed Reiter's syndrome; and, of the 61 patients treated with oxytetracycline (4 g.), one had a mild epididymitis and one developed Reiter's syndrome.

Side-Effects of Treatment.—These were uncommon and never serious (Table III). Of the patients receiving streptomycin combined with Sulphatriad, one developed a sulphonamide erythema and another experienced temporary dizziness, which was attributed to the sulphonamide rather than to the streptomycin. Nausea, looseness of stools, and pruritus ani were noted by some of the patients treated with oxytetracycline, but no case is known in which these side-effects interrupted therapy.

Discussion

Although selection of cases was avoided as far as possible, the total number in each treatment category varies for several reasons. All were previously untreated out-patients and some were unable to attend for streptomycin on three consecutive days and were accordingly given oral treatment. Again, in some patients who were due to have the potassium citrate schedule, the severity of the urethritis called for their being allotted to what was felt would be a more potent treatment schedule. This latter policy was adopted because, early in the study, two cases, treated with potassium citrate only, developed complications: one had epididymitis and in the other case well marked signs of Reiter's syndrome appeared. The occurrence of these complications in two patients of the potassium citrate group may well have been solely fortuitous, but one was subsequently influenced by the thought that these complications might not have arisen if an antibiotic had been given. For these reasons, the number of cases assigned to the potassium citrate schedule is smaller (35) and that for the oxytetracycline schedule (61) is greater than the other four schedules. In our present state of ignorance, we do not know what bias this minor degree of selection has introduced into the assessment of the results obtained. If severity of symptoms is an index to the difficulty of cure, then the bias would be in favour of the

TABLE III
DEGREE OF SEVERITY OF NON-GONOCOCCAL URETHRITIS, COMPLICATIONS OF THE DISEASE,
SIDE-EFFECTS OF TREATMENT, RELAPSE, AND RE-INFECTION

State of the Disease			Potassium Citrate (35 cases)	Sulphatriad (51 cases)	Sulphatriad + Streptomycin (49 cases)	Streptomycin (56 cases)	Oxytetra-cycline 2g. (50 cases)	Oxytetra-cycline 4g. (61 cases)
Severity of NGU	Mild*	No.	12	9	8	13	11	12
		Per cent.	35	18	17	24	22	20
	Severe†	No.	23	42	41	43	39	49
		Per cent.	65	82	83	76	78	80
Relapse‡			Nil	One	Nil	One	Two (one of these after alcohol)	One
Re-infection			Nil	Nil	Two	One	Nil	Nil
Complications of NGU			One Reiter's syndrome One Epi-didymo-orchitis (unilateral)	One Epi-didymitis (unilateral)	Nil	Nil	Two Reiter's syndrome	One Left epi-didymitis One Reiter's syndrome
Side-Effects of Treatment			Nil	Nil	One Erythe-matous rash One Dizziness	Nil	One Nausea and vomiting One Perianal irritation	Two Nausea and vomiting Three Periana-irritation

* Mild cases: Scanty urethral discharge, urine clear with threads.

† Severe cases: Well-marked urethral discharge, urine hazy with threads.

‡ Relapse: Urethral discharge cleared up within 7 days and patient returned with NGU within 3 months (further risk denied).

potassium citrate schedule and against oxytetracycline (4 g.), but it is far from certain that such an assumption is justified. It is clear, however, that any bias arising from this minor degree of selection is, by itself, insufficient to explain the superior results obtained with oxytetracycline (4 g.). The six treatment groups are otherwise strictly comparable in respect of the severity of the urethritis (see Table III).

The age, marital status, and race of the patients allotted to each of the six treatment schedules were essentially similar (Table I). The age of NGU patients is usually greater than that of gonorrhoea patients, and more of the NGU cases are married; in these two respects, the patients of the present study are typical. The percentages for total white and total coloured patients are given in the lower part of Table I, and four of the treatment groups are comparable. In the groups treated with Sulphatriad and oxytetracycline (4 g.), the proportion of coloured patients is equal, but is only one half of that in the other four treatment groups. As the results obtained with Sulphatriad were so poor and those with oxytetracycline (4 g.) were so good, it seems unlikely that this small difference in the racial composition of the two groups is of any significance.

In a study of the effects of different treatments in a condition which some workers claim is often a self-limiting disease, it is obviously important to consider the duration of symptoms before therapy was started. This information is given in Table IV, and here again the composition of the six groups is essentially similar. About 85 per cent. of all patients appear to have commenced treatment within 7 days of the recognition of clinical manifestations, but, in mild cases of NGU, the onset of symptoms may be difficult to date, and the patient's estimate of this time may be less accurate than in the case of acute gonorrhoea.

The total cases treated (Item 1), the number of cases which did not return at all after treatment (Item 3), and the cases in which some follow-up was

possible (Item 2) are shown, for each treatment schedule, in Table II. Of the cases seen 7 days after the start of treatment, the failure-rate (Item 6) was lowest in those given 4 g. oxytetracycline (9 per cent.) and highest in those given potassium citrate (85 per cent.); failure-rates at 7 days for the other treatment schedules were Sulphatriad (78 per cent.); streptomycin (38 per cent.); Sulphatriad plus streptomycin (24 per cent.); and 2 g. oxytetracycline (41 per cent.).

Clinical cure was noted 7 days after commencing treatment (Table II, Item 4) as follows: potassium citrate (11 per cent.); Sulphatriad (17 per cent.); streptomycin (40 per cent.); Sulphatriad plus streptomycin (60 per cent.); 2 g. oxytetracycline (39 per cent.), and 4 g. oxytetracycline (55 per cent.).

When seen 7 days after starting treatment, the frank failures were removed from the study and given other therapy. After deducting those classified as having achieved clinical cure 7 days after starting treatment and those who defaulted after this visit (Item 4), there were 41 cases who could be classified as "presumptive cures" 21 days after commencing treatment (Table II, Item 5). Of these 41 cases, "presumptive cure" occurred with potassium citrate (3 per cent.); Sulphatriad (4 per cent.); streptomycin (21 per cent.); Sulphatriad plus streptomycin (16 per cent.); 2 g. oxytetracycline (19 per cent.), and 4 g. oxytetracycline (36 per cent.).

Combining the cases of clinical cure at 7 days (Table II, Item 4) and those of "presumptive cure" at 21 days (Item 5), the following percentages of cures are obtained: potassium citrate (14 per cent.); Sulphatriad (21 per cent.); streptomycin (61 per cent.); Sulphatriad plus streptomycin (76 per cent.); 2 g. oxytetracycline (58 per cent.), and 4 g. oxytetracycline (91 per cent.). These cure rates compare with rates of 75 per cent. (oxytetracycline 5-6 g.), 62 per cent. (streptomycin 2-4 g.), 60 per cent. (sulphonamides 20-28 g.), and 32 per cent. (placebo) found by Willcox (1957).

Judged on the criteria considered in the preceding four paragraphs, this study has shown that the 4 g.

TABLE IV
DURATION OF SYMPTOMS (DAYS) BEFORE TREATMENT BY TREATMENT SCHEDULES

Duration of Symptoms (days)	Potassium Citrate		Sulphatriad only		Streptomycin only		Streptomycin + Sulphatriad		Oxytetracycline (1g. × 2)		Oxytetracycline (1g. × 4)	
	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.
7	28	80	46	90	48	86	40	82	42	84	51	83
7-14	4	11	4	8	5	9	5	10	6	12	6	10
15-21	2	6	0	—	2	3	1	2	1	2	4	7
>21	1	3	1	2	1	2	3	6	1	2	0	—

oxytetracycline schedule has been most successful. It had been hoped for reasons of economy that the 2 g. oxytetracycline schedule might prove equally effective, but this is apparently not the case. The combination of Sulphatriad and streptomycin has achieved results not very inferior to those obtained with 4 g. oxytetracycline, and this has confirmed us in our policy of normally making this combination the first line of attack in the routine treatment of NGU. Streptomycin alone was effective in about 60 per cent. of the cases, but this study shows that somewhat superior results are achieved when it is combined with sulphonamides. The poor response to potassium citrate and to Sulphatriad alone does not contradict the view that NGU may be a self-limiting disease, but the results of the other four treatment schedules show that the course of the condition can be shortened by therapy.

It is reasonable to assume that many of those cases not returning at all after the initial treatment were, in fact, clinically cured. These cases, if included in the cure rate (Table II, Item 8), give an overall cure rate of 93 per cent. with 4 g. oxytetracycline, 81 per cent. with streptomycin plus Sulphatriad, and 34 per cent. with potassium citrate, and further emphasize the beneficial effect of treatment in shortening the natural course of the condition.

Summary

The response to six different treatment schedules in 302 cases of NGU has been analysed. Selection of cases was largely avoided and the patients in each of the six treatment groups were comparable in respect of age, race, marital status, and the duration and severity of symptoms. As a result of default, 235 cases were available for assessment after 7 days, and only 41 after 21 days. Complications were few and consisted of epididymitis and Reiter's syndrome. Combining the cases of "clinical" cure at 7 days with those of "presumptive" cure at 21 days, the highest percentage cures were recorded with 4 g. oxytetracycline (90 per cent.) and Sulphatriad plus streptomycin 76 per cent. Side-effects of treatments were rare and in no case of serious importance.

REFERENCES

- Fowler, W. (1957). *British Journal of Venereal Diseases.*, 33, 45 (Discussion of Prebble, 1957).
 Gartman, E., and Leibovitz, A. (1955). *Ibid.*, 31, 92.
 Harkness, A. H. (1953). *Ibid.*, 29, 134.
 Lyall, T. (1953). *Ibid.*, 29, 151.
 Prebble, E. E. (1957). *Ibid.*, 33, 43.
 Willcox, R. R. (1953). *Ibid.*, 29, 225.
 —(1957). *Ibid.*, 33, 52.