

Single-session treatment of uncomplicated gonorrhoea in men, using penicillin combined with cotrimoxazole

Controlled trial comparing four different treatment schedules with observations on antibiotic sensitivities of gonococci and a review of the literature

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This controlled trial of penicillin alone compared with penicillin combined with cotrimoxazole (trimethoprim plus sulphamethoxazole) in the treatment of uncomplicated male gonorrhoea was undertaken in the not necessarily forlorn hope of finding a 100 per cent. single-session cure. The search for some such completely successful 'one-shot' or, as the French call it, 'one-minute' treatment approaching this ideal, must continue. Although a 100 per cent. cure rate may be expected in individuals with prolonged treatment consisting of repeated doses of one antibiotic or another, this must depend upon the patient's co-operation, which is never 100 per cent. in a venereal disease clinic.

Defaulter rate X failure rate

All clinics have a defaulter rate. Nearly all treatments, with perhaps one or two Scandinavian exceptions, carry a failure rate. The product of these two factors will give, with certain statistical reservations, a calculable figure representing the maximum number of patients with gonorrhoea who return to sexual circulation uncured. The initial defaulter rate at the Newcastle General Hospital between January and June, 1970, was 32 per cent., *i.e.* 32 per cent. of men treated for gonorrhoea failed to return on the 3rd or 4th day as requested. Reminder letters sent by the social unit to those who failed to attend within 7 days resulted in a final complete defaulter rate of only 14 per cent.

The standard treatment for gonorrhoea in 1968 in Newcastle, consisting of 1.25 mega units Triplopen* intramuscularly, carried an apparent failure rate of 13 per cent. amongst a total of 423 male cases, but this figure was derived without analysis to determine the proportion of re-infections nor did it exclude any

initially complicated cases. It did exclude those who left the area with a V15 or a V44 (record of treatment). It follows that uncured male cases returning to the infectious pool could have amounted at the most to 4.2 per cent. (32×13 per cent.) without the help of the social unit and 1.8 per cent. (14×13 per cent.) with such help. Neither of these figures should be tolerated. On a national scale in England and Wales alone, with defaulting between 10 and 30 per cent., and treatment failure between 2 and 12 per cent., it is fair to assume some 100 to 1,500 uncured cases per annum go back into circulation. On a global scale the situation is incalculable.

The epidemiological importance of 'feed back' has been stressed by Willcox (1965) and the effect of defaulting in the interpretation of treatment results by Hewitt (1969). If defaulting is related to irresponsibility, then such patients may incline to a sexually promiscuous life. If a 100 per cent. cure is ever achieved with one-session treatment, then defaulting will cease to be of much importance, provided always that the necessary epidemiological enquiry has been satisfactorily concluded at the patient's first attendance. Moreover, it is to be expected on *a priori* grounds that the treated but uncured and defaulting patient would be more likely to carry a strain of gonococcus relatively resistant to the drug used in the original treatment. Apart from the contribution of human behaviour to the spread of venereal disease in general, this is what the gonorrhoea problem is all about.

Change in sensitivity patterns

(1) UNITED KINGDOM

The degree of resistance to penicillin and the number of strains of gonococci that are partially resistant are both said to be increasing, a fact frequently and quite rightly proclaimed by venereologists in their attempts to arouse public, medical, or official concern. Few reports of alternative drug trials commence without

*Benthamine penicillin G 475 mg. (500,000 u.), procaine penicillin 250 mg. (250,000 u.), sodium penicillin G 300 mg. (500,000 u.)—Glaxo Laboratories Ltd.

this observation. The statement, which would appear to be self-evident from the almost universal need for a steady increase over the years in the amount of penicillin necessary for the treatment of gonorrhoea, nevertheless requires some qualification. Curtis and Wilkinson (1958) quoted eight series between 1945 and 1954, comprising a total of 847 strains of gonococci with none less sensitive than would succumb to 0.125 u./ml. (0.075 µg./ml.) penicillin. Their own subsequent series of 302 strains contained 14.2 per cent. that were less sensitive. As others have commented, the writing seemed to be on the wall over a decade ago. Letchner and Nicol (1961), however, found that strains needing more than 0.05 u./ml. (0.03 µg./ml.) for inhibition fell from 19 to 9 per cent. between 1958 and 1960 and they attributed this to the introduction of a higher dosage of penicillin in the treatment of gonorrhoea. Nicol, Ridley, and Symonds (1968) found 37 per cent. of strains isolated in 1966 to be partially resistant to penicillin. Lynn, Nicol, Ridley, Rimmer, Symonds, and Warren (1970) found this figure to be 35.1 per cent., an apparent improvement probably not statistically significant. But at least there had been no worsening of the situation. A year previously, Leigh, Le Franc, and Turnbull (1969) had found 90 per cent. of strains sensitive to 0.2 u./ml. (0.125 µg./ml.) or less. Thus they found 10 per cent. relatively insensitive strains by their standards. In the present series occurring in Newcastle, the authors have found 77 per cent. sensitive to 0.125 µg./ml. (0.2 u./ml.) or less leaving 23 per cent. relatively insensitive by these standards. But the line of demarcation between sensitivity and relative insensitivity in this series and others, *e.g.* Rees and Annels (1969) is accepted as occurring between 0.06 and 0.125 µg./ml. (0.1 and 0.2 u./ml.) and therefore the percentage of sensitive strains (*i.e.* to 0.06 µg./ml. or less) is to be recorded as 63.8 per cent., and of relatively insensitive strains as 36.2 per cent., which almost coincides with the figure of Lynn and others (1970) just referred to. This is also the line of demarcation accepted by Hilton (1971) who found 18.1 per cent. of strains requiring more than 0.05 u./ml. (0.03 µg./ml.) for inhibition between 1964 and 1966 and 31.7 per cent. resistant by this standard between 1966 and 1969.

(2) SCANDINAVIA

When looked at over a wider horizon we find Olsen and Lomholt (1969) recording a reduced sensitivity rate of 86 per cent. in certain areas of Greenland in 1963. In 1964-5, also in Greenland, 54 per cent. of 309 strains showed a diminished sensitivity to penicillin, and in 1966-7 only 19 per cent. of 646 strains showed such resistance. This remarkable

change in sensitivity was at that time attributed to the extremely successful treatment regime undertaken over a period of time. The logic of this is not apparent, however. One would expect sensitive and relatively insensitive strains to be reduced equally by this expedient and a reduction in the percentage of less sensitive strains could only be accounted for by importation of sensitive strains. Ödegaard and Gjessing (1967) noted that gonococcal resistance to penicillin in Norway reached its peak in 1964 and had declined by 1966. Nielsen (1970), quoting Reyn (1969), reported that less sensitive strains in Denmark had decreased from 57 to 30 per cent. between 1962 and 1968. Wols-Van der Wielen (1971) found relative insensitivity (MIC > 0.1 u. [0.06 µg./ml.]) in 70.1 per cent. of 201 seamen but only in 35.6 per cent. of 216 non-seafaring residents of Rotterdam during 1968-69.

(3) AFRICA, INDIA, THE FAR EAST, AND U.S.A.

On the other hand Arya and Phillips (1970) and Arya, Pearson, Rao, and Blowers (1970) recorded two series with 80 and 86 per cent. less sensitive strains in Uganda, their dividing line being the same as in Newcastle. Amies (1969) recorded from Toronto an increasing number of strains resistant to 0.1 u./ml. (0.06 µg./ml.) penicillin, from 3 per cent. in 1959 to over 50 per cent. in 1968. 30 per cent. of strains are currently resistant to 0.3 u./ml. (0.18 µg./ml.) and he forecast the eventual uselessness of penicillin in the treatment of gonorrhoea. Warren (1968) has drawn attention to the different proportions of resistant strains at home and abroad as seen in Southampton. Willcox (1970a) referred to the 'increased resistance of the gonococcus to antibiotics in South East Asia', both with regard to the number of resistant strains and the degree of resistance attained by some. He cited many contributors testifying to this assertion. Keys, Halverson, and Clark (1969) noted that 73 per cent. of 242 strains in the Philippines required 0.4 u./ml. (0.24 µg./ml.) to 1.6 u./ml. (0.96 µg./ml.) for inhibition.

Somewhere between the alarming state of affairs in the far Pacific and the reasonably tolerable situation in Europe lie the unwelcome figures for the U.S.A. provided by Martin, Lester, Price, and Schmale (1970), who stated that between 1945 and 1954, only 0.6 per cent. of gonococcal strains required more than 0.05 u./ml. (0.03 µg./ml.) for inhibition. By 1965, this figure had risen to 42 per cent. and by 1968-9 to 65 per cent. In Newcastle, by these standards, the 1970 figure stands at 45 per cent. These same workers found the percentage of strains needing more than 0.5 u./ml. (0.3 µg./ml.) for

inhibition to have risen from 5 per cent. in 1965 to 14 per cent. in 1968-9 (Newcastle 5 per cent. in 1970). When testing gonococci from cases of penicillin failure, they found the highest MIC in the period 1955 to 1958 to be 0.2 u./ml. (0.12 µg./ml.); in 1962 it had risen to 0.7 u./ml. (0.42 µg./ml.) and since 1962 to 3.5 u./ml. (2.1 µg./ml.). Some anxiety must prevail also in India. Moses, Desai, Bhosle, and Trasi (1971) found 56 per cent. of 216 strains in Bombay isolated in 1968-69 to be partially resistant to penicillin (MIC > 0.17 u./ml. [0.1 µg./ml.]).

There is clear need for agreement concerning definitions of sensitivity, *i.e.* where to draw the line and for standardization of testing dilutions using agreed amounts of penicillin measured once and for all in micrograms or units. Silver and Darling (1971) interposed an intermediate grade of sensitivity making comparison difficult. Bro-Jørgensen and Jensen (1971) preferred to use the 50 per cent. inhibitory concentration. Even a *British Medical Journal* leading article (1972) stated that one-third of gonococcal strains in London require 0.06 µg./ml. (0.1 u./ml.) or more for inhibition, thus adding to the confusion. Close parallels are difficult to define in an atmosphere of scientific babel. Nevertheless, it would appear from the evidence that the number of relatively resistant strains in the United Kingdom has remained fairly steady at around 35 per cent. over the past 5 or 6 years. Gray, Phillips, and Nicol (1970) noted little change from 37 per cent. in 1967 to 35 per cent. in 1968-9. In those countries where it has been possible to apply some uniformity of intensive treatment, the resistant strains are declining in numbers. In other areas, where more or less indiscriminate half-hearted abortive or even dangerous prophylactic treatment has been or is being undertaken, which is not to be confused with intelligently applied epidemiological treatment, the number of partially resistant strains and the degree of their resistance has risen out of all proportion to what should be the case were the control of this world-wide human scourge attempted rationally on a global plan.

Successful treatment claims

(1) ONE DRUG IN SINGLE SESSION

In today's climate of antibiotic therapeutics no clinic should rest content with less than a 90 or even 95 per cent. cure rate and many workers have claimed this kind of result. Therapeutic trials achieving 90 to 95 per cent. success with one drug administered in single session include:

Butler, Brewer, Condit, and Johnston (1952)—93 per cent. success with 2 g. chloramphenicol;

Barrett and Burton (1953)—92 per cent. cure with 2 g. chloramphenicol;

Alergant (1963)—95 per cent. success with 1 g. oral ampicillin;

Gjessing and Ödegaard (1967)—91.5 per cent. success with 1 g. chloramphenicol (200 patients);

McLone, Kiley and Hackney (1967)—93.8 per cent. success in males with 1.5 g. tetracycline (96 hrs' surveillance);

Oller (1967)—94.8 per cent. success with 2 g. cephaloridine;

McLone, Billings, Hardegree, and Hackney (1968)—90 per cent. success in females with 2 g. cephaloridine (96 hrs' surveillance only);

Jouhar and Fowler (1968)—92.9 per cent. success with 2 g. cephaloridine;

Morrison, Cobbold, Bor, Spitzer, Foster, and Willcox (1968)—91.5 per cent. success with 1.2 m.u. and 94.2 per cent. success with 2.4 m.u. aqueous procaine penicillin by single injections;

Fluker and Hewitt (1969)—93.3 per cent. success with 3.6 m.u. procaine penicillin given to previous penicillin failure cases;

Ongom (1971)—94.8 per cent. success with rifampicin 1,200 mg. given orally to 38 male cases and 94.7 per cent. success with 2.5 m.u. Triptopen given intramuscularly to 56 male cases;

Masterton and Schofield (1972)—93.6 per cent. success in males with 300 mg. doxycycline hydrochloride (Vibramycin);

Moffett, McGill, Masterton, and Schofield (1972)—94.2 per cent. success in women using the same treatment (though Baytch and Rankin (1972) found only 47 per cent. success in men with this dosage in Australia).

Between 95 and 98 per cent. success, still with one drug in single session, has been claimed by:

Greaves, Macdonald, Romansky, and Taggart (1950)—96 per cent. success with 0.75 g. chloramphenicol before the upsurge of resistant strains;

McLone, Scotti, and Mackey (1968b)—96.8 per cent. success with 1.5 g. tetracycline in women;

Cornelius and Domesick (1970)—95.7 per cent. success with 4 g. spectinomycin hydrochloride given to seventy women in two injection sites at once. These same workers claimed 100 per cent. success with half this dose (2 g.) given intramuscularly to 108 men and 28 women (96 hrs' surveillance).

A semblance of single-session treatment might be conceded to those workers who have used one drug in divided doses at a 5 to 6-hr interval.

Willcox (1971) found 91 per cent. success with 1.2 g. triple tetracycline (Deteclo) given twice at 5 to 6-hrly intervals;

Willcox (1969) achieved 95.7 per cent. success with demethylchlortetracycline 1.2 g. given orally to 107 cases twice at 5 to 6-hrly intervals;

Groth and Hallqvist (1970) claimed 99 to 100 per cent. success in 311 men and women treated with 2 g.

ampicillin given in two doses of 1 g. at 5 hrs interval (95 per cent. followed; ten subsequently positive cases being regarded as re-infections).

(2) TWO DRUGS IN SINGLE SESSION

There are some clinicians who frown upon the practice of prescribing more than one bactericidal or bacteriostatic drug at the same time in the treatment of gonorrhoea, in spite of the example set by those who treat tuberculosis with three drugs and those who used to treat syphilis with two. Minor objections to this practice include not knowing which drug to credit in the event of success or finding one's armamentarium reduced in the event of failure. More pertinent objections to the use of more than one remedy include the possibilities of

- (a) Inducing drug antagonism rather than achieving either synergism or an additive effect, as suggested by Jawetz and Gunnison (1953);
- (b) Producing cross-resistance so that neither drug is effective, a matter of some concern already in the Far East (Willcox, 1970a);
- (c) Increasing the incidence of unpleasant or even serious reactions to treatment.

These objections could not readily apply to the use of two varieties of one drug, *e.g.* procaine penicillin and benzyl penicillin, or two different drugs, one being a potentiator of the other, *e.g.* probenecid and penicillin or trimethoprim and sulphamethoxazole. Thus, two drugs in single session have produced a range of results as follows:

Fluker and Hewitt (1969)—94.5 per cent. success with 3.6 m.u. procaine penicillin plus 2 g. ampicillin given to cases of previous penicillin failure;

Cobbold, Morrison, Spitzer, and Willcox (1970)—93.2 per cent. success with 1 g. probenecid and 1.2 m.u. procaine penicillin.

Gjessing and Ödegaard (1965, 1966, 1967)—97 per cent. success with 600,000 u. procaine penicillin and 1 g. ampicillin given in 500 male cases and 96 per cent. success with 600,000 u. procaine penicillin and 0.75 g. chloramphenicol; 98 per cent. success with 600,000 u. procaine penicillin and 0.5 g. chloramphenicol given to 250 male cases; 98.2 per cent. success with 600,000 u. procaine penicillin plus 1 g. chloramphenicol given to 500 cases.

Gundersen, Ödegaard, and Gjessing (1969)—96.2 per cent. success in those followed (441 out of 500) who were given 1.2 m.u. procaine penicillin and 1 m.u. sodium penicillin G; 98.6 per cent. success in those followed (437 out of 500) who were given 1 g. probenecid plus 2 g. ampicillin, all failures occurring among cases with less sensitive strains of gonococci.

Olsen and Lomholt (1968) claimed 99 per cent. success but later (1969) suggested (and were credited by others (Gundersen and others, 1969) with 100 per cent. success using 1 g. probenecid plus (30 minutes later) 5 m.u. sodium penicillin G in 8 ml. of 0.5 per cent. lignocaine in 832

cases (eight subsequently positive cases being considered to be re-infections because all admitted to renewed coitus and all responded to the same treatment);

Lomholt and Berg (1966) had previously reported 99.6 per cent. success in 228 cases using this same treatment schedule;

Gray and others (1970), having achieved 96.9 per cent. success with 2.4 m.u. Distaquaine fortified (procaine penicillin + benzyl penicillin) also achieved 99.5 per cent. success with 1 g. probenecid and 5 m.u. benzyl penicillin.

(3) TWO DRUGS IN MULTIPLE SESSION—POTENTIATORS

Finally, there remain to be noted the results of those trials employing more than one drug in divided doses. Because 100 per cent. cure can be expected with most antibiotics alone or combined, in sufficient dosage over a sufficient period, only those employing potentiators will be mentioned. In single dosage these have already been referred to. In multiple dosage the following results have been reported:

Holmes, Johnson, and Floyd (1967)—98.3 per cent. success with 2.4 m.u. procaine penicillin plus 1 g. probenecid followed by 0.5 g. probenecid \times 3 in 18 hrs;

Smithurst (1970)—94.8 per cent. success in 212 cases with 2 to 2.4 m.u. procaine penicillin in equal divided doses and 1 g. probenecid followed by a further 0.5 g. after 8 and 16 hrs; but only 92.9 per cent. success in 562 cases with 3 m.u. aqueous procaine penicillin and 2 g. probenecid given in a similar manner;

Hilton (1971)—93.2 per cent. success between 1966 and 1969 with 1.2 m.u. procaine penicillin and 2 g. probenecid (0.5 g. 6 hrly \times 4) when strains of gonococci partially resistant to penicillin amounted to 31.7 per cent.; and 97.9 per cent. success with 1.2 m.u. PAM (procaine penicillin in oil and aluminium monostearate) and the same probenecid schedule between 1964 and 1966 when partially resistant strains amounted to 18.1 per cent. only.

Cotrimoxazole

Hardly within the 24-hr parameter under discussion but apposite to this paper must be mentioned:

Csonka and Knight (1967)—93 per cent. success with trimethoprim 200 mg. and sulphamethoxazole 1,000 mg. given twice daily for 4 days;

Carroll and Nicol (1970)—93 per cent. success in 42 women and 95.5 per cent. in 111 men given trimethoprim 320 mg. and sulphamethoxazole 1,600 mg. once daily for 5 days;

Arya and others (1970)—96 per cent. success with trimethoprim 320 mg. and sulphamethoxazole 1,600 mg. for three or four doses at 12-hrly intervals;

Jefferiss (1971)—90.3 per cent. success with trimethoprim 160 mg. and sulphamethoxazole 800 mg. twice daily for 5 days.

This combination of drugs was tried and condemned by Wright and Grimble (1970) who achieved

only 62 per cent. success; they prescribed one drapsule (trimethoprim 80 mg. and sulphamethoxazole 400 mg.) four times daily for 5 days.

Factors vitiating fair comparison

With such diverse treatment regimes given, with few exceptions, to relatively small numbers of cases over approximately a 10-year period in different countries and different parts of one country, it is well-nigh impossible to compare their respective efficacy. Different failure rates of between 3 and 8 per cent. are not statistically significant when total cases remain in the region of 100. Sensitivity of gonococci will vary from time to time, place to place, and drug to drug. Multiple dosage carries its inevitable drawbacks of patient default or forgetfulness and consequent incomplete dosage. Workers adopt diverse standards of cure and interpret their own results in varied ways according to whether account is taken of numbers treated or numbers followed. Few trials can escape some criticism and amongst those with the bigger success claims and those involving larger series of patients we may cite the following by way of example:

Neither Morrison and others (1968) nor Smithurst (1970) with his 774 cases looked for gonococci at follow-up in the absence of urethral discharge, while Olsen and Lomholt (1969) did not tell us whether they looked or not in the absence of a discharge.

Gray and others (1970) looked for gonococci on the first day of surveillance, but refer only to 'tests of cure' thereafter.

Gjessing and Ödegaard (1966, 1967) used chloramphenicol, now in disfavour.

Cornelius and Domescik (1970), with their 100 per cent. 'cure' following 2 g. spectinomycin hydrochloride and their 4.3 per cent. failure rate with twice this dose, assessed their results after only 96 hrs, barely enough time for staunch gonococci to recover from the insult.

The series here presented suffers from paucity of numbers for statistical significance and the available resources did not permit estimations of the MICs of penicillin for strains isolated from female consorts. Though routine smears were undertaken in the absence of any discharge on the 3rd, 4th, or 7th day, *i.e.* at the first follow-up attendance, they were not performed at a later attendance so that asymptomatic relapse could not be excluded. Furthermore, some 32 patients were treated with tetracycline for non-gonococcal urethritis within the first 8 days' surveillance. Although these patients were all negative for *N. gonorrhoeae* on smear after treatment, it is conceivable that they also might have exhibited a delayed relapse of gonorrhoea.

Desiderata for therapeutic trials

Meaningful results are most likely to be derived from controlled trials involving large numbers in which all strains are cultured and assayed for sensitivity, all treatment is clinic supervised, all relapses are shown to involve gonococci of the same sensitivity as at first demonstrated and if possible, the demonstration of an identical strain in the patient and the sexual contact, both in first infections and in re-infections, as mentioned by Gunderson and others (1969). Olsen and Lomholt (1969) noted the need for double deviation in the sensitivity pattern as one of three criteria to be satisfied before re-infection is accepted as such, *i.e.* the supposedly new strain must show a different sensitivity to two out of three antibiotics, the other two criteria being an admission of fresh coitus with a known or suspected case of gonorrhoea and the existence of one negative culture after initial treatment. Follow-up must be for a reasonable and agreed minimum length of time, no less than 2 weeks. Moreover, it is important to correlate treatment failure with drug sensitivity, so that we may not only perhaps learn to supplement our routine treatment in, say, cases relatively insensitive to penicillin with another drug (*e.g.* tetracycline, as practised by Rees and Annels (1969), who thus claimed to reduce the incidence of post-treatment salpingitis), but also discover causes other than drug insensitivity for treatment failure.

Correlation between sensitivity levels and treatment results.

Several workers have, in fact, correlated their treatment failures with reduced sensitivity of gonococci to penicillin.

Schmidt (1962) observed a 2 per cent. failure rate after 300,000 u. penicillin in patients harbouring sensitive strains of gonococci (MIC < 0.038 µg./ml. [0.06 u./ml.]), but a 38 per cent. failure in those with less sensitive strains (MIC 0.038 µg./ml. [0.06 u./ml.] or more).

Gjessing and Ödegaard (1966) had a 5.1 per cent. failure rate in cases due to less sensitive strains (MIC 0.125–2 u./ml. [0.075–1.2 µg./ml.]) but an overall failure rate of 3 per cent.

Gundersen and others (1969) had six failures out of 166 cases (3.6 per cent.) with less sensitive strains (0.125–2 u./ml. [0.075 µg.–1.2 µg./ml.]) but no failure in 334 cases with sensitive strains (0.06–0.15 u./ml. [0.036 to 0.09 µg./ml.]).

Leigh and others (1969) found 90 per cent. of strains sensitive to 0.2 u./ml. (0.12 µg./ml.) or less and obtained an 86 per cent. success rate using 1.2 m.u. aqueous procaine penicillin; they related treatment failure to penicillin sensitivity.

Hilton (1971) produced figures from which one can deduce that his failure rate was 2.3 per cent. with sensitive strains and 10.7 per cent. with less sensitive strains, but

his dividing line occurred at a 10-fold dilution between an MIC of 0.05 u./ml. (0.03 µg./ml.) and 0.5 u./ml. (0.3 µg./ml.).

The present series recorded from Newcastle shows a similar tendency and is discussed later.

Factors leading to present trial

The most successful and practical single-session treatment for uncomplicated gonorrhoea to date is that tried and advocated by Olsen and Lomholt (1968) and attested by Gray and others (1970) in which 1 g. probenecid by mouth is followed by 5 m.u. sodium penicillin G or benzyl penicillin dissolved in 8 ml. of 0.5 per cent. lignocaine given intramuscularly. This regime produces a 99.5 to 100 per cent. cure rate and is authoritatively advocated by Nicol (1971) and in a leader in the *British Medical Journal* (1972). It is closely followed by that of Gunderson and others (1969) with a 98.8 per cent. success using 1 g. probenecid and 2 g. ampicillin by mouth, recently advocated by a leader in the *Lancet* (1972). Nevertheless, if one has to inject 5 m.u. penicillin in 8 ml. fluid in order to achieve a near 100 per cent. cure rate, then the search for an alternative must continue for reasons other than those adduced already, for many stalwart men, to say nothing of delicate women, would demur at receiving more than 2.5 m.u. penicillin at once and many a squeamish doctor would likewise hesitate to approach a patient with such a large dose.

Preliminary reports on the use of cotrimoxazole (now marketed in tablets or drapsules comprising trimethoprim 80 mg. and sulphamethoxazole 400 mg.) in the treatment of gonorrhoea, were most encouraging (Csonka and Knight, 1967). Penicillin failures were successfully treated with cotrimoxazole and cotrimoxazole failures were successfully treated with penicillin. The present trial involved combining penicillin and cotrimoxazole in the hope that each drug might eliminate the other's failures. Cotrimoxazole was chosen as an additive to penicillin in preference to a bacteriostatic broad-spectrum antibiotic, such as tetracycline, because the component parts of cotrimoxazole together exert a bactericidal effect by interfering at two different stages in the synthesis of folic acid. As penicillin exerts its lethal effect by interfering with the development of the bacterial cell wall, the combined treatment suggested a strategic advance in therapeutics for it offered a double bactericidal onslaught on the gonococcus.

The success with cotrimoxazole, already referred to, had followed its administration over 2 to 4 days. As the object of the present exercise was to find a 100 per cent. effective one-session treatment, the

question arose as to how much could be given at one swallow. According to the manufacturing firm, it was thought that a total of twelve tablets of cotrimoxazole could be tolerated before causing nausea or vomiting and it was known that this dose was well within the safety level. On the strength of this information a preliminary series of eight uncomplicated cases of gonorrhoea in males was treated, each with six tablets of cotrimoxazole dissolved in a tumbler of water. There were no untoward reactions. Of these eight patients, seven were cured, although four developed non-gonococcal urethritis and had subsequently to be given tetracycline. There was one failure who had to be re-treated with penicillin. The fact that some success had been achieved seemed to justify a further trial which is described below.

Methods

Four treatment schedules were laid down as follows: SCHEDULE A 1.25 m.u. Triplopen (benzathine penicillin G 475 mg. [500,000 u.], procaine penicillin G 250 mg. [250,000 u.], and sodium penicillin G 300 mg. [500,000 u.]) intramuscularly.

This had been the standard treatment at Newcastle for a number of years and was continued for the sake of comparison with the trial schedule, for the latter could not be compared retrospectively with previous years lest the penicillin sensitivity pattern had changed.

SCHEDULE B 2.5 m.u. Triplopen intramuscularly.

This was undertaken to see if doubling the dose of penicillin would have a similar effect to combining it with cotrimoxazole. It was also felt that this might have become the standard treatment of other workers by the time the trial was complete, and the present series might therefore provide a basis for comparison with the experience of other workers.

SCHEDULE C Six tablets cotrimoxazole dissolved in water and swallowed at the clinic.

SCHEDULE D 1.25 m.u. Triplopen intramuscularly plus six tablets of cotrimoxazole given orally at the same time. The trial applied only to cases of uncomplicated gonococcal urethritis in men. Patients were given schedule A, B, C, or D in rotation. Excluded from the series were itinerants, such as long-distance lorry drivers and merchant seamen, who perforce left the clinic with a V15 or V44 (record of treatment). These were all treated with 2.5 m.u. Triplopen but were subsequently included in Schedule B if, contrary to expectations, they remained in Newcastle for their follow-up period.

Also excluded from the series were known regular defaulters who could not be relied upon to co-operate, and patients who gave a history of penicillin sensitivity. Schedules A, C, and D were not used unless the patient affirmed that he intended to stay in the neighbourhood. It was intended that patients on

cotrimoxazole alone who subsequently announced their intention of leaving the district were automatically to be given 2.5 m.u. Troplophen, but in the event none did so.

The initial diagnosis was made in the conventional manner by demonstrating Gram-negative intracellular diplococci in urethral smears. Specimens from all urethral discharges thus diagnosed were sent for culture and for gonococcal sensitivity testing to penicillin and to other antibiotics referred to later. Each patient was instructed concerning the avoidance of sexual intercourse and alcohol and the need for surveillance. Each was asked to attend on the 3rd or 4th day after treatment, again on the 7th day and again on the 14th day. Serological tests for syphilis were done on all patients at their first attendance.

At the first follow-up attendance urethral smears or scrapes were taken, using a saline-moistened loop if necessary, as judged by the dryness of the meatal orifice. Positive slides after treatment were in each case confirmed by a responsible member of the staff, who to avoid bias was never told before microscopic examination what the original treatment of the patient had been. It was intended that all cases that were positive on microscopy after treatment should be subjected to fresh culture and sensitivity tests, but not all such relapses and re-infections were thus investigated. Without waiting for the results of these tests these patients were all treated with 2.5 m.u. Triplophen, except those in Schedule B who had initially received this dosage of penicillin. These patients were subsequently treated with tetracycline by mouth, 500 mg. 6 hrly for 5 days.

Patients who were negative for gonorrhoea after the initial treatment were subsequently managed as follows:

If there was a urethral discharge or hazy urine on the 3rd or 4th day, they were given mist. potassium citrate (British National Formulary) and asked to return on the 7th day.

If they had no discharge and a clear urine on the 3rd or 4th day, they likewise had to come back on the 7th day.

If, on the 7th day, they had a urethral discharge or hazy urine or even a clear urine with many threads, the discharge or urine was examined by Gram-staining, and if negative for gonococci non-gonococcal urethritis was diagnosed; they were then given tetracycline, 500 mg. four times a day for 5 days and asked to return on the 14th day.

If, on the 7th day, they had no urethral discharge and their urine was clear, they were asked to return on the 14th day, those with a few threads present being given mist. potassium citrate.

On the 14th day the presence of non-gonococcal urethritis on any evidence (discharge, hazy urine, threads) resulted in a prescription for tetracycline and routine follow-up of the non-gonococcal urethritis.

If they were without discharge on the 14th day and had a clear urine, they were invited to return at the 6th week and at the 13th week after last coitus for intermediate and final serological tests for syphilis.

Bacteriological methods

Chocolate agar plates containing polymyxin (2,500 i.u. per ml.) and ristocetin (0.5 µg./ml.) were inoculated in the clinic. These were incubated in candle-jars for 16 hrs at 36°C. The next day the plates were transferred to the laboratory, which is adjacent to the clinic. Positive cultures were identified as *Neisseria gonorrhoeae* by (i) colonial appearance, (ii) Gram-stained film, (iii) oxidase test. When there was the slightest doubt as to the identity of the organism, sugar fermentation tests were undertaken. This applied to only a few strains, all of which were confirmed as *N. gonorrhoeae*.

All positive cultures were tested for antibiotic sensitivity by the disc-diffusion method, measuring zone sizes and comparing them with that for the Oxford staphylococcus (NCTC No. 6571). The antibiotic discs used were penicillin 1.5 µg., trimethoprim 1.25 µg., sulphamethoxazole 25 µg., cotrimoxazole (trimethoprim and sulphamethoxazole combined 1.25 µg./25 µg.), sulphafurazole 200 µg., tetracycline 25 µg., and streptomycin 25 µg. The MIC of penicillin was assayed by plating on to a series of chocolate agar plates containing doubling concentrations of benzyl penicillin (Gjessing and Ødegaard, 1962), the plates giving final concentrations between 0.0075 µg. (0.0125 u./ml.) and 0.96 µg./ml. (1.6 u./ml.).

For the latter test the inoculum was prepared by emulsifying a loopful from an 18-hr subculture in 1 ml. glucose phosphate broth and shaking for 5 min. on a flask shaker. This gave a uniform suspension with a density approximating to 1 in 5 dil. of Ba₂SO₄ standard (U.S. P.H.S., 1963). A small loopful of this suspension was then streaked on to the penicillin plates and a control plate not containing penicillin. Six test strains and two controls were inoculated on to each plate. (The Oxford staphylococcus and three strains of gonococci of known MIC provided by Dr. A. E. Wilkinson, V.D. Reference Laboratory, London, were used as controls.) All test strains were assayed in duplicate on a different set of plates. The plates were read after incubation in candle-jars for 48 hrs at 36°C. The MIC was taken as the lowest concentration on which there was no growth visible to the naked eye. Strains giving different results in the duplicate assay were retested.

Clinical data

335 fresh gonococcal infections involving 315 men, occurring between August 1, 1969, and July 17, 1970, formed the basic material of the trial. 298 were infected once, sixteen twice, and one five times (Table I). There were twenty re-infections included in the trial but only two of these occurred within the first 2 weeks of surveillance and had therefore to be differentiated from relapse. Eight further re-infections were excluded because

they occurred after the trial period was over. Thus, 26 re-infections occurred after the routine 2 weeks' surveillance after initial treatment. Single individuals (210) were exactly twice as numerous as married (105). Their age distribution followed the familiar pattern, 27 (8.6 per cent.) being teenagers (Table II). Racial origin was not recorded for the numbers of overseas patients were negligible (many cases from the merchant navy perforce departing with V44's).

TABLE I 315 individuals responsible for 335 infections

Individuals	Re-infections	Infections
298	Nil	298
16	16	32
1	4	5
Total 315	20	335

TABLE II Marital status and age group of 315 patients

Marital status		Age group (yrs)			
Single	Married	<20	20-24	25-29	30+
210	105	27	111	76	101

Table III shows that a preponderance (74.3 per cent.) of infections were known to be acquired in the locality served by the clinic, *i.e.* Northumberland and North West Durham, including the City of Newcastle upon Tyne and the Borough of Gateshead. The ratio of single (203) to married (104) persons acquiring their infections

TABLE III Locality where infection was first acquired

Locality	Marital status		Total	
	Single	Married	No.	Per cent.
Newcastle region	162	87	249	74.3
Elsewhere in U.K.	27	12	39	11.6
Abroad	14	5	19	5.7
Unsure	23	5	28	8.4
Total	226	109	335	100

locally or away from the region (*i.e.* Table II totals minus those who were 'unsure') showed no variation from that relating to all infections (2 : 1), but rather more single than married patients (23 : 5) were not sure where their infections were acquired, which suggests possibly that marital infidelity is more memorable an occasion than pre-marital indulgence.

Sensitivities to penicillin

All urethral discharges positive on Gram-staining were cultured and when gonococci were grown they were sub-cultured and tested for penicillin sensitivity (Table IV). Of 335 specimens cultured, the gonococcus was grown and sub-cultured in 240, grown but lost on sub-culture in 58, and not isolated at all in 37. Thus gonorrhoea was regarded as proven in 298 cases (89 per cent.) but was accepted though unproven in 37 cases (11 per cent.). Those with MICs of 0.1 u. down to 0.0125 u. penicillin (0.06-0.0075 µg./ml. were classed as sensitive to penicillin and totalled 153 (63.8 per cent.); those with MICs of 0.2 u. up to 1.6 u. (0.12-1.0 µg./ml. were classed as less sensitive and totalled 87 (36.2 per cent.) (Table V). It is from these 240 cases in which the sensitivity levels were assessed that much of the results were recorded and deductions made.

TABLE IV Proportion of strains of gonococcus grown and subcultured, grown but lost, and not isolated

Gonococcus	No.	Per cent.	No.	Per cent.
Grown and sub-cultured	240	72		
Grown but lost	58	17	Proven cases 298	89
Not isolated	37	11	Unproven cases 37	11
Total	335	100	335	100

When the numbers and percentages of sensitive and less sensitive strains of gonococci are considered as they occurred in infections derived locally, elsewhere in the U.K., and abroad, it is observed from Table V that the ratio of sensitive to less sensitive strains (121 to 60) acquired locally is similar to the present-day national pattern, *i.e.* 2 : 1. Infections acquired elsewhere in the United Kingdom (sensitive 13, less sensitive 12) and abroad (sensitive 7, less sensitive 7) give ratios of 1 : 1.

It is of interest in this context to compare the Newcastle figures for 1970 with the Southampton figures for 1958 to 65 (Warren, 1968). Although some of the figures for Newcastle are small and none of the differences achieve statistical significance, the pattern is similar to that of Southampton. In order to make this comparison, however, it must be noted that Warren's line of demarcation was drawn between MICs of 0.03 u./ml. (0.018 µg./ml.) or less for sensitive organisms and 0.06 u./ml. (0.036 µg./ml.) or more for less sensitive organisms. The Newcastle figures had therefore to be calibrated with this

TABLE V *Distribution of cases according to penicillin sensitivities and numbers of cases for each sensitivity level acquired locally, elsewhere in the U.K., and overseas*

Gonococcus	MIC		Locality					Total
	u/ml.	(µg/ml.)	Newcastle region	Elsewhere in U.K.	Abroad	Not known		
							Per cent.	
Less sensitive	1.6	1.0	1	—	1	—	2	
	0.8	0.5	8	—	—	2	10	
	0.4	0.25	34	3	3	4	44	
	0.2	0.125	17	9	3	2	31	
	Total	No.	60	12	7	8	87	
	Per cent.	33.2	50	50	40	36.2		
Sensitive	0.1	0.06	14	3	1	2	20	
	0.05	0.03	15	1	—	—	16	
	0.025	0.015	31	4	2	3	40	
	0.0125	0.0075	61	5	4	7	77	
	Total	No.	121	13	7	12	153	
	Per cent.	67	50	50	60	63.8		

distinction in mind and they produced an expected increase in the percentage of locally acquired gonococcal infections that were due to less sensitive organisms. Within the regions served, 17.1 per cent. of Southampton infections were due to less sensitive organisms between 1958 and 1965. In 1970, 49.2 per cent. (89 out of 181 cases) of infections acquired in Newcastle were due to less sensitive organisms. Infections acquired elsewhere in the United Kingdom and abroad for the same period in Newcastle in the present series totalled 39, of which 24 were due to less sensitive organisms. In both Southampton and Newcastle there was a greater proportion of less sensitive organisms in cases derived from outside their respective catchment areas than in cases derived locally; we may postulate that those who acquire infections away from their home town are more likely to consort with promiscuous strangers

than with known girl friends, and that such willing females might well be expected to harbour less sensitive strains of gonococci.

Sensitivities to other antibiotic drugs

The results of disc sensitivities for sulphafurazole, tetracycline, cotrimoxazole, and streptomycin are shown in Table VI and are correlated with the penicillin sensitivities for the 240 strains tested. Only one strain (penicillin sensitive) was insensitive to sulphafurazole and none was insensitive to tetracycline or cotrimoxazole. 64 (73.5 per cent.) of 87 penicillin insensitive strains were also resistant to streptomycin and 132 (86.3 per cent.) of 153 penicillin sensitive strains were sensitive to streptomycin. Thus, 196 out of 240 strains showed a statistically highly significant parallelism (81.6 per cent.) between

TABLE VI *Sensitivities of 240 strains of gonococci to antibiotics other than penicillin in relation to penicillin sensitivity. 196 out of 240 strains (81.6 per cent.) showed parallelism between penicillin and streptomycin sensitivities*

Drug	Penicillin	Sulphafurazole		Tetracycline		Cotrimoxazole			Streptomycin	
		Sens.	Insens.	Sens.	Insens.	Sens.	Insens.	Not done	Sens.	Insens.
Relatively insensitive to penicillin MIC 0.125-1.0 µg/ml. (0.2-1.6 u./ml.)	87	87	—	87	—	85	—	2	23	64 (73.5% of 87)
Sensitive to penicillin MIC 0.06-0.0075 µg/ml. (0.1-0.0125 u./ml.)	153	152	1	153	—	150	—	3	132 (86.3% of 153)	21 (13.7%)
Total	240	239	1	240	—	235	—	5	155	85

their sensitivities to penicillin and to streptomycin. Not shown in Table VI is the fact that no strain was sensitive to trimethoprim alone, thus indicating that it is this fraction of cotrimoxazole which potentiates sulphamethoxazole and not *vice versa*, and that these two components are not additive in their effect. There were five cases in which cotrimoxazole disc sensitivities were not undertaken (three in Schedule B and two in Schedule D). All these five strains were sulphonamide sensitive.

Results of treatment and discussion

The overall findings with regard to cultures, sensitivities to penicillin, results of treatment, and occurrence of non-gonococcal urethritis are shown in the Master Table.

Cases in which gonococci persisted or re-appeared within the first 2 weeks after treatment were classed as treatment failures, provided the patients denied sexual intercourse. Out of 335 patients treated, there were 26 such failures, none of whom admitted intercourse since treatment (Table VII). There were two re-infections within the first 2 weeks following treatment (see Master Table). Of eighteen re-infections occurring after the first 2 weeks, none denied intercourse. There were 25 (7.5 per cent.) complete defaulters, after which the law of diminishing returns operated. 262 (78.2 per cent.) were

followed for 2 weeks. There were no known relapses after 2 weeks' surveillance.

Table VII shows, for each treatment schedule, the number of cases treated and the number of treatment failures; the numbers defaulting completely and those followed up for 3 to 4, 7, and 14 days are also shown.

Percentage cure rates have been calculated according to different premises. At one extreme is the assumption that all patients treated, except the known failures, are to be regarded as successes ('apparent' cure rate). At the other extreme the failures are calculated in relation to the numbers of patients known to be cured at the 14th day ('real' cure rate). Also recorded are 53 cases requiring further treatment for concomitant non-gonococcal urethritis; excluding these from the successful results, a combined 'clinical and bacteriological' cure rate can be obtained.

Schedule C, consisting of six tablets of cotrimoxazole taken orally in one dose with a glass of water, produced seven failures in the first 25 cases and was forthwith abandoned as unethical and wholly unacceptable. Such a failure rate so early in the trial led to the tacit assumption that a 100 per cent. cure rate could not be expected from Schedule D (1.25 m.u. Triplopen intramuscularly and six tablets of cotrimoxazole). The trial as a whole was nevertheless continued in order to ascertain if the addition of a

TABLE VII *Results of treatment for each of four schedules together with numbers of defaulters, follow-up rates, and incidence of non-gonococcal urethritis*

Treatment schedule	No. treated	No. relapsing (i.e. gonococci positive within 2 wks)	Percentage cure ('apparent')	No. defaulting completely	No. followed-up (days)			Percentage cure ('real')	Incidence of NGU			Combined bacteriological and clinical success rate (per cent.)
					3/4	7	14		Noted 1st week	Noted 2nd week	Total	
A 1.25 m.u. Triplopen	103	9	91.3	5	98	87	81	88.9	9	6	15	76.7
B 2.5 m.u. Triplopen	103	7	93.2	8	95	85	81	91.4	9	8	17	76.7
C Cotrimoxazole Tabs. 6	25	7	72	2	23	17	14	50	6	0	6	48
D 1.25 m.u. Triplopen + Cotrimoxazole Tabs. 6	104	3	97.1	10	94	88	86	96.5	8	7	15	82.7
Total	335	26		25	310	277	262		32	21	53	

For calculation of cure rates, see text

MASTER TABLE Showing for each of four treatment schedules the numbers treated, defaulting, developing non-gonococcal urethritis, relapsing and becoming re-infected, together with culture results and minimum inhibitory concentrations of penicillin

Schedule	Dosage	Patients	MIC										Total	
			Gonococcus		Relatively insensitive				Sensitive					
			Not isolated	Isolated but lost	(u./ml.)		(μg./ml.)		(u./ml.)		(μg./ml.)			
					1·6	0·8	0·4	0·2	0·1	0·05	0·025	0·0125		
		1·0	0·5	0·25	0·125	0·06	0·03	0·015	0·0075					
A	Tripropen 1·25 m.u.	Total	12	21	1	3	10	9	4	8	7	28	103	
		Defaulted	—	1	—	—	1	2	—	1	—	—	5	
		Followed-up												
		Gc. neg.	NGU—	7	16	1	2	7	4	4	6	4	22	73
		NGU+	2	3	—	—	—	1	—	1	3	5	15	
Gc. pos.	Relapse	3	1	—	1	1	2	—	—	—	1	9		
	Re-infection	—	—	—	—	1	—	—	—	—	—	1		
B	Tripropen 2·5 m.u.	Total	13	18	1	2	12	8	7	3	18	21	103	
		Defaulted	2	2	—	—	—	1	—	—	1	2	8	
		Followed-up												
		Gc. neg.	NGU—	9	15	—	2	6	6	6	2	11	13	70
		NGU+	1	—	—	—	4	—	—	1	5	6	17	
Gc. pos.	Relapse	1	1	1	—	1	1	1	—	1	—	7		
	Re-infection	—	—	—	—	1	—	—	—	—	—	1		
C	Cotrimoxazole 6 tabs	Total	3	6	—	1	6	1	1	2	3	2	25	
		Defaulted	—	1	—	—	—	—	—	1	—	—	2	
		Followed-up												
		Gc. neg.	NGU—	1	3	—	—	1	1	1	1	—	2	10
		NGU+	2	1	—	1	—	—	—	1	1	—	6	
Gc. pos.	Relapse	—	1	—	—	5	—	—	—	1	—	7		
	Re-infection	—	—	—	—	—	—	—	—	—	—	—		
D	Cotrimoxazole 6 tabs + Tripropen 1·2 m.u.	Total	9	13	—	4	16	13	8	3	12	26	104	
		Defaulted	—	1	—	1	3	2	—	—	2	1	10	
		Followed-up												
		Gc. neg.	NGU—	9	10	—	3	9	9	7	1	7	21	76
		NGU+	—	2	—	—	3	1	1	2	3	3	15	
Gc. pos.	Relapse	—	—	—	—	1	1	—	—	—	1	3		
	Re-infection	—	—	—	—	—	—	—	—	—	—	—		

single large dose of cotrimoxazole could statistically improve upon the results obtained by giving Tripropen alone.

In Schedule A (1·25 m.u. Tripropen), Schedule B (2·5 m.u. Tripropen), and Schedule D (combined therapy), there were treated 103, 103, and 104 cases respectively with nine, seven and three failures respectively. Table VII suggests that the addition of a single large oral dose of cotrimoxazole (6 tablets) to 1·25 m.u. Tripropen given intramuscularly appears to increase the chances of bacteriological cure from 91·3 to 97·1 per cent. ('apparent') and from 88·9 to 96·5 per cent. ('real'). These differences, however, could have occurred by chance and are not statically significant, though the improvement to the 'real' cure rate only just fails to achieve significance at the 5 per cent. level. With such results as are here recorded, it is not possible to decide whether any

real enhancement from combined therapy would be an additive or a synergistic phenomenon.

Doubling the dose of Tripropen from 1·25 to 2·5 m.u. made an insignificant difference to the cure rate, from 91·3 to 93·2 per cent. ('apparent') and from 88·9 to 91·4 per cent. ('real').

Until the tidal wave of gonorrhoea has been stemmed, the essential consideration must be that of bacteriological cure, *i.e.* the elimination of the gonococcus. As physicians we also have a responsibility to individual patients and the results of treatment are less gratifying when concomitant non-gonococcal urethritis is taken into account. The addition of cotrimoxazole to the routine treatment with penicillin would seem to offer no improvement other than the statistically nonsignificant differences already noted, the combined bacteriological and clinical cure rate being 76·7 per cent. for Schedules

A and B and 82.7 per cent. for Schedule D. These are calculated as percentages of the total treated after subtracting cases of non-gonococcal urethritis and cases of gonococcal relapse.

As is to be expected, more treatment failures occur with relatively insensitive organisms than with sensitive organisms. Of the 26 failures, seven occurred in patients for whose infections the MIC of penicillin in culture was unknown (Master Table). Fourteen out of nineteen of the remaining failures occurred in cases due to relatively insensitive gonococci. These have been extrapolated from the Master Table and are shown or referred to in Table VIII. The difference in failure rate on Schedule A as between less sensitive strains (17.4 per cent.) and sensitive strains (2.1 per cent.) is, for the number of cases treated, highly significant, and yet Schedule B with twice the dose of penicillin does not produce a statistically significant difference (13 and 4.1 per cent. respectively). Of interest and concern to the trial is the difference in failure rate for less sensitive strains of gonococci as between Schedules A and B on the one hand (17.4 and 13 per cent. respectively) and Schedule D on the other (6.1 per cent.). These figures are not statistically valid but suggest that the addition of cotrimoxazole may be of value in cases with less sensitive strains.

Changes in penicillin sensitivities upon re-infection and in relapse

Both the patients who became re-infected during the first 2 weeks of surveillance harboured organisms with MICs of 0.4 u./ml. (0.25 µg./ml.) at their first infection and of 0.2 u./ml. (0.125 µg./ml.) at the second, but these differences cannot be regarded as significant. Not all schedules are strictly followed. Many plans go awry. Of the nineteen relapsing patients for whom the original MICs were known,

the subsequent culture was lost in one, neither the MIC nor disc sensitivity was ascertained in ten, and MICs were ascertained in four out of the remaining eight cases. Two showed identity of MIC at the level of 0.2 u./ml. (0.125 µg./ml.) in one case and 0.4 u./ml. (0.25 µg./ml.) in the other; two showed disparity, from 0.4 u./ml. (0.25 µg./ml.) to 0.1 u./ml. (0.06 µg./ml.) and to 0.025 u./ml. (0.015 µg./ml.) respectively. In the four remaining cases disc sensitivities were recorded as follows: three originally insensitive strains were still insensitive at relapse and one originally sensitive strain showed insensitivity upon relapse.

Adverse reactions

There were no untoward or adverse reactions to any of the four treatment schedules.

Summary

This trial was undertaken on the assumption that combining penicillin and cotrimoxazole would constitute a double onslaught on the gonococcus and might lead to a 'near 100 per cent.' success rate in single-session treatment.

Four schedules of single-session treatment were used in men with uncomplicated gonorrhoea:

- (A) 103 patients received 1.25 m.u. Triplopen with nine failures;
- (B) 103 patients received 2.5 m.u. Triplopen with seven failures;
- (C) 25 patients received six tablets of cotrimoxazole (each tablet containing trimethoprim 80 mg. and sulphamethoxazole 400 mg.) with seven failures;
- (D) 104 patients received 1.25 m.u. Triplopen plus six tablets of cotrimoxazole with three failures.

Schedule C was abandoned early in the trial. The 'apparent' cure rates for schedules A, B, and D,

TABLE VIII *Difference in failure rate for three treatment schedules, according to whether the gonococci were less sensitive or more sensitive to penicillin*

Schedule	A Triplopen 1.25 m.u.			B Triplopen 2.5 m.u.			D Triplopen 1.25 m.u. + Cotrimoxazole		
	Total treated	Failures		Total treated	Failures		Total treated	Failures	
Sensitivity		No.	Per cent.		No.	Per cent.		No.	Per cent.
Less sensitive 0.2 u./ml. (0.125 µg./ml.) or more	23	4	17.4	23	3	13	33	2	6.1
More sensitive 0.1 u./ml. (0.06 µg./ml.) or less	47	1	2.1	49	2	4.1	49	1	2

based on the numbers treated, were 91·3, 93·2, and 97·1 per cent. respectively. The 'real' cure rates, based on the numbers followed-up for 14 days, were 88·9, 91·4, and 96·5 per cent. respectively.

The literature is reviewed concerning changing patterns of gonococcal sensitivity to penicillin as they occur in the United Kingdom, Scandinavia, Africa, Asia, and America, and attention is drawn to a steady state of relative insensitivity of strains of about 35 per cent. for the past 6 years or so in Europe.

The literature concerning successful treatment claims (over 90 per cent. success) is reviewed, as they relate to one or two drugs at a single session; to the addition of potentiators; and to cotrimoxazole.

In Schedules A, B, and D, the failure rates among the penicillin sensitive group (MIC equal to or less than 0·1 u./ml. [0·06 µg./ml.]) amounted to 2·1, 4·1, and 2 per cent. respectively. Among the less sensitive group (MIC equal to or greater than 0·2 u./ml. [0·125 µg./ml.]) the failure rates amounted to 17·4, 13, and 6·1 per cent. respectively.

Neither doubling the dose of penicillin nor the addition of cotrimoxazole affected the incidence of concomitant non-gonococcal urethritis.

There were no adverse reactions.

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Traitement en une seule séance de la gonococcie masculine non compliquée par la pénicilline combinée au Cotrimoxazole

SOMMAIRE

Cet essai a été entrepris sur l'hypothèse que l'association de pénicilline et de Cotrimoxazole aurait une double action sur le gonocoque et pourrait conduire, par un traitement en une seule séance, au 'presque cent pour cent' de succès.

Quatre schémas de traitement en une seule séance furent utilisés:

(A) 103 malades reçurent 1,25 M.U. de Triplopen, 9 échecs.

(B) 103 malades reçurent 2,5 M.U. de Triplopen, 7 échecs.

(C) 25 malades reçurent six comprimés de Cotrimoxazole (chaque comprimé contenant 80 mg de triméthoprime et 400 mg de sulfaméthoxazole), 7 échecs.

(D) 104 malades reçurent 1,25 M.U. de Triplopen plus 6 comprimés de Cotrimoxazole, 3 échecs.

Le schéma C fut vite abandonné au cours de l'essai. Les taux 'apparents' de guérison pour les schémas A, B et D, reposant sur les nombres de sujets traités, furent respectivement de 91,3; 93,2 et 97,1 pour cent. Les taux de guérison 'réelles', reposant sur le nombre des cas suivis quatorze jours, furent respectivement de 88,9; 91,4 et 96,16 pour cent.

On passe en revue la littérature traitant des modifications de l'allure de la sensibilité du gonocoque à la pénicilline telles qu'on les observe au Royaume-Uni, en Scandinavie, en Afrique, en Asie et en Amérique et l'attention est attirée sur la fixité de la relative insensibilité des souches pendant les six dernières années ou à peu près (environ 35 pour cent).

On passe en revue la littérature sur les succès thérapeutiques publiés (plus de 90 pour cent) après une seule séance, avec un ou deux médicaments, sur l'action additive des potentialisateurs et du Cotrimoxazole.

Pour les schémas A, B et D, les taux d'échec parmi les malades à souches sensibles à la pénicilline (CMI égale ou inférieure à 0,2 U/ml [0,12 µg/ml]) fut notée à 4,1 et à 2 pour cent respectivement. Pour les malades à souches moins sensibles (CMI égale ou supérieure à 0,1 U/ml [0,06 µg/ml]), les taux d'échec montèrent respectivement à 17,4; 13,0 et 6,1 pour cent.

L'incidence d'urétrites non gonococciques concomitantes ne fut modifiée ni en doublant la dose de pénicilline ni en ajoutant du Cotrimoxazole.

Il n'y eut pas des réaction secondaire.