

## TREATMENT OF GONORRHOEA WITH PENBRITIN\* A REPORT OF 200 CASES

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Although Sheehan (1958) had synthesized the penicillin nucleus 6-aminopenicillanic acid in 1958, it was not until 1959 that workers at the Beecham Research Laboratories (Batchelor, Chain, and Rolinson, 1961; Rolinson, Batchelor, Butterworth, Cameron-Wood, Cole, Eustace, Hart, Richards, and Chain, 1960) discovered a method of producing this compound on a large scale and made possible for the first time the synthesis of innumerable penicillin compounds.

The first compound to stem from this research was phenethicillin (Broxil)—an acid-stable preparation and hence suitable for oral administration. This preparation gives blood levels some two to three times higher than those obtained with penicillin V and as high or higher than those obtained with intramuscular injections of penicillin G. Unfortunately, however, this compound is eight times less effective *in vitro* against the gonococcus than is penicillin G., and various clinical trials gave disappointing results, the failure rate being as high or higher than with the earlier oral preparation penicillin V.

Broxil was followed a year later by Methicillin (or Celbenin), an acid-labile penicillin which required to be given by intramuscular injection. We know of no published reports of its use in gonorrhoea, but a small personal trial in penicillin-resistant gonorrhoea showed that even multiple injections were completely ineffective. The outstanding property of Celbenin is its total resistance to penicillinase and its activity against bacteria other than staphylococci is low.

Broxil and Celbenin were followed in 1961 by Penbritin 6 (D (-)  $\alpha$ -aminophenylacetamido) penicillanic acid (Ampicillin). Like Broxil, Penbritin is acid-stable and can thus be given orally. After a single dose of 1 g. the blood level rises comparatively slowly to reach a peak of between 6 and 7  $\mu\text{g./ml.}$  2 hours after administration, significant concentrations being still present after 6 hours (Figs 1 and 2). Like other penicillins Penbritin is bactericidal and has a wide range of activity against both Gram-positive and Gram-negative organisms.

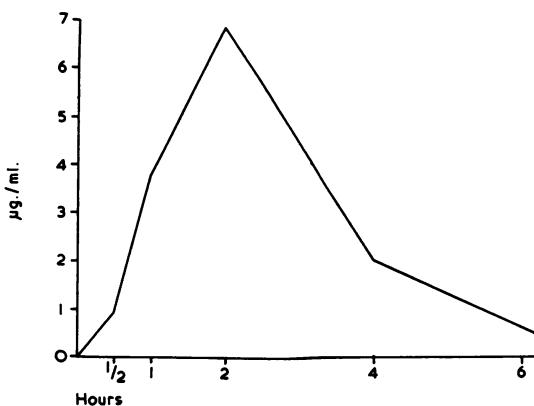


FIG. 1.—Fasting blood levels after ingestion of 1 g. Penbritin. Mean of ten patients.

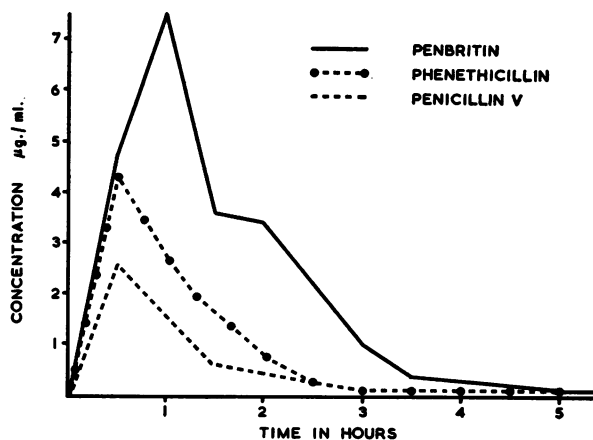


FIG. 2.—Mean serum concentrations in groups of five dogs after ingestion of 20 mg./kg. Penbritin, phenethicillin, and Penicillin V (Brown and Acred, 1963). Courtesy of the *British Medical Journal*.

No data were available concerning the activity of the new compound against the gonococcus, and a trial in the treatment of gonorrhoea in the male was started in February, 1962.

\* Paper read at the M.S.S.V.D. meeting in Copenhagen on June 7, 1963.

### Present Study

**Material.**—The subjects of the trial were adult males suffering from uncomplicated gonorrhoea attending the Special Clinic at the Liverpool Royal Infirmary. Their ages ranged from 16 to 56 years. About 26 per cent. of the patients were coloured, but only 3 per cent. of the infections had been acquired abroad, the remainder having been contracted in the United Kingdom. Although the number of cases treated was 200, the number of persons involved was rather less as some patients presented with repeated infections during the period of the trial.

**Diagnosis.**—This was invariably made by Gram-stained smear, and before starting treatment cultures were taken of the urethral discharge.

**Treatment.**—Each patient was then given four 250-mg. capsules, which were swallowed under supervision. Instructions were given to refrain from sexual intercourse and from alcohol, to drink liberal amounts of bland fluids, and to report again at the end of 48 or 72 hours with a full bladder.

**Follow-up.**—Patients were normally seen again at the end of a week, at the end of a fortnight, and again 2 weeks later. Patients who failed to attend for follow-up were presumably relieved of their symptoms and have been presumed cured.

**Results.**—Failures followed a pattern that we have observed previously. Either the discharge appeared to have ceased at the end of 48–72 hours, but recurred a day or two later and was apparent both to patient and observer at the time of the second visit, or the discharge was completely unaffected from the start. Where a recurrence of the discharge occurred later than the 14th day there was invariably a history of re-exposure to risk and these cases were classed as re-infections.

Initially it had been decided to treat only every other case with Penbritin, alternate cases being treated with a single injection of 600,000 units P.A.M. At the end of 4 months the results were reviewed, and it was found that the number of failures in each group was identical. Subsequently all cases were treated with Penbritin.

### Discussion

Out of 200 cases treated there were 130 positive cultures—a figure which would have been considerably higher but for a thermostat failure in the clinic incubator where plates were left overnight or longer before transfer to the laboratory. Positive cases were further subcultured and sensitivities to Penbritin and penicillin G., to streptomycin, chloramphenicol and tetracycline were determined by the tube dilution method.

For purposes of comparison, Penbritin and penicillin G. were first tested against a subculture of *Sarcina lutea* ATC 9341. It was found that a minimal inhibitory concentration of 0.02 µg. Penbritin was equivalent to a minimal inhibitory concentration of 0.03 µg. penicillin G.

The organisms tested showed a wide variation in sensitivity both to Penbritin and to penicillin G. (Fig. 3).

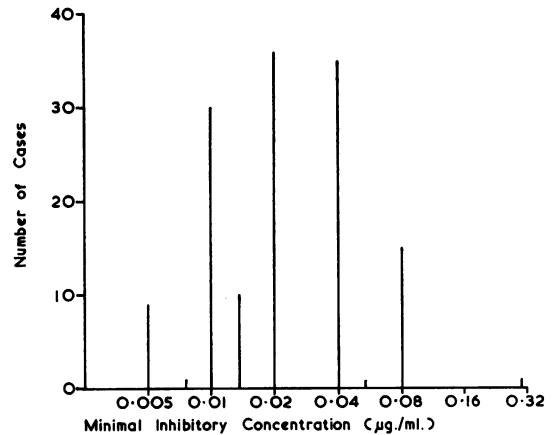


Fig. 3.—Range of sensitivity to Penbritin. Minimal inhibitory concentrations in µg./ml. Penbritin.

In general, sensitivity to Penbritin and penicillin G. ran parallel (Fig. 4, opposite). Thus, in 91 of the strains examined, the organism was equally sensitive to both penicillin G. and Penbritin. However, 37 strains were found to be more sensitive to penicillin G. than to Penbritin, and in five strains the reverse was the case. We were unable to confirm the findings of Ödegaard (1962) who, comparing the sensitivity of 100 strains of gonococci to Penbritin and penicillin G., concluded that, “whereas Penbritin showed weaker effect against most strains of gonococci, it showed better effect than penicillin G. against the least sensitive strains”.

Tests *in vitro* can be only a rough guide to results *in vivo*. Patients failing to respond to P.A.M. may respond to Penbritin and *vice versa*, although sensitivity of the strain may be identical.

Only two patients complained of side-effects: one developed a transient urticaria, and the second vomited shortly after taking the capsules and complained of dizziness and severe skin irritation but soon recovered.

There were ten failures in the series—a failure rate of 5 per cent. This is considerably lower than that reported with any previous preparation of oral penicillin. All the failures but one were with less sensitive strains, though certainly not with the least

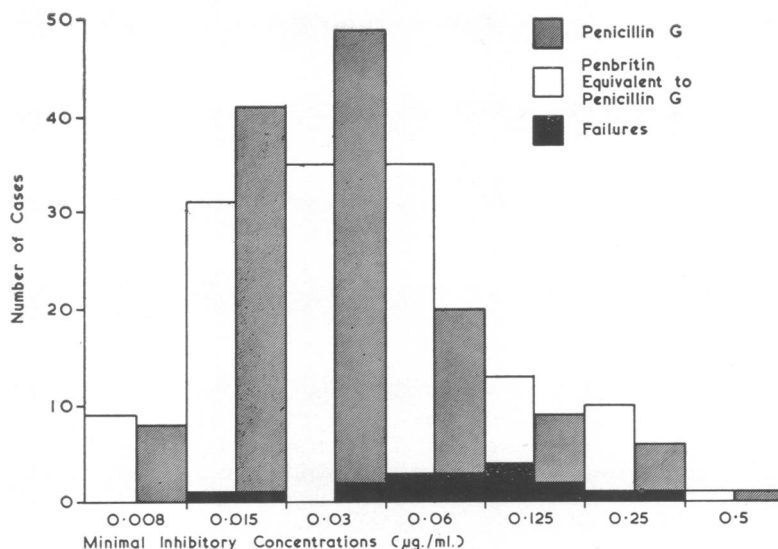


FIG. 4.—Comparison of sensitivity to Penicillin G and Penbritin. Minimal inhibitory concentrations in µg./ml. Penicillin G.

sensitive strain in the series. As absorption of the drug is only maximal when taken on an empty stomach, variable absorption may explain the lack of a closer correlation between results *in vivo* and *in vitro*.

During the earlier part of the trial, when four of the failures occurred, three were successfully re-treated with a single injection of 600,000 units P.A.M. The fourth case failed to respond to P.A.M. but was successfully re-treated with tetracycline. On the other hand, three of four P.A.M. failures which occurred during this period were successfully re-treated with Penbritin; the fourth was re-treated with tetracycline by mistake.

The remaining six failures were re-treated with two doses of Penbritin—1 g. followed by 1 g. 4 hours later—and all six were successful.

### Summary

A trial is described of Penbritin administered as a single 1-g. dose in the treatment of uncomplicated gonorrhoea in the male. The cure rate (95 per cent.) is higher than that obtained with any previous oral preparation of penicillin. On grounds of efficiency Penbritin may be considered as a suitable alternative to penicillin by injection in the treatment of gonorrhoea.

Although further experience is clearly desirable, it is suggested that two doses of Penbritin should be considered the first choice when re-treating cases which have failed to respond to routine treatment.

I wish to thank my colleagues at the Liverpool Royal Infirmary for their co-operation in this trial and I am particularly indebted to Prof. D. T. Robinson of the Public Health Laboratories, Liverpool, for the sensitivity determinations.

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### Traitement de la blennorrhée par la Penbritine

#### RÉSUMÉ

Une seule dose de 1g. de Penbritine fut donnée à des hommes atteints de gonorrhée simple. Les résultats (95% des cas furent guéris) sont meilleurs que ceux obtenus auparavant par n'importe quelle préparation orale de pénicilline.

L'efficacité de la Penbritine indique qu'on peut l'utiliser au lieu de la pénicilline intramusculaire.

Tandis qu'il faut toujours continuer à faire des essais, l'auteur constate que les malades qui ne répondent pas au traitement conventionnel peuvent bien être traités par deux doses de Penbritine.