

PENICILLIN G—TREATMENT OF URINARY INFECTION IN PARAPLEGIA*

By

E. W. COLLEY, M.R.C.S., L.R.C.P., D.Path.

Pathology Department, Stoke Mandeville Hospital

and

H. L. FRANKEL, M.B., B.S., M.R.C.P.

National Spinal Injuries Centre, Stoke Mandeville Hospital

Introduction. Penicillin G is not generally considered to be an effective antibiotic in the treatment of Gram-negative urinary infections. Originally penicillin was successfully used to treat Gram-positive coccal urinary infections by Abraham *et al.* (1941) and Officer *et al.* (1944). When more penicillin became available attempts were made to treat infections caused by Gram-negative organisms with good results in some cases (Exley, 1946; Peeney, 1947). Yates Bell in 1947 advocated prophylactic penicillin in prostatic surgery during the period when an indwelling catheter was present.

With the introduction of streptomycin and other antibiotics and antimicrobial drugs penicillin became somewhat neglected for the treatment of urinary infections although it was successfully used to treat *Proteus* septicaemia (Cook, 1946; Hutchinson & Randall, 1947; Holloway & Scott, 1956). It is not clear how frequently penicillin is now used in urinary infection; most laboratories do not report the sensitivity of urinary pathogens to penicillin.

At the National Spinal Injuries Centre, penicillin has been used to treat urinary infections since 1944 (Guttman, 1953). However, streptomycin, the broad spectrum antibiotics, nitrofurantoin and sulphonamides were for many years so effective that penicillin was not needed to treat chronic infections. It was still used empirically for treating acute urinary 'flare-ups'. In the late 1950s resistance of Gram-negative organisms in this hospital to the antibiotics then available became an increasing problem and in 1959, when members of the Paracolon group were separately identified (Milner, 1963), it was found that most of the organisms we had previously called Paracolon were Providence. Most of the strains of Providence at that time were resistant to the usual antibiotics, both clinically and by laboratory disc sensitivities. One patient who had been unsuccessfully treated with Furadantin, tetracycline and streptomycin for a chronic Providence infection, was cured of the infection while having treatment with penicillin for a superficial boil. His urine has now remained sterile for three years.

This reawakened our interest in the use of penicillin for urinary infection.

This paper describes:

1. The results of experiments to determine the sensitivity of Gram-negative urinary pathogens to penicillin G.
2. The sensitivity of Providence strains to 12 antibiotics.
3. The results of treating urinary Providence infections with Penicillin G.

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Material and Methods. 1. The sensitivity of 255 pathogenic organisms isolated at random from patients with urinary infection was determined using an Agar diffusion method. No attempt was made to demonstrate penicillinase production.

2. The 30 strains of Providence were examined in greater detail. Twenty-two were isolated from patients in the spinal unit, six from other wards in this hospital and two from another hospital. The organisms were identified as described by Milner (1963) using the medium of Shaw and Clark (1955). Biotypes were determined as described by Ewing, Tanner and Dennard (1954).

In vitro sensitivities of the 30 Providence strains to the following antibiotic and antibacterial drugs were determined: penicillin (Penicillin G), ampicillin (Penbritin), methicillin (Celbenin), cloxacillin (Orbenin), phenethicillin (Broxil), propicillin (Brocillin), tetracycline, streptomycin, nitrofurantoin, colomycin, trimethoprim and kanamycin.

All sensitivities except to kanamycin were carried out by doubling dilutions in broth, using as inoculum 0.025 ml. of a 1 in 10,000 dilution of an overnight broth culture of the organism. Kanamycin sensitivities were determined by the disc method, using discs containing 30 μ g. per ml. of kanamycin.

3. Thirty-two patients (31 male, 1 female) with Providence urinary infection were treated with Penicillin G, 1,000,000 units six-hourly intramuscularly for six to ten days. All the patients had bladder dysfunction, 30 due to traumatic paraplegia and two due to disseminated sclerosis. All had established urinary infection with Providence which had been isolated in pure culture on at least two consecutive occasions over a period of at least a week immediately before treatment. (Duration of Providence infection one week to seven months, average 7.4 weeks.) No patient had an indwelling catheter and the residual urine in all cases was 120 ml. or less. All patients had pyuria and bacilluria but were afebrile. There were no other complicating factors in the urinary tract and the blood urea was normal in all cases. The urine was cultured after treatment and at intervals during the follow-up (one month to three years; average 9.7 months).

Six of the patients were studied in greater detail: the minimum inhibitory concentration of Penicillin G for the infecting organism was determined before treatment began, the biotype of each organism was determined. Mid-stream specimens of urine were examined microscopically and cultured on blood agar and MacConkey's medium daily during treatment.

Results. 1. The minimum inhibitory concentrations of penicillin for 255 urinary pathogens are shown in Table I.

2. The minimum inhibitory concentrations of eleven antibiotic and antibacterial drugs for the 30 Providence strains are shown in Table II. All 30 strains showed some sensitivity to kanamycin discs. Biotypes: Twenty-three Providence strains were of biotype 21 and seven were of biotype 27. Four of the strains isolated from the six patients studied in detail were of biotype 21 and two were of biotype 27.

Results of Treatment. 3. At the end of treatment the urine was sterile in 21 of the 32 patients. In nine cases the Providence infection had been replaced by infection with other organisms. *Pseudomonas pyocyanea* (6) and *Proteus* (3). In two patients the Providence persisted. Of the six patients studied in detail, in five

the urine was sterile by the 3rd day and in one the Providence had been replaced by *Pseudomonas pyocyanea*. In these six patients the minimum inhibitory concentration of penicillin for the infecting organisms was 25 units/ml. or less.

Providence infection recurred in five patients, but in no case in less than four weeks, two of these patients were treated again and in one the Providence was eliminated and the urine remained sterile for two and a half years, in the other patient Providence recurred three times after penicillin.

TABLE I

Sensitivity to penicillin of Enterobacteriaceae Isolated from Urinary Tract Infections

	Number of strains tested	Minimum inhibitory concentration (units per ml.)							
		> 200	200	100	50	25	12.5	6.2	3.1
<i>Providence</i>	30	2	3	3	4	5	7	4	2
<i>Escherichia coli</i>	69	-	3	16	34	13	3	-	-
<i>Klebsiella aerogenes</i>	53	53	-	-	-	-	-	-	-
<i>Pseudomonas pyocyanea</i>	45	45	-	-	-	-	-	-	-
<i>Proteus mirabilis</i>	25	11	7	5	2	-	-	-	-
<i>Proteus rettgeri</i>	10	10	-	-	-	-	-	-	-
<i>Proteus vulgaris</i>	7	7	-	-	-	-	-	-	-
<i>Proteus morgani</i>	5	5	-	-	-	-	-	-	-
<i>Serratia marcescens</i>	6	6	-	-	-	-	-	-	-
<i>Citrobacter group</i>	5	5	-	-	-	-	-	-	-

TABLE II

Antibiotic Sensitivity of 30 Providence Strains

	Minimum inhibitory concentration units/ml. for penicillin and $\mu\text{g}/\text{ml}$. for others								
	> 200	200	100	50	25	12.5	6.2	3.1	1.5
Penicillin	2	3	3	4	5	7	4	2	-
Ampicillin	1	1	-	2	8	13	4	1	-
Phenethicillin	5	7	6	11	1	-	-	-	-
Propicillin	2	7	9	11	1	-	-	-	-
Cloxacillin	2	6	8	13	1	-	-	-	-
Methicillin	11	11	7	1	-	-	-	-	-
Trimethoprim	-	-	-	-	-	1	13	13	3
Streptomycin	8	5	7	4	2	2	2	-	-
Nitrofurantoin	1	6	10	6	3	2	2	-	-
Colomycin	30	-	-	-	-	-	-	-	-
Tetracycline	17	11	2	-	-	-	-	-	-

At the end of follow up the state of the patients was as follows:

Sterile	19
Infected with Providence	6
Infected with other pathogens	7

DISCUSSION

Our results of the *in vitro* sensitivity of various Gram-negative urinary pathogens to penicillin bear a striking resemblance to those of Peeney (1947) who found 53 per cent. of 125 urinary pathogens were inhibited by concentrations readily attainable in the urine. Gould *et al.* (1952) tested the sensitivity of 17 urinary pathogens to five antibiotics; although all strains of *E. coli* were sensitive to 30 microgrammes ml. or less of penicillin, they did not treat any of the infections with penicillin because all the organisms were sensitive to other antibiotics. Goodier and Parry (1959) found only 5 per cent. of 1725 organisms isolated from genito-urinary infections to be sensitive to penicillin using paper strips impregnated with 20 units ml. on solid media. Our finding that *Proteus mirabilis* is often sensitive to penicillin is in accordance with the findings of Holloway and Scott (1957) who from their own results and a review of other work concluded that '*Proteus mirabilis* appears to be relatively more sensitive to penicillin than other strains of *Proteus* and that *Proteus mirabilis* accounts for a large majority of the species of *Proteus* isolated from clinical material'.

Middleton (1958) tested the *in vitro* sensitivity of 40 strains of *Providence* to various antibiotics. He found all strains to be resistant to penicillin using discs containing 2.5 units ml. of penicillin; he commented on the paucity of chemotherapeutic agents available for use in infection due to some strains of *Providence*.

We have had excellent clinical results using intramuscular penicillin for *Providence* urinary infections. We have only treated *Providence* infections of biotype 21 and biotype 27, but these two comprise the majority of strains isolated from urinary tract infections (Milner, 1963). Twenty-two of the 30 strains of *Providence* examined were isolated from patients in one unit of this hospital over a period of 18 months, and some of the infections are probably the result of cross infection (Milner, 1963). Within the limits of these considerations it is evident that penicillin in the doses employed is an effective antibiotic for *Providence* urinary infections.

All our patients were in hospital and the majority having paraplegia felt no pain from the injections. Our *in vitro* results suggest that for outpatients or where it was desired to avoid intramuscular injections, oral Ampicillin may be effective. Ampicillin is much more expensive than penicillin and would not give the high peak serum- and tissue-levels which follow large intramuscular injections of penicillin.

Our *in vitro* sensitivities suggest that intramuscular penicillin is still a useful antibiotic for urinary infections with *E. coli* and *Proteus mirabilis*, especially if these organisms are resistant to other antibiotics. However, *E. coli* infections are extremely rare in pure culture in this unit (Milner, 1963), and *Proteus mirabilis* infections are so often associated with calculi that we have been unable to perform a therapeutic trial. We would suggest that the sensitivity of these organisms to levels of at least 200 units ml. of penicillin should be determined.

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SUMMARY

The sensitivity to penicillin of 255 Gram-negative urinary pathogens was determined to a maximum concentration of 200 units/ml. All strains of *E. coli*, nearly all strains of Providence and more than half the strains of *Proteus mirabilis* were inhibited by concentrations easily attainable in urine. All the other Gram-negative pathogens were resistant to 200 units ml.

Of the 30 strains of Providence twenty-three were of biotype 21 and seven of biotype 27, the *in vitro* sensitivity of the Providence strains against 12 antibiotics was determined. Nearly all strains were sensitive to penicillin and ampicillin, all strains were sensitive to trimethoprim and Kanamycin but only a few were sensitive to the other antibiotics.

Thirty-two paraplegic patients with Providence urinary infections were treated with Penicillin G 1,000,000 units 6-hourly for 6 to 10 days; Providence was eliminated in 30 patients, but there was a late recurrence in 5 patients.

It is concluded that penicillin is an effective antibiotic for the treatment of Providence urinary infection; it should also be considered for infections with *E. coli* and *Proteus mirabilis* which are resistant to other antibiotics.

RÉSUMÉ

La sensibilité pour penicillin de 255 pathogènes urinaires, gram négatifs, à une concentration maximum de 200 unités de pénicilline par millilitre a été déterminée. Toutes les souches de *E. Coli*, presque toutes les souches de Providence et plus de la moitié des souches de *Proteus Mirabilis* furent inhibées par des concentrations facilement obtenus dans l'urine.

Des 30 souches de Providence, 23 appartenaient au biotype 21, sept au biotype 27. La sensibilité, *in vitro*, des ces souches a été déterminée en fonction de 12 antibiotiques. Presque toutes furent sensibles à la pénicilline et l'ampicilline, toutes furent sensibles à la Triméthoprim et à la Kanamycine, mais quelques unes seulement aux autres antibiotiques.

32 paraplegiques atteints d'infection urinaire causée par Providence furent traités avec la Penicilline 'G' à raison d'un million d'unités toutes les six heures pendant six à dix jours; ce germe fut éliminé dans trente cas mais fut retrouvé ensuite dans cinq cas.

En Conclusion: La Penicilline est un antibiotique efficace dans le traitement des infections urinaires causées par le Providence, le même traitement peut être considéré pour les infections urinaires causés par *E. Coli* et *Proteus Mirabilis* qui peuvent être résistants aux autres antibiotiques.

ZUSAMMENFASSUNG

Die Sensitivität für Penicillin von 255 Gram-negativen Bakterien im Urin wurde bis zu einer maximalen Konzentration von 200 Einheiten pro ccm bestimmt. Das Wachstum aller Varianten von Bakt. Coli, beinahe aller Varianten von Providence und mehr als der Hälfte von *Proteus mirabilis* wurde durch im Urin leicht erreichbare Konzentrationen verhindert.

Alle anderen Gram-negativen Bakterien waren resistent gegenüber 200 Einheiten pro ccm.

Von den 30 Varianten des Providence gehörten 23 zum Biotypus 21 und 7 zum Biotypus 27. Die *in vitro* Sensitivität der Providence Erreger wurde gegen 12 Antibiotica geprüft. Beinahe alle Varianten waren sensitiv für Penicillin und Ampicillin, alle waren sensitive für Trimethoprim und Kanamycin, aber nur wenige für andere Antibiotica.

32 Patienten mit Providence Urin-Infektionen wurden mit Penicillin G 1,000,000 Einheiten 6 stündlich für 6-10 Tage behandelt.

Providence wurde in 30 Patienten eliminiert. In 5 Patienten gab es aber später Rückfälle.

Es wurde festgestellt, dass für Urin-Infektionen mit Providence Penicillin ein wirksames Behandlungsmittel darstellt. Man sollte auch an Penicillin denken, wenn sich Infektionen mit *B. coli* and *Proteus mirabilis* als resistent gegen andere Antibiotica erweisen.

REFERENCES

- ABRAHAM, E. P., CHAIN, E., FLETCHER, C. M., FLOREY, H. W., GARDNER, A. D., HEATLEY, N. G. & JENNINGS, M. A. (1941). *Lancet*, **2**, 177.
- COOK, G. T. (1946). *Brit. med. J.* **1**, 955.
- EXLEY, M. (1946). *J. Urol.* **55**, 435.
- EWING, W. H., TANNER, K. E. & DENNARD, D. H. (1954). *J. infect. Dis.* **94**, 134.
- GOODIER, T. E. W. & PARRY, W. R. (1959). *Lancet*, **1**, 356.
- GOULD, J. C., BOWIE, J. H. & CAMERON, J. D. S. (1952). *Lancet*, **1**, 361.
- GUTTMANN, L. (1953). *British History of the Second World War*, Vol. Surgery, 474. London: H.M.S.O.
- HOLLOWAY, W. J. & SCOTT, E. G. (1957). *Antibiot. Med.* **4**, 104.
- HUTCHINSON, R. I. & RANDALL, R. J. (1947). *Lancet*, **1**, 22.
- MIDDLETON, J. E. (1958). *J. clin. Path.* **11**, 270.
- MILNER, P. R. (1963). *J. clin. Path.* **16**, 39.
- OFFICER, R., LOEWENTHAL, J. & PERRY, J. W. (1944). *Med. J. Aust.* **2**, 473.
- PEENEY, A. L. P. (1947). *Proc. R. Soc. Med.* **40**, 433.
- SHAW, C. & CLARK, P. H. (1955). *J. gen. Microbial.* **13**, 155.
- YATES BELL, J. G. (1947). *Lancet*, **2**, 347.