BRL 1241 consider the pain of injections is comparable. No other toxic effects were encountered.

Blood and Urine Levels.—These were assayed on patients who were being treated with BRL 1241 whenever this was possible. In all cases assayed, blood levels showed a range of concentration between 18 and 21 $\mu\text{g./ml.}$ at half an hour, 13 to 20 $\mu\text{g.}$ at one hour, 5 to 9 $\mu\text{g.}$ at two hours, and 1.5 to 2.7 $\mu\text{g.}$ at three hours. By the fourth hour serum concentrations were invariably below 2 $\mu\text{g.}$ Urinary assay showed that 75% of the dose administered in one day was excreted in the urine—for example, six injections of 1 g. were given in 24 hours and 4,372 mg. were excreted in the urine over the same period, which is 73% of the injected dose. Knudsen and Rolinson (1960), in their studies of absorption and excretion, showed similar results.

Discussion

The real test of effectiveness of this drug is whether it failed to eradicate staphylococci in any instance or caused such severe side-effects that it had to be withdrawn. So far in our limited experience no case failed to respond to treatment.

In Case 4, with staphylococcal infection of the lung, the organism was eliminated but the patient died of his underlying cor pulmonale. It was not thought that any antibiotic treatment would have made much difference to his cardiac condition.

Stewart *et al.* (1960) report one patient (Case 14, aged 2) who relapsed after treatment of her multiple boils with BRL 1241. They report that staphylococcal infection was eradicated in all their other cases but was not necessarily extirpated from the anterior nares.

Summary and Conclusions

A clinical trial of BRL 1241, a derivative of 6-aminopenicillanic acid, is reported.

Thirteen cases of staphylococcal infection resistant to penicillin G and/or other antibiotics are recorded.

No serious toxic effects were encountered. The drug was successful in eradicating staphylococci in all.

The results reported suggest strongly that the drug is effective against the resistant staphylococcus.

We are grateful for supplies of BRL 1241 to Beecham Research Laboratories Limited, whose registered trade name for this drug is "celbenin." Our thanks are due to the physicians and surgeons at Guy's Hospital who allowed us to treat their cases.

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A NEW PENICILLIN (BRL 1241) ACTIVE AGAINST PENICILLIN- RESISTANT STAPHYLOCOCCI

BY

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The discovery of 6-aminopenicillanic acid, which has been described as the penicillin "nucleus" (Batchelor, Doyle, Nayler, and Rolinson, 1959), has led to the synthesis of new penicillins, some of which show antibacterial activity very different from that of penicillin G. One of these, BRL 1241 ("celbenin") shows remarkable activity against penicillin-resistant staphylococci (Rolinson, Stevens, Batchelor, Cameron-Wood, and Chain, 1960). The present paper describes some laboratory studies of this compound and some comparisons between it and three other penicillins. BRL 1241 is sodium 6-(2,6-dimethoxybenzamido)penicillanate monohydrate.

Methods

BRL 1241 and "broxil" (phenethicillin) (Knudsen and Rolinson, 1959) were obtained from Beecham Research Laboratories. Penicillin G and penicillin V were commercial preparations from Glaxo Laboratories Ltd. Commercial penicillinase from Burroughs Wellcome and Co. was used. Antibacterial activity of the different antibiotics was measured, usually in nutrient broth, by the serial tube dilution test, using young broth cultures undiluted or in various dilutions. Cultures were incubated at 37° C. and minimum inhibitory concentrations read at intervals. Bactericidal tests were carried out as described in the text.

Antimicrobial Activity of BRL 1241

The serial tube dilution test was used to compare the antimicrobial activity of BRL 1241, penicillin G, penicillin V, and broxil against some common micro-organisms of medical importance. The results are summarized in Table I. These confirm and extend the

TABLE I.—Antibacterial Activity of Four Different Penicillins

	Minimum Inhibitory Concentration ($\mu\text{g./ml.}$)			
	Pen. G	Pen. V	Broxil	BRL 1241
"Oxford" staphylococcus	0.02	0.01	0.01	1.0
<i>Staph. pyogenes</i> (E3)	125	62	>250	2.0
<i>Str. pyogenes</i> (group A)	0.005	0.01	0.01	0.2
<i>Str. viridans</i>	0.01	0.01	0.02	0.1
* <i>N. meningitidis</i>	0.2	0.2	0.2	6
<i>Proteus vulgaris</i>	15	>250	>250	>250
<i>Ps. pyocyanea</i>	>250	>250	>250	>250
<i>Salm. typhi</i>	7.5	62	>250	>250
"paratyphi A"	7.5	125	>250	>250
"B"	31	>250	>250	>250
"C"	0.2	7.5	62	62
<i>E. coli</i>	15	125	>250	>250

Inoculum: 0.02 ml. of 1/100 dilution of overnight broth cultures inoculated into 1 ml. of broth containing serial doubling dilutions of antibiotic. Minimum inhibitory concentrations read after 18 hours, incubation at 37° C.

* This was tested in serum broth and the inoculum was 0.02 ml. of undiluted serum broth culture.

observations of Garrod (1960), who pointed out that there may be significant differences in the action of different penicillins and that it is unwise now to assume that a micro-organism sensitive to one penicillin will necessarily be sensitive to another. It can be seen that BRL 1241 was still inhibitory in a concentration of about 2 $\mu\text{g./ml.}$ against a penicillin-resistant staphylococcus, which under the conditions of the test was

capable of growing in high concentrations of penicillin G, penicillin V, or broxil. Yet against *Salmonella paratyphi C*, which was inhibited by a concentration of 0.2 $\mu\text{g./ml.}$ of penicillin G, BRL 1241 was ineffective in a concentration less than 62 $\mu\text{g./ml.}$ On the other hand, BRL 1241 was highly active against the streptococci tested and moderately active against *Neisseria meningitidis* in serum broth. There is thus considerable selectivity and specificity in the activity of these different penicillins, and much further work will be needed to assess the importance of these differences.

The effect of inoculum size has been investigated with a few strains. Table II shows that against a highly resistant strain (E3), freshly isolated from one of the patients described by Douthwaite and Trafford (1960), BRL 1241 was equally effective (at about 4 $\mu\text{g./ml.}$) whether the inoculum was a few hundred or a few million organisms. This is in complete contrast to penicillin G, penicillin V, and broxil, with which the

TABLE II.—Effect of Inoculum Size on Sensitivity of Four Strains of *Staphylococci* to Four Different Penicillins

Strain	Dilution	No. Inoculated	Minimum Inhibitory Concentration ($\mu\text{g./ml.}$)				
			Pen. G	Pen. V	Broxil	BRL 1241	
						Expt. 1	Expt. 2
"Oxford"	1/1	5 $\times 10^8$	0.03	0.03	0.06	2	2
	1/10 ²	5 $\times 10^4$	0.007	0.007	0.03	1	0.5
	1/10 ⁴	500	0.007	0.003	0.01	0.25	0.06
P27	1/1	3 $\times 10^8$	2	2	0.5	2.4	
	1/10 ²	3 $\times 10^4$	0.5	0.25	0.25	2.4	
	1/10 ⁴	300	0.1	0.1	0.1	2	
P5	1/1	4 $\times 10^8$	62	250	16	2.4	
	1/10 ²	4 $\times 10^4$	2	2	0.1	0.25	
	1/10 ⁴	400	2	2	0.1	0.125	
E3	1/1	5 $\times 10^8$	>500	>500	>500	4-8	
	1/10 ²	5 $\times 10^4$	2	4	1	4	
	1/10 ⁴	500	0.25	0.5	0.25	4	

Inoculum: 0.02 ml. of overnight broth cultures diluted as shown, inoculated into 1 ml. of broth containing doubling dilutions of antibiotic. Incubation at 37° C. overnight.

largest inocula were resistant to 500 $\mu\text{g./ml.}$ or more, while the smallest inocula were sometimes sensitive to as little as 0.25 $\mu\text{g./ml.}$ Another freshly isolated strain (P27) slightly resistant to the other penicillins showed a similar independence of inoculum size with BRL 1241. With a third strain (P5) and the "Oxford" staphylococcus there was an effect of inoculum size in the sense that small inocula were inhibited by concentrations of BRL 1241 much lower than 2-4 $\mu\text{g./ml.}$ From these results, and from the large number of strains investigated by Rolinson *et al.* (1960) and Thompson, Harding, and Simon (1960), it seems clear that at the present time, though some strains of *Staph. pyogenes* may be sensitive to less than 2 $\mu\text{g.}$ of BRL 1241 per ml., especially when the inoculum is small, none so far has been found resistant to more than 4 $\mu\text{g./ml.}$, at any rate after overnight incubation. It is to be hoped that many more strains will soon be examined, so as to obtain a reliable baseline before the drug is widely used.

On prolonged incubation, however, large inocula (of the order of 10⁸ cells per ml.) do begin to grow in progressively higher concentrations, and after seven days' incubation growth has occurred in tubes which initially contained 50 $\mu\text{g./ml.}$ of BRL 1241. The explanation of this "climb up" is being investigated.

Effect of Penicillinase

It is well recognized that the apparent resistance of freshly isolated staphylococci to penicillin depends on the speed with which the organisms can produce enough

penicillinase to destroy the penicillin before it destroys them. The activity of BRL 1241 against penicillinase-producing staphylococci is clearly due in part to the fact that it is not appreciably destroyed by staphylococcal penicillinase (Rolinson *et al.*, 1960). In further experiments the activity of all four penicillins against the Oxford staphylococcus was tested in the presence of different concentrations of added penicillinase (Burroughs Wellcome). Table III shows the results.

TABLE III.—Effect of Penicillinase on Antimicrobial Activity of Different Penicillins

	Minimum Inhibitory Concentration ($\mu\text{g./ml.}$) in Presence of Penicillinase			
Experiment 1:	1/50	1/500	1/5,000	None
Penicillin G	>100	4	0.8	0.03
BRL 1241	2-4	2	2	2
Experiment 2:	1/100	1/1,000		None
Penicillin G	>100	4		0.03
"V"	>100	4		0.16
Broxil	>100	0.16		0.16
BRL 1241	4	0.8		0.8

Inoculum: 0.02 ml. of a 1/100 dilution of an overnight broth culture of the Oxford staphylococcus. Penicillinase used was commercial penicillinase (Burroughs Wellcome).

Whereas with penicillin G, penicillin V, and broxil antibacterial activity was progressively reduced in the presence of increasing amounts of penicillinase, with BRL 1241 the minimum inhibitory concentrations remained almost unchanged even in the presence of relatively high concentrations of penicillinase.

Bactericidal Effect

BRL 1241 was found to have a bactericidal effect both on the Oxford staphylococcus and on the penicillinase-producing staphylococcus E3 recently isolated from a patient (see Table IV). Eighteen-hour cultures of these

TABLE IV.—Bactericidal Effect of BRL 1241
(a) *Oxford Staphylococcus*

Tube	No. Inoculated	No. of Viable Organisms in a Standard Loop at Different Intervals after adding Antibiotic							
		3 hr.		5 hr.		10 hr.		24 hr.	
		Pen. G	1241	Pen. G	1241	Pen. G	1241	Pen. G	1241
1	23 $\times 10^8$	C	C	C	C	SC	C	SC	C
2	23 $\times 10^4$	C	C	C	C	7	60	3	84
3	23 $\times 10^3$	C	C	SC	C	24	150	0	40
4	2,300	SC	C	SC	25	20	4	100	1
5	230	40	C	SC	23	3	1	48	1
6	23	5	200	20	12	0	0	0	1

(b) *Penicillinase-producing Staph. pyogenes E3*

Tube	No. Inoculated	No. of Viable Organisms in a Standard Loop at Different Intervals after Adding Antibiotic									
		1½ hr.		3 hr.		5 hr.		7 hr.		24 hr.	
		Pen. G	1241	Pen. G	1241	Pen. G	1241	Pen. G	1241	Pen. G	1241
1	53 $\times 10^8$	C	C	C	C	C	C	C	C	C	UC
2	53 $\times 10^4$	C	C	C	C	C	C	C	C	C	UC
3	53 $\times 10^3$	C	C	C	C	C	C	21	C	C	UC
4	5,300	C	C	C	C	9	C	5	C	C	UC
5	530	C	C	6	C	1	C	0	C	C	0
6	53	43	3	41	9	17	3	85	0	C	0

Incubation at 37° C. For further details see text. C=Confluent growth. SC=Semi-confluent growth. UC=Uncountable colonies. Figures give the number of colonies on plating out.

two strains were diluted in nutrient broth in tenfold steps (tubes 1 to 6). These different dilutions in broth were then incubated for one and a half hours, at which time penicillin G, 0.5 $\mu\text{g./ml.}$, or BRL 1241, 5 $\mu\text{g./ml.}$, was added. Samples were removed and viable counts performed at intervals after the addition of the anti-

biotics. Viable counts were performed on plates over half of which was spread penicillinase.

In the concentration used, BRL 1241 was rapidly bactericidal against both strains—an effect, moreover, which was not reversed by penicillinase. Penicillin G, on the other hand, was effective only against the Oxford staphylococcus. It is true that with the larger inocula the bactericidal effect against the E3 strain was not complete. But the concentration of 5 $\mu\text{g.}$ of BRL 1241 per ml. used in this experiment was deliberately chosen as being only slightly greater than the bacteriostatic level of 2–4 $\mu\text{g./ml.}$, whereas the concentration of 0.5 $\mu\text{g.}$ of penicillin G per ml. used was about one hundred times greater than its minimum inhibitory concentration against the Oxford staphylococcus. Certainly it is clear that BRL 1241 in concentrations well below those easily reached in the blood (Knudsen and Rolinson, 1960) had a remarkable bactericidal effect against both penicillin-sensitive and penicillin-resistant strains of *Staph. pyogenes*. Under appropriate conditions BRL 1241 was lytic as well as bactericidal to both strains but, as with penicillin G, lysis can be demonstrated only if the cells are in a metabolically active state (Knox, 1945).

Effect of BRL 1241 on Penicillinase Formation

BRL 1241 was found to be a powerful inducer of staphylococcal penicillinase in staphylococci already possessing some penicillinase. Thus, though it is not an effective substrate for the enzyme (Rolinson *et al.*, 1960), it is capable of strongly stimulating the further production of penicillinase by penicillinase-producing staphylococci. Experiments are in progress to determine whether it can induce penicillinase activity in penicillin-sensitive staphylococci.

Attempts to Develop Resistance to BRL 1241

By serial subculture in tubes containing BRL 1241, attempts were made to “train” staphylococci to become resistant to it. These experiments have been carried out both with penicillin-sensitive and with penicillin-resistant organisms, but they are still in a preliminary stage. An interesting observation has, however, been made with the penicillinase-producing staphylococcus E3. After three subcultures in increasing concentrations of BRL 1241 it was found that this strain was able to grow in concentrations up to 18 $\mu\text{g./ml.}$, though only after several days' incubation. The organisms “trained” in this way, however, grew normally when subcultured in BRL-1241-free medium. When these were tested for their resistance to BRL 1241 and penicillin G, penicillin V, and broxil, the results shown in Table V were ob-

TABLE V.—Loss of Penicillinase by *Staph. pyogenes* E3 After “Training” to BRL 1241

		Minimum Inhibitory Concentration ($\mu\text{g./ml.}$)			
		Pen. G.	Pen. V	Broxil	1241
“Untrained”	18 hours	100	100	10	5
	2 days	1,000	1,000	1,000	20
“Trained”	18 hours	0.1	0.1	0.1	5
	2 days	1	1	0.1	40

tained. Whereas the original penicillinase-producing strain was capable of growing in up to 1,000 $\mu\text{g./ml.}$ of penicillin G, penicillin V, or broxil, the organisms which had been “trained” by serial subculture in BRL 1241 were now found, even if a very heavy inoculum was used, to be sensitive to as little as 0.1 $\mu\text{g.}$ of penicillin G, penicillin V, or broxil per ml. Furthermore, suspensions

prepared from these organisms showed complete loss of ability to destroy penicillin, as shown by incubating them with 1,000 $\mu\text{g.}$ of penicillin G per ml. and estimating the rate of disappearance of penicillin by the hydroxylamine method.

The “trained” organisms were of the same phage type (77) as the original strain. When tested in parallel with the original strain in serial doubling dilutions of BRL 1241, they did not appear to be significantly more resistant, though they did eventually, after several days' incubation, grow in higher concentrations than the “untrained” strain. The loss of penicillinase was not observed when the original penicillinase-producing strain E3 was “trained” to penicillin G, penicillin V, or broxil. After repeated passage through these antibiotics the organisms showed no loss of penicillinase activity. This loss therefore occurred only in the presence of BRL 1241.

It is well known that penicillinase-producing staphylococci may lose their penicillinase in some conditions (Barber, 1949, 1953; Chandler, Davidson, Long, and Monnier, 1951; Fairbrother, Parker, and Eaton, 1954). But the process is erratic and the conditions which promote it are ill-defined. The most reliable way of producing the change seems to be incubation at 44° C. as described by Fairbrother *et al.* (1954), but only some of the strains they studied showed loss of penicillinase, and even then only after many subcultures at 44° C. With BRL 1241 loss of penicillinase has occurred in several experiments, though not consistently. On two occasions the change appears to have been complete in the sense that penicillinase-negative cells have completely replaced the originally penicillinase-positive population. Further work is in progress to determine whether this is only one more example of a process which has already been described with a variety of other agents or whether it has any greater significance.

Discussion

BRL 1241 is the first penicillin known which combines considerable antibiotic activity with almost complete resistance to the action of staphylococcal penicillinase (Rolinson *et al.*, 1960). In the laboratory it inhibits the growth of both penicillin-sensitive and penicillin-resistant staphylococci in a concentration of about 2–4 $\mu\text{g./ml.}$ It is also effective in even lower concentrations against many organisms which are sensitive to “conventional” penicillins. It is highly bactericidal in concentrations not much greater than the minimum inhibitory concentration found in bacteriostatic tests. In two respects it is rather similar to cephalosporin C, since it combines the properties of inducing formation of staphylococcal penicillinase and at the same time of resisting almost completely the action of the formed enzyme (Pollock, 1957), but it seems to be greatly superior to cephalosporin C in antibiotic activity. Clinically it is easy to administer and appears to be virtually non-toxic.

If we consider the four penicillins—G, V, broxil, and BRL 1241—it seems that there is a continuous gradation in anti-staphylococcal action from the first to the last. Garrod (1960), in comparing penicillin G, penicillin V, and broxil, showed that, against some staphylococci resistant to penicillin G, penicillin V had some *in vitro* activity and broxil had considerably more. A paper by Gourevitch, Hunt, and Lein (1960) indicates that broxil is less rapidly destroyed by penicillinase both from staphylococci and from *B. cereus* than penicillin G or V. Broxil might therefore be expected to show some

advantages over both penicillin G and V in infections due to staphylococci producing small amounts of penicillinase or where the infecting dose was small. But it would be dangerous to rely even on broxil in serious cases of infection due to penicillinase-producing staphylococci, and it is certainly not true now to describe broxil, as Garrod (1960) has done, as the "penicillin of choice" in this type of infection. Of all the penicillins so far known BRL 1241 is unique, since it is at present equally effective against all strains of *Staph. pyogenes* so far isolated (Thompson *et al.*, 1960), whether they are sensitive or resistant to penicillin G and whether or not they produce large amounts of penicillinase.

BRL 1241, besides being effective against all types of *Staph. pyogenes*, is also effective against many other organisms which are sensitive to "conventional" penicillins. Clinical experience alone will determine the place of BRL 1241 in chemotherapy and the indications for its use. The laboratory evidence available suggests that its greatest merit is its unique activity against penicillin-resistant staphylococcal infections for which the only antibiotics hitherto available have been toxic, difficult to administer, or only feebly bactericidal. Concentrations of BRL 1241 in the blood greatly in excess of those necessary to inhibit or kill staphylococci can easily be obtained and maintained (Knudsen and Rolinson, 1960), and, further, BRL 1241 is not appreciably inactivated in the presence of serum (Rolinson *et al.*, 1960). Clinical evidence so far (Douthwaite and Trafford, 1960; Stewart, Nixon, and Coles, 1960) strongly suggests that BRL 1241 will prove a valuable addition to the drugs available for the treatment of "resistant" staphylococcal infections.

It is already clear that there are really important differences in the antibacterial action of different penicillins. It is almost certain that our ideas of the scope of penicillin therapy will need radical revision in the next few years and that the discovery of 6-aminopenicillanic acid has opened the way for the development of penicillins with hitherto quite unexpected ranges of activity.

Summary

A new penicillin (BRL 1241), in a concentration of around 1–4 $\mu\text{g./ml.}$, inhibits the growth both of penicillin-sensitive staphylococci and of penicillinase-producing staphylococci capable of growing in high concentrations of penicillin G, penicillin V, or broxil.

In a concentration of 5 $\mu\text{g./ml.}$, BRL 1241 is rapidly bactericidal to both penicillin-sensitive and penicillin-resistant staphylococci.

Although it is a powerful inducer of staphylococcal penicillinase, BRL 1241 is itself not appreciably destroyed by it. Its activity against penicillinase-producing staphylococci is relatively unaffected by inoculum size, and its antibacterial action is unaffected by concentrations of cell-free penicillinase which completely inactivate high concentrations of penicillin G, penicillin V, and broxil.

Some preliminary experiments suggest that a penicillinase-producing strain of *Staphylococcus pyogenes* (E3), after several subcultures in the presence of BRL 1241, has reverted to the penicillin-sensitive state and no longer produces penicillinase. This effect is not produced by repeated subculture in penicillin G, penicillin V, or broxil. Further work is in progress to determine the nature of this effect.

Apart from its unique effect on penicillinase-producing staphylococci, BRL 1241 is active, though not in such high dilutions as penicillin G, against a number of penicillin-sensitive organisms.

Comparison of penicillin G, penicillin V, broxil, and BRL 1241 makes it clear that different penicillins show quite large differences in the range of their antibacterial activity. It is therefore no longer possible to treat all penicillins as though they were equivalent.

My thanks are due to Beecham Research Laboratories for supplying BRL 1241; to Dr. E. T. Knudsen, Dr. G. N. Rolinson, and Mr. F. R. Batchelor for opportunities for ready exchange of ideas and experimental data; to Dr. Mary Duncan for phage-typing the strain E3; and to Mr. N. House and Miss B. Whittamore for skilful and enthusiastic technical help.

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The Leeds Mental Health Service has been recognized as one of the foremost in the county. The first occupational centre for males was opened by a voluntary committee in October, 1923, and was the forerunner of the present North Leeds Centre for adult males, which has recently been rehoused in modern hutments with accommodation for 150 patients. There is, in addition, a sheltered workshop where felting and assembly work is carried out and which can accommodate 25 patients. The first occupational centre for children was opened in the Armley district in January, 1929. There are now altogether five such centres in Leeds, including two for children under 16 years of age which have 228 places. Both these centres are housed in modern buildings, specially designed for the purpose, and one has special accommodation for the spastic mentally handicapped child who can scarcely walk or talk and requires individual attention. There are two centres catering for female patients over 15 years of age: one at Armley Grange, which accommodates 50 young women, and a pioneer laundry for 35. Here about 10,000 articles a week are laundered for corporation departments. Nowell House, a short-stay home, was opened in June, 1955 and can take 12 children under 15 years for short-term care during periods of domestic crisis for holiday periods. The programme for the future includes the provision of three residential hostels for patients discharged from mental hospitals and institutions who have no one to look after them. Premises at Rutland Lodge have been adapted for 40 male patients at a cost of nearly £14,000 and a new occupational centre is being built on the Armley Grange site at a cost of £25,000, while the existing premises are being adapted for the residential accommodation of 25 mentally handicapped female patients. Plans have also been approved by the Ministry for the erection of a £64,000 hostel for 45 female patients on a site adjoining the East Leeds Centre.