be extended to 72 hours before organic hyperinsulinism can be confidently excluded. Happily, there is reason to believe that patients might be spared these marathon fasts by combining starvation with *muscular activity* (see Case 5—Morley, 1952).

The presence of organic hyperinsulinism can be confidently inferred if the requirements of Whipple's (1938) triad are fulfilled. These are: the advent of neuropsychiatric symptoms after fasting; a concomitant blood-sugar level below 50 mg./100 ml.; and banishment of symptoms by the administration of glucose.

Summary

The literature relating to endogenous hypoglycaemia is briefly reviewed. Two cases of hypoglycaemia due to insulinomata of the pancreas are described, mental symptoms so dominating the clinical picture that the patients were admitted to psychiatric hospitals. The abolition of all symptoms by successful operations for the removal of the tumours are recorded. Points of particular interest in the case reports are commented upon, and the differential diagnosis of hypoglycaemia is discussed.

We regret that shortage of space prevents our thanking all those to whom we are indebted for assistance with these cases, but we are especially grateful for the help we have received from Dr. M. J. Parsonage (director) and Dr. J. Dundas (assistant), of the E.E.G. Department of the General Infirmary at Leeds; Mr. J. T. Towers, chief laboratory technician of Menston Hospital; Professor P. R. Allison, professor of surgery in the University of Oxford; and Mr. J. R. P. O'Brien, Nuffield Director of Chemical Biochemistry at the Radcliffe Infirmary, Oxford.

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A recommendation that the use of motor horns should be forbidden at all times in built-up areas, except when necessary to avoid danger, is one of the chief points made by the Committee on the Problem of Noise in its interim report to Lord Hailsham, Minister for Science. The committee also recommends that legislation should be introduced to ensure that new vehicles when tested should not exceed certain defined noise levels; that drivers making unnecessary noise should be liable to prosecution; and that further research should be done on developing a meter which is better suited to the measurement of vehicle noise than those at present available, and into the principles of reducing noise from motor vehicles. Drivers, concludes the report, play an essential part in cutting down the noise that vehicles make.

BRL 1621: A COMPARISON WITH OTHER ISOXAZOLYL PENICILLINS

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Many isoxazoly penicillins (Doyle *et al.*, 1961) have been synthesized, and three (BRL 1400, 5-methyl-3-phenyl-4-isoxazoly penicillin; BRL 1577, 5-methyl-3-*p*-chlorophenyl-4-isoxazoly penicillin; and BRL 1621, 5-methyl-3-*o*-chlorophenyl-4-isoxazoly penicillin) were selected as being the most promising for clinical use. Clinical results using BRL 1400 (P 12) have been reported elsewhere (White and Smith, 1962; Bunn and Amberg, 1961), and given here is a clinical comparison of the other two with a laboratory study of all three isoxazoly penicillins suggesting that the best of the three is BRL 1621 (marketed as "orbenin").

Materials and Methods

Ten patients were treated with BRL 1577 and 18 with BRL 1621 in a dosage of 0.25 to 0.5 g. four times daily for 7 to 10 days. Clinical response to treatment, serum concentrations, and the sensitivity of staphylococci to the isoxazoly penicillins were assessed as described by Trafford *et al.* (1962).

In the investigation of methicillin-resistant organisms 0.02 ml. amounts of 1/100 diluted broth cultures were inoculated on the surface of agar plates containing penicillin and the results read after 9 hours' incubation.

Results

Infections with Staphylococci.—Ten patients with infections due to penicillinase-producing coagulase-positive staphylococci were treated with 0.5 g. of BRL 1577 four times daily by mouth. Four patients with pneumonia responded satisfactorily and one with septicaemia failed to respond until he was given methicillin. Of five patients with abscesses and wound infections in various sites who were treated two failed to respond and three improved satisfactorily.

The reasons for the failure of the drug in these three cases were analysed. In one patient a chronic fistula had developed following appendicectomy. After treatment with BRL 1577 staphylococci were again cultured, though in reduced numbers, and as the clinical effect of the drug was negligible the antibiotic therapy was changed. The other patient had a post-mastectomy wound infection from which staphylococci were eliminated during treatment, but post-treatment cultures were again positive.

In contrast the organism was not eliminated from the third patient, who had a staphylococcal septicaemia, and

the clinical condition did not improve until methicillin was substituted for BRL 1577. Although no blood levels were determined the organism was sensitive *in vitro* to BRL 1577, and we feel that this was one of the patients where the drug absorption was defective (*vide infra*). The other two treatment failures did show some effect of the drug, and we have no reason to suppose that the absorption was defective. We have no means of knowing the concentration in the tissues concerned, but we assessed these as failures on the grounds that the staphylococci were not completely eliminated and that the clinical response was disappointing.

The other isoxazolyl penicillin used in this hospital, BRL 1621, is the subject of another paper (Report, 1962), and it will be seen from this that it is a more reliable antibiotic than BRL 1577. Absorption is more predictable and the clinical results are more satisfactory. In our own series of 18 patients in that report 17 responded adequately and one failed to respond because we think he was not given a sufficient dose.

Serum Concentration.—The serum concentrations achieved after a 1 g. oral dose are shown in Table I.

TABLE I.—Mean Serum Concentrations After 1 g. Orally of Two Isoxazolyl Penicillins

Penicillin Serum μg./ml.	Time (Hours)			
	½	1*	2*	4
BRL 1577 ..	7.7 (1.9)	9.2 (1.3)	7.6 (0.9)	1.6 (0.8)
BRL 1621 ..	11.1 (2.5)	20.6 (2.3)	13.8 (2.2)	2.5 (0.4)

The standard deviation of the mean is given in parenthesis.

* These results are significantly different at a probability of 0.01.

Thirteen healthy volunteers were given BRL 1577 and 11 were given BRL 1621. It can be seen that in equivalent dosage BRL 1621 produces significantly higher average serum concentrations than BRL 1577 1 to 2 hours after administration.

Bacteriological Studies.—The sensitivities of 49 strains of coagulase-positive penicillinase-producing *Staph. aureus* were determined for methicillin and the three isoxazolyl penicillins by the tube-dilution method. These strains had been found to be resistant to penicillin G by the disk method (5 units per disk). It can be seen (see Table II) that methicillin possessed only about

TABLE II.—Number of Strains Sensitive to Methicillin and the Isoxazolyl Penicillins. (M.I.C.=Minimum Inhibitory Concentration)

M.I.C. (μg./ml.):	10	5	2.5	1.25	0.63
Methicillin ..		7	39	3	
M.I.C. (μg./ml.):	2	1	0.5	0.25	0.13
BRL 1400 ..	3	19	19	8	
BRL 1577 ..		5	26	13	5
BRL 1621 ..	1	3	17	21	7

1/5 to 1/10 of the activity of the isoxazolyl penicillins. Among the latter there was some difference in activity; BRL 1621 inhibited most strains at a concentration of 0.25 μg./ml., whereas with BRL 1400 and BRL 1577 at least twice this concentration was required.

A naturally occurring methicillin-resistant strain of *Staph. aureus* 13137 and a variant 13137/1000 isolated by repeated subcultures in methicillin (see Knox and Smith, 1961) were tested for sensitivity to methicillin and the three isoxazolyl penicillins. The results (Table III) show that though 13137/1000 was more resistant to methicillin than 13137 both strains had the same

sensitivity to any one isoxazolyl penicillin. Of the isoxazolyl penicillins BRL 1400 and BRL 1577 were less effective than methicillin against both strains of *Staph. aureus*, whereas BRL 1621 was more effective than methicillin. These strains destroyed the isoxazolyl penicillins at similar low rates when tested by the method of Knox and Smith (1962); thus the superiority of BRL 1621 does not seem to be due to greater stability.

TABLE III.—Minimum Inhibitory Concentrations (μg./ml.) for Methicillin Resistant Strains

	<i>Staph. aureus</i>	
	13137	13137/1000
Methicillin ..	31.2	125
BRL 1400 ..	250	250
BRL 1577 ..	250	250
BRL 1621 ..	15	15

Discussion

For several reasons it seems that of the three isoxazolyl penicillins BRL 1621 is likely to be the most effective. (1) When given by mouth it produces consistently higher blood levels than BRL 1577. (2) It has given, in our hands, better clinical results than BRL 1577. (3) Against penicillinase-producing penicillin-G-resistant staphylococci it was slightly more effective *in vitro* than BRL 1577 or BRL 1400, and much more effective than methicillin. (4) Against two methicillin-resistant staphylococci BRL 1621 is still active in concentrations obtainable in the serum by therapeutic doses. On the basis of the clinical results and serum concentrations it would seem that 0.5 g. taken orally four times daily is an effective therapeutic dose. Thus in adequate dosage BRL 1621 seems to be an advance in the treatment of infections caused by penicillinase-producing staphylococci.

Summary

Two penicillins (BRL 1577 and BRL 1621), members of the isoxazolyl series of acid and penicillinase-resistant penicillins, were assessed clinically and a laboratory investigation was carried out on methicillin and three isoxazolyl penicillins (BRL 1400, BRL 1577, and BRL 1621) against penicillinase-producing staphylococci.

Clinically BRL 1621 was slightly superior to and produced higher serum concentrations than BRL 1577.

In the laboratory investigation the isoxazolyl penicillins were 5 to 10 times more active than methicillin against penicillinase-producing staphylococci. Of the isoxazolyl penicillins BRL 1621 was more active than BRL 1400 or BRL 1577; in addition, it was more effective than the other two against a naturally occurring methicillin-resistant strain.

Thus BRL 1621 represents an advance in the treatment of infections caused by penicillinase-producing staphylococci.

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