

THE PROBLEM OF PENICILLIN RESISTANT GONOCOCCI*†

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The incidence of relative resistance to penicillin among gonococci appears to have been increasing for some years. This study was undertaken in order to reassess the occurrence of penicillin resistant strains in one clinic and to correlate this with the incidence of failure of a single dose of penicillin to cure gonococcal urethritis in the male.

Material and Methods

Clinical

Between August and September, 1966, 98 cultures yielding gonococci were obtained from 98 consecutive male patients in whom a diagnosis of gonococcal urethritis had been made by examination of stained smears.

Diagnosis, treatment, and assessment of these patients were carried out by the staff of the Venereal Diseases Department at St. Thomas' Hospital. Diagnosis was based on findings in Gram-stained urethral smears made by the clinic staff and assessment of the result of treatment was made by the same staff, who worked without knowledge of the culture results or of the penicillin sensitivity of the isolates. Treatment consisted of one intramuscular injection of 600,000 units of procaine penicillin. Patients were followed up for 3 months and serological tests for syphilis were done at the first and last visit to the clinic. If gonococci re-appeared during follow-up and the reappearance was considered to be due to relapse, then Triplopen (Glaxo) 2.5 million units was given; this preparation is a mixture of benzathine penicillin (40 per cent.), procaine penicillin (20 per cent.), and sodium benzyl penicillin (40 per cent.); it is claimed that a single dose maintains therapeutic concentrations for 3 to 4 days. If, however, the reappearance of the gonococci was thought to be due to re-infection, the routine treatment of 600,000 units of procaine penicillin was simply repeated. The distinction between relapse and re-infection is discussed later in this paper. If penicillin treatment unmasked a co-incident non-gonococcal infection, this was treated

in the first instance with tetracycline 500 mg. three times a day by mouth for 5 days.

Bacteriological

Urethral swabs were sent to the laboratory in Stuart's transport medium. *Neisseria gonorrhoeae* were isolated on hydrocoele or chocolate agar plates and identified by standard sugar reactions. The minimal inhibitory concentrations (MICs) of penicillin were determined by making doubling dilutions of the antibiotic in chocolate agar plates; the plates were inoculated with a multiple inoculating device delivering approximately 0.03 ml. of a heavy suspension of each strain on to the plates. The plates were incubated for 24 hours in an atmosphere of 5 per cent. CO₂ and the MIC was read as the lowest concentration of antibiotic which caused total inhibition of growth; the Oxford staphylococcus and resistant gonococci from previous test batches were always included on all plates as controls.

Results

Clinical Results

In 91 patients the initial gonococcal urethritis was treated routinely as described. These patients are classified by age and race in Table I. Seven other patients were treated differently for various reasons (*e.g.* because of penicillin hypersensitivity or the presence of a genital lesion suspected of being syphilitic) and are, therefore, not considered further.

TABLE I
CLASSIFICATION OF PATIENTS BY AGE, RACE, AND MEANS OF ACQUIRING INFECTION

Classification		No. of Patients	
Age (yrs)	Under 24	22	91
	24 and over	69	
Race	White	48	91
	Negro	35	
	Other	8	
Source of Infection	Heterosexual	84	91
	Homosexual	7	

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As expected, the follow-up of patients posed a problem; the extent of the follow-up actually achieved is shown in Table II.

TABLE II
FOLLOW-UP, AND APPARENT RESULT OF
ROUTINE TREATMENT

Type of Follow-up	Total No. of Cases	Treatment presumed successful	Post-treatment Gonorrhoea due to Relapse or Re-infection
(1) None	4	4	
(2) Returned at least once but defaulted before 3 weeks	44	44	
(3) Followed-up for at least 3 weeks	43	21	22
Total	91	69	22

The distinction between relapse and re-infection in those in whom the gonococcus reappears is arbitrary to a considerable extent. Evans (1966) defined relapse as follows: "If the gonococci reappear within 14 days of treatment and if further sexual intercourse is denied by the patient." We have followed these criteria so that a reasonable comparison can be made between our results and those of Evans.

The incidence of post-treatment gonorrhoea is shown in Table III. Of the 91 patients given an initial dose of 600,000 units of procaine penicillin nearly a quarter were subsequently found to have gonococci in urethral smears. Of these thirteen (14.3 per cent.) were classified as relapses, and nine (9.8 per cent.) as re-infections. Evans (1966) found a relapse rate of 11.4 per cent. in 2,258 male patients who had been given the same treatment at three different centres during 1962-63.

Bacteriological Results

The minimal inhibitory concentrations of benzyl penicillin for the 91 strains of *N. gonorrhoeae* are

TABLE IV
MINIMAL INHIBITORY CONCENTRATIONS OF BENZYL PENICILLIN FOR 91 STRAINS OF GONOCOCCI

Presumed Result of Treatment	Source of Strains	No. of Strains	No. of Strains Inhibited by Penicillin ($\mu\text{g./ml.}$)							Percentage of Strains Relatively Resistant (MICs 0.1-0.5 $\mu\text{g./ml.}$)
			0.005	0.01	0.025	0.05	0.1	0.25	0.5	
Failure	Relapses	13		1	1	1	2	6	2	76.9
	Re-infections	9	2	1	2	1	1	2		33.3
Successful	Followed for 3 weeks or more	21	4	6	4	1	3	2	1	28.5
	Followed for less than 3 weeks	44	7	13	5	6	7	5	1	29.5
	No follow-up	4			2			1	1	50.0
Total Strains		91	13	21	14	9	13	16	5	37.3

TABLE III
POST-TREATMENT GONORRHOEA
(RELAPSES AND RE-INFECTIONS)

Patients	Number	Percentage of those Treated
Number treated	91	100
Relapses	13	14.3
Re-infections	9	9.8
Total post-treatment gonorrhoea	22	24.1

shown in Table IV. No less than 37.3 per cent. of these strains were classified as relatively resistant with MICs of 0.1 $\mu\text{g./ml.}$ or more. This is a much higher incidence of resistance than previously reported in Great Britain by Cradock-Watson, Shooter, and Nicol (1958), Curtis and Wilkinson (1958), Letchner and Nicol (1960), and the M.R.C. Working Party (1961). It is, however, very similar to the incidence reported more recently from Australia by Smith and Levey (1967). These various reports are compared in Table V. It should be noted that in this study we have followed the practice of reporting results in $\mu\text{g./ml.}$, whereas

TABLE V
REPORTS OF RELATIVE RESISTANCE TO
PENICILLIN OF *N. GONORRHOEAE*

Authors	Date	Year of Study	No. of Strains Tests	Percentage Relatively Resistant to Penicillin
Curtis and Wilkinson	1958	1958	302	19.5
Cradock-Watson Shooter and Nicol	1958	1958	200	19.0
Letchner and Nicol	1960	1960	99	8.8
MRC Working Party	1961	1959-60	1984	13.2
Present Study	1968	1966	91	37.3
Smith and Levey	1967	1966	104	44.0

previous reports have been based upon units/ml. The degree of resistance reported here, is therefore, slightly greater than that in these previous reports, in which MICs between 0.125 and 0.5 units/ml. (0.075 to 0.3 µg./ml.) have been taken as indicating resistance.

It is clear from Table IV that there is a reasonable degree of correlation between the independent clinical assessment of patients in terms of relapse or re-infection and the presence of resistant strains in these same patients. Of thirteen patients classified by the clinic staff as relapses, ten were infected with resistant strains compared with only three of nine patients considered to be cases of re-infection. The possible dissemination of resistant strains by patients who defaulted must, however, be a cause for concern; 48 out of 91 patients defaulted before 3 weeks and fifteen of these patients were originally infected with resistant strains. Six patients who were infected with resistant strains and followed up for 3 weeks were, however, apparently cured by the standard treatment of 600,000 units of procaine penicillin.

Discussion

There is no doubt that penicillin resistance of *N. gonorrhoeae* has now become a major problem (*Brit. med. J.*, 1968). The incidence of partially resistant strains has more than doubled in the last 10 years despite increasing awareness of the problem. Failure to cure with a single dose of 600,000 units of procaine penicillin is now too frequent and must lead to further dissemination of resistant strains. There are two possible methods of dealing with this problem; to increase the dose and duration of penicillin treatment or to use some alternative antibacterial therapy. Increase of the dose of penicillin has been progressively used but has not prevented the gradual increase in incidence of penicillin resistant strains. In this clinic the routine treatment with penicillin was increased from 300,000 units to 600,000 units in 1960 (Letchner and Nicol, 1961) and more recently the dose has again been raised to 2.5 million units.

The use of drugs other than penicillin has also been tried and more recently combinations of drugs have been advocated and tried both *in vitro* and *in vivo* with apparent success (Garrod and Waterworth, 1968; Csonka and Knight, 1967). The importance of this work lies in finding a simple, cheap, effective treatment that cures after the first and perhaps the only attendance of the patient. There is abundant evidence with other bacteria

and even with *N. gonorrhoeae* itself, that withdrawal of the use of an antibacterial agent is followed by a decline in the incidence of strains resistant to that antibiotic. Restriction upon the use of benzyl penicillin was shown to lead to a reduction in penicillin resistant staphylococci (Barber, Csillag, and Medway, 1958) and a similar decline in sulphonamide resistant gonococci has almost certainly occurred since the replacement of sulphonamide by penicillin (Garrod and Waterworth, 1968).

It is important that the best alternative treatment of gonococcal urethritis be quickly found and used in place of penicillin therapy for a period in the hope that penicillin resistant strains become far less frequent. Such a policy would need to be widespread in order to have maximum effect.

Summary

To determine whether the incidence of strains of gonococci partially resistant to penicillin continues to increase, a sample survey was conducted in a central London Venereal Diseases Clinic in the latter part of 1966. 91 men with gonorrhoea were each treated with a single injection of procaine penicillin 600,000 units and in all cases isolates were tested for sensitivity to penicillin; a MIC of 0.1 µg./ml. was chosen as the level indicating partial resistance so as to correspond approximately with criteria used in similar previous investigations. Post-treatment gonorrhoea developed in 22 of the 91 cases. On clinical grounds thirteen were considered treatment failures and nine re-infections; partially resistant organisms had been isolated in ten of the thirteen cases of treatment failure but in only three of the nine cases of re-infection. The overall incidence of partially resistant organisms was 37.3 per cent. indicating that the increasing incidence continues.

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Le problème des gonocoques résistants à la pénicilline

RÉSUMÉ

Afin de déterminer si l'incidence des souches de gonocoques qui sont partiellement résistantes à la pénicilline continue à augmenter, un relevé d'échantillons de gonocoques a été fait dans un dispensaire de maladies vénériennes du centre de Londres dans les derniers mois de 1966. 91 hommes atteints de blennorragie avaient été chacun traité par une injection unique de 600,000 unités de procaïne pénicilline et dans tous ces cas des "isolates" avaient été testés pour leur sensibilité à la pénicilline; un

MIC de 0,1 $\mu\text{g./ml.}$ était choisi comme niveau indiquant une résistance partielle afin de correspondre approximativement à des critères employés dans les recherches précédentes semblables. La blennorragie après traitement avait apparu chez 22 des 91 cas. Pour des raisons cliniques treize ont été considérés comme des cas d'insuccès au traitement et neuf comme des réinfections; des gonocoques partiellement résistants avaient été isolés chez dix des treize cas d'insuccès au traitement mais chez trois seulement des neuf cas de réinfection. Au total l'incidence des gonocoques partiellement résistants était de 37,3 pour cent indiquant que l'incidence qui va en augmentant continue dans cette direction.