

THE TREATMENT OF ACUTE UNCOMPLICATED GONORRHOEA IN THE MALE BY MEANS OF A SINGLE INTRAMUSCULAR INJECTION OF OILY PENICILLIN B.P.¹

BY

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IN 1945 Romansky and Rittman reported that a single intramuscular injection of a suspension of 300,000 units of calcium penicillin in 1 c.c. of a 4.8 per cent beeswax and peanut-oil mixture maintained an effective level of penicillin in the blood serum for a period of about twenty-four hours. Previously the same workers had reported that eleven out of twelve patients with gonorrhoea had been cured by a single injection of penicillin in beeswax-peanut-oil mixture.

Since 1944, a number of papers have been written on the treatment of acute gonorrhoea by means of a single injection of penicillin in oil-wax suspension. Manson, Meads, Maxwell and Finland (1946), in an analysis of the literature through 1945, stated that single injections of oily penicillin and multiple aqueous intramuscular injections appear to give about equally good results, but that recent data would seem to suggest that an oily suspension in two doses gave better results, owing to the longer maintenance of the level of penicillin in the blood serum. Leifer, Martin and Kirby (1945) obtained a 91 per cent cure rate in 91 patients who received a single intramuscular injection of 300,000 units of penicillin in various concentrations of beeswax and peanut-oil. These cases were followed bacteriologically for three weeks. Frost, Allende, Kirby and Ginsberg (1947) treated 200 cases of acute gonorrhoeal urethritis by means of a single subcutaneous injection of 300,000 units of penicillin suspended in 4.8 per cent beeswax and peanut-oil mixture. These observers obtained a cure rate of 88.5 per cent during a follow-up of twenty-one days.

Oily suspensions of penicillin have not been in general use in the Army for the treatment of gonorrhoea. It was therefore decided to treat, and follow up for a period of three months, a series of patients suffering from acute uncomplicated gonorrhoea by means of a commercial brand of Oily Penicillin B.P. of dependable potency in the V.D. wards of the Royal Herbert Hospital, Woolwich. The

¹This paper describes the results of an investigation carried out at the instigation of the Sub-Committee on Venereology of the Army Medical and Personnel Research Panel.

use of Oily Injection of Penicillin B.P. was decided upon as being the preparation of the type most readily available at the time. In view of the formula of Oily Injection of Penicillin B.P. (125,000 units of calcium penicillin suspended in 1 c.c. of arachis oil and 4.5 per cent beeswax) it was decided to use a dosage of 250,000 units (2 c.c. of the preparation). This was given as a single intramuscular injection on admission immediately following diagnosis.

Although the treatment is reduced to one injection as compared with four in the routine Army treatment (viz. a total of 200,000 units in four injections of 50,000 units at three-hourly intervals), the use of this preparation is not without its drawbacks, owing to the viscosity of the preparation at room temperature. In this connexion, recently, good results have been claimed using a new preparation of penicillin beeswax and peanut-oil which is fluid at room temperature (Hirsh, Dowling, Vivino and Rotman-Kavka, 1947). Also Brindle, Fairbrother and Jackson (1947) describe a preparation of non-hygroscopic sodium penicillin in 1 per cent beeswax and arachis oil (300,000 units per ml.) which is stated to give effective levels of penicillin after twenty-four hours. However, a routine was very soon devised and injections were given without difficulty or loss of the preparation, either from failure to empty the vial or syringe, or leakage from the syringe. The vial was warmed until the suspension was suitably fluid. The syringe and needle were heated at the same time. Care was taken that the syringe was completely dry before use. A 19 gauge needle was found to be the most convenient.

SELECTION, DIAGNOSIS AND SURVEILLANCE OF PATIENTS; ETC.

The only selection of cases was by area in which stationed, and length of Army service remaining, it being necessary, in order to ensure adequate follow-up, to restrict this form of treatment to patients from units in the vicinity and to those who, as far as could be foretold, were not due for foreign or other postings, or for release in the immediate future.

Diagnosis in all cases was made by means of a urethral smear stained by Gram's method, which was confirmed by the culture of infective material inoculated on to a chocolate agar plate (using 5 per cent laked horse blood) and incubated immediately for twenty-four hours at 37° in an atmosphere containing approximately 10 per cent carbon dioxide. A specimen of blood for Wassermann reactions and quantitative Kahn test was taken in all cases prior to the commencement of treatment.

Treatment was commenced immediately following diagnosis by examination of urethral smear. This consisted of 2 c.c. of Oily Injection of Penicillin B.P. injected intramuscularly at the upper and outer quadrant of the buttock.

The morning following admission, if a urethral discharge or moisture was present a smear was made, stained by Gram's method and examined microscopically, and a culture plate inoculated with material expressed from the meatus. Even in the absence of obvious urethral discharge a culture plate was inoculated by platinum loop from the urethra. The patient's urine was also examined. If the results of these investigations proved to be negative the patient was dis-

charged to duty to attend for post-treatment surveillance. Post-hospital surveillance was carried out as follows:—

(i) Examination of the patient for urethral discharge, inspection of urine for presence of pus or threads was carried out weekly for the first three weeks after discharge from hospital. The skin and mucosæ were also examined for signs of concomitant syphilis.

(ii) At the end of one month after completion of treatment, the patient was examined as in (i) above. In addition the prostate and vesicles were massaged, and the resultant secretion examined microscopically (bead and stained smear) and culturally.

(iii) Three months after completion of treatment the examination described in (i) and (ii) above were repeated. Wassermann reaction and quantitative Kahn test were also carried out. The patient was advised to have the W.R. and Kahn test repeated after a further interval of three months in order to exclude syphilitic infection masked by the penicillin treatment.

Treatment failure was postulated as the persistence of symptoms and/or positive microscopical and cultural findings during the period immediately following treatment, and relapse as the recurrence of symptoms or positive laboratory findings during surveillance.

In addition to the foregoing investigations, in a certain number of cases the presence or absence of penicillin in the patient's blood serum was determined at intervals of six, twelve, eighteen and twenty-four hours after treatment.

RESULTS OF TREATMENT.

In spite of every care in selection (*see* above), it was found impossible to follow up all patients for the full period of three months, owing to unpredictable postings and transfers of patients. Also, of the 65 patients examined at one month, prostatic cultures were not performed in 4 cases owing to lack of facilities at the station at which examination was carried out. This includes one patient who was asymptomatic but had a positive culture following prostatic massage when examined at the end of surveillance. Apart from these 4 patients all examinations during surveillance were carried out by one of us.

Of the total of 74 patients originally treated, 60 (including one asymptomatic patient with positive prostatic culture) were followed for the full three months. Of the remaining 14, 8 relapsed (*see* Table I) during this period, and 5 were lost

TABLE I.—ANALYSIS OF FOLLOW-UP

No. of cases treated	No. followed for		No. followed for		Total	100%		
	three months	81%	over one month and under three months	under one month				
74	60*	81%	5*	6.7%	5*	12%	74	100%

*Including cases relapsing.

owing to the exigencies of the Service, and one case could not be considered, as he was found to be a latent syphilitic on first examination and was treated for this by means of 4 mega units of penicillin. No patient failed to respond to

treatment, and apart from a slight mucoid discharge (rarely with up to 4 pus cells per field) all patients were asymptomatic the day following treatment, and in all cases urethral cultures were negative.

In no case were there any local or general reactions following the injection of oily penicillin, apart from a slight local discomfort persisting at the most for a few minutes.

Seven patients reported with a recurrence of symptoms during the first four weeks of their surveillance and, on examination, urethral smears revealed the presence of gonococci. These findings were confirmed by culture in each case.

Of the 65 patients who remained asymptomatic at the end of four weeks' surveillance, the prostatic secretion was found to be normal on microscopic and cultural examination in all of the cases, viz. 61 in which full investigations were carried out (*see above*).

Of the 61 patients followed for a period of more than one month, only one patient reported with a urethral discharge during the second and third months of surveillance, and in this patient gonococci were found to be present in the urethral discharge. As regards the remaining 60 who were followed for a full three months, all were found to be free from symptoms, and laboratory findings were negative in all cases, except for one patient, from whom gonococci were cultured from the prostatic secretion following prostatic massage (*see Table II*).

TABLE II.—INCIDENCE OF RELAPSE IN RELATION TO PERIOD OF SURVEILLANCE.

<i>Week following treatment</i>	<i>Total No. of cases relapsing</i>	<i>No. of relapse cases without history of fresh exposure</i>	<i>No. of cases admitting fresh exposure</i>
1	1	1	—
2	1	1	—
3	3	1	2
4	2	1	1
5	—	—	—
6	—	—	—
7	—	—	—
8	—	—	—
9	—	—	—
10	1	—	1
11	—	—	—
12	1	1*	—
	—	—	—
	Total 9	5	4

*Diagnosed by prostatic culture.

As will be seen from Table V, in all cases in which the gonococcus was found on microscopical examination of a smear, this was confirmed by the cultural findings. In one case, examined at the end of three months, stained smears of prostatic secretion, were negative, but gonococci were found in culture.

Relapse occurred in the majority of cases during the first four weeks—7 out of 9 cases (*see Table II*). It will be seen from Table III that out of 68 patients

TABLE III.—RESULTS OF TREATMENT.

No. of cases originally treated	No. of treatment failures	No. of cases defaulting before completion of surveillance	No. relapsed	No. of cases completing surveillance successfully	Total
74	0	6*	9	59	74

*Includes one case treated for concomitant syphilis.

followed up for three months or until relapse occurred, 9 relapsed—a cure rate of 87 per cent. Of the 9 patients shown as having relapsed, 4 admitted exposure to reinfection within a few days of the recurrence of symptoms, having previously been symptom-free (see Table IV). If, as is possible, these patients were

TABLE IV.—ANALYSIS OF RELAPSE CASES IN RELATION TO EXPOSURE TO REINFECTION

Total No. cases relapsed	No. relapse cases without history of fresh exposure	No. of relapse cases admitting exposure with known infected contact	No. of relapse cases admitting exposure with unknown contact
9	5	2	2

TABLE V.—ANALYSIS OF BACTERIOLOGICAL FINDINGS.

No. patients treated	Positive before treatment		Positive day following treatment		No. patients with recurrence of symptoms	Positive on examination	
	Urethral smear	Urethral culture	Urethral smear	Urethral culture		Urethral smear	Urethral culture
74	74	74	0	0	8	8	8
No. patients examined one month after treatment	Negative after one month		Final examination at three months after treatment		Prostatic Smear		
	Prostatic smear	Prostatic culture	Prostatic smear	Prostatic culture	positive	negative	Prostatic Culture positive negative
65*	61	61	0	60	1	59	

*Includes 4 patients examined at outstations where cultural examinations not possible.

in reality reporting with a reinfection and not a relapse, then the cure rate obtained would naturally be higher, viz. 92.7 per cent.

Those patients who relapsed were treated by means of 400,000 units of penicillin in aqueous solution in eight three-hourly intramuscular injections each of 50,000 units. All responded to treatment, except one patient, who had a further relapse two weeks later. This patient finally responded to a course of 600,000 units of penicillin over a period of thirty-three hours, followed by 5 gm. of sulphathiazole daily for five days.

No case under treatment developed syphilis during the period of surveillance.

As has been stated previously, in a certain number of the patients treated the serum penicillin was investigated at intervals following the administration of oily penicillin. Our experience was similar to that of many others in that the results obtained were found to be very variable. In 10 out of 33 sera, there was a slight degree of penicillin activity at twenty-four hours, as evidenced by the partial inhibition of the growth of the Oxford staphylococcus by pure serum. Somewhat more definite evidence of active penicillin in the serum was obtained after eighteen hours, since complete inhibition of the staphylococcus was produced by pure serum in 15 out of 24 of the sera examined at this interval. At

twelve hours, of 17 sera examined complete inhibition occurred in 4 at a dilution of 1:8; in 1 at a dilution of 1:4; in 2 at a dilution of 1:2; and in 3 in pure serum. Partial inhibition of growth occurred with pure serum in the case of 2 specimens, and in 5 no inhibition occurred at all. 11 were examined at six hours. Of these 2 showed complete inhibition at a dilution of 1:4; 6 at 1:2; 1 in pure serum. One specimen caused partial inhibition with pure serum, and one failed to cause inhibition at all (see Table VI).

TABLE VI.—TABLE TO SHOW THE HIGHEST TITRE AT WHICH PENICILLIN IN SERUM OF PATIENTS FOLLOWING TREATMENT WITH A SINGLE INTRAMUSCULAR INJECTION OF 2 C.G. OF OILY SUSPENSION OF PENICILLIN B.P. CAUSED INHIBITION OF THE GROWTH OF STANDARD OXFORD STAPHYLOCOCCUS AT VARIOUS INTERVALS.

Case No.	6 hours	12 hours	18 hours	20 hours	24 hours
1	Nil	$\frac{1}{2}$	—	—	—
2	Pure ; p. $\frac{1}{2}$	Nil	—	—	—
3	$\frac{1}{2}$; p. $\frac{1}{4}$	$\frac{1}{8}$	—	—	Nil
4	$\frac{1}{2}$; p. $\frac{1}{4}$	Pure ; p. $\frac{1}{2}$	—	—	—
5	p. pure	p. pure	—	—	Nil
6	$\frac{1}{2}$	Nil	—	—	Nil
7	$\frac{1}{2}$	$\frac{1}{4}$	—	—	Nil
8	$\frac{1}{4}$; p. $\frac{1}{8}$	$\frac{1}{2}$; p. $\frac{1}{4}$	—	—	Nil
9	$\frac{1}{2}$; p. $\frac{1}{4}$	$\frac{1}{8}$	—	—	Nil
10	$\frac{1}{4}$	$\frac{1}{8}$	—	—	Nil
11	$\frac{1}{2}$	Pure	—	—	Nil
12	—	$\frac{1}{8}$	$\frac{1}{2}$	—	Nil
13	—	Nil	$\frac{1}{2}$	—	Nil
14	—	Pure	Pure	—	Nil
15	—	p. pure	p. pure	—	Nil
16	—	Nil	Unsatisfactory	—	Nil
17	—	Nil	Nil	—	Nil
18	—	—	Pure ; n. $\frac{1}{2}$	Nil	Nil
19	—	—	Pure ; n. $\frac{1}{2}$	Nil	Nil
20	—	—	Pure ; p. $\frac{1}{2}$	Nil	Nil
21	—	—	Pure ; n. $\frac{1}{2}$	Pure ; n. $\frac{1}{2}$	p. pure
22	—	—	Pure ; n. $\frac{1}{2}$	Pure ; n. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$
23	—	—	Pure ; n. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$
24	—	—	Pure ; p. $\frac{1}{2}$	Pure ; p. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$
25	—	—	Pure ; p. $\frac{1}{2}$	Pure ; n. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$
26	—	—	Pure ; p. $\frac{1}{2}$	Pure ; p. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$
27	—	—	Nil	Nil	Nil
28	—	—	Nil	Nil	Nil
29	—	—	p. pure ; n. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$	Nil
30	—	—	Pure ; p. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$
31	—	—	p. pure ; n. $\frac{1}{2}$	Nil	Nil
32	—	—	Pure ; p. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$	p. pure ; n. $\frac{1}{2}$
33	—	—	p. pure	Nil	Nil
34	—	—	p. pure	Nil	Nil
35	—	—	Pure ; p. $\frac{1}{2}$; n. $\frac{1}{4}$	Pure ; p. $\frac{1}{2}$; n. $\frac{1}{4}$	p. pure ; n. $\frac{1}{2}$
36	—	—	—	$\frac{1}{2}$; p. $\frac{1}{4}$	p. $\frac{1}{2}$; n. $\frac{1}{4}$

Pure — Complete inhibition in neat serum. p. = Partial inhibition. Nil = Nil inhibition in neat serum. n. = Nil inhibition. $\frac{1}{2}$ = Inhibition in serum diluted 1:2. $\frac{1}{4}$ = Inhibition in serum diluted 1:4. $\frac{1}{8}$ = Inhibition in serum diluted 1:8.

SUMMARY.

(1) The treatment of 74 male patients suffering from uncomplicated acute gonococcal urethritis by means of a single intramuscular injection of 2 c.c. of oily injection of penicillin B.P. (250,000 units) is described and the results tabulated and discussed.

(2) Of the 68 patients in the series who were adequately followed up, 59 (87 per cent) successfully completed three months' surveillance, and 8 had a recurrence of symptoms and bacteriological findings and 1 patient was found to have a positive prostatic culture at twelve weeks, although asymptomatic. Of the 8 patients cited as having relapsed, 4 were possible reinfections.

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