considerable falls in blood-pressure. In two patients (Cases 4 and 13) no extra effect was produced by the addition of a ganglion-blocking drug. Case 4 had a grossly raised blood-pressure during the time she was receiving two dummies and developed a retinal haemorrhage within three weeks. The usefulness of chlorothiazide is therefore not confined to patients with only moderate degrees of hypertension.

The Chart shows the correlation between the time that had elapsed since the last dose of chlorothiazide alone and the reduction in the standing systolic blood-pressure. A relationship of this kind may vitiate the results of any trial in which blood-pressure is recorded

Relationship between changes in standing systolic blood-pressure and the time since the last dose of chlorothiazide in nine patients.

infrequently. In this instance there was an even distribution of times between dosage and blood-pressure measurement, so that the results may be representative of the effect of chlorothiazide alone.

There was no evidence that the arterial pressure was affected in patients taking pentolinium alone. In all but one the initial arterial pressure, three to five years

previously, was much higher than that recorded in the control period of the present trial, and four of them (Cases 11, 12, 13, and 15) presented with hypertensive neuroretinopathy. It is impossible, on the available evidence, to prove that this reduction in blood-pressure was due to the drugs used. But, if it were so, the question would arise whether such treatment, for a limited period, may not effect a remission in the course of the disease.

Summary

It has been shown that it is possible to carry out a double-blind controlled trial of ganglion-blocking agents, since the incidence of side-effects was no less when dummy tablets were used than when active drugs were employed. Reports of side-effects by the patients did not influence the readings of the blood-pressure.

Chlorothiazide produced a significant fall of blood-pressure in 5 out of 15 patients when given alone in a dose of 250 mg. three times daily.

Chlorothiazide enhanced the reduction of blood-pressure achieved by mecamlamine in all of eight patients, and increased the effect of pentolinium in one of seven patients.

Our thanks are due to Professor Sir George Pickering for his criticism and advice, to Miss Susan Partridge and Miss Joyce Hollobon for their help in the clinic, and to the pharmaceutical department for dispensing the tablets. We also acknowledge with gratitude the supply of inert tablets by Messrs. May & Baker and Messrs. Merck Sharp and Dohme.

REFERENCE

Hall, R., and Owen, S. G. (1959). *Lancet*, 1, 129.

RELATIVE ANTIBACTERIAL ACTIVITY OF THREE PENICILLINS

BY

L. P. GARROD, M.D., F.R.C.P.

Bacteriologist, St. Bartholomew's Hospital; Professor of Bacteriology, University of London

A new oral penicillin, the potassium salt of 6-(alpha-phenoxypionamido) penicillanic acid, has recently been marketed in this country under the name "broxil." The only published information about it relates to its absorption, which is claimed to be much more nearly complete than that of phenoxymethylpenicillin (penicillin V); the blood levels attained are about double those produced by the same dose of penicillin V, and equivalent to those produced by an intramuscular injection of the same dose of benzylpenicillin (penicillin G) (Knudsen and Rolinson, 1959). Information about its antibacterial activity was communicated to the Seventh Annual Antibiotics Symposium in Washington in November last, but is not yet in print. Some of this information suggested a superior action against penicillin-resistant staphylococci, apparently owing to its slower inactivation by penicillinase (Report, 1959).

Since broxil, which is referred to here as penicillin B, is recommended for use in a wide variety of infections, further assessment of its activity against not only staphylococci but other bacteria is evidently called for, and the following preliminary observations were made with this object. Comparison was made with penicillins G and V. It is known that these two are not identical in activity. G is more active against streptococci and V against some staphylococci, but differences hitherto recorded have been only of the order of twofold (Martin, Nichols, and Heilman, 1955; Zischka, 1956; Lund, 1957).

Methods

The plate-dilution method, with a dilute inoculum, described by Garrod and Waterworth (1956), was used for all species, the medium being nutrient agar for non-exacting species, with the addition of saponin-lysed horse blood for *Str. pyogenes* and *Str. pneumoniae*, and "chocolate" agar for *H. influenzae*. The inoculated areas were separated by ditches in tests of *Proteus*.

A second series of tests was done with penicillin-resistant strains of *Staph. pyogenes*. 2.5 ml. of broth containing concentrations of penicillin falling by four-fold from 512 $\mu\text{g./ml.}$ being inoculated with one 0.02-ml. drop of undiluted broth culture and read for presence or absence of turbidity after 18 hours. When this large inoculum is used the result is determined by whether preformed penicillinase in the inoculum, the amount of which varies greatly between different strains, can destroy the penicillin before it exerts its bactericidal effect. Penicillin-sensitive strains of this organism were also tested by this method, the concentrations falling by twofold from 0.12 $\mu\text{g./ml.}$

All the organisms used were recently isolated from clinical material except some strains of *Str. pyogenes* and *Str. pneumoniae*.

Results

Staph. Pyogenes. — The findings obtained with sensitive strains were so uniform as only to require description in general terms. In the plate-dilution test

each of 36 strains was inhibited by either 0.015, 0.03, or 0.06 $\mu\text{g./ml.}$ of all three forms of penicillin, and there was never more than a difference of one tube between them for any one strain. For what differences of one tube are worth, 1 strain was most sensitive to G, 12 were most sensitive to V, 2 more sensitive to V and B than to G, and 10 more sensitive to V and G than to B, while 11 were equally sensitive to all three. Repetitions of these tests by the tube-dilution method gave similar results. Resistant (penicillinase-forming) strains likewise showed only differences of one tube in sensitivity to the three penicillins in the plate-dilution test, and, with the small inoculum used for this, nearly all the inhibitory concentrations were $<1 \mu\text{g./ml.}$ A very different picture is produced by the tube-dilution test with a large inoculum. The results obtained with this are given in Table I, the 38 strains being graded

TABLE I.—Minimum Inhibitory Concentrations of Three Penicillins for Resistant Staphylococci (Tube-dilution Test With Heavy Inoculum)

No. of Strains	M.I.C. ($\mu\text{g./ml.}$)			No. of Strains	M.I.C. ($\mu\text{g./ml.}$)		
	G	V	B		G	V	B
2	0.5	0.12	0.03	3	32	8	2
1	0.5	0.5	0.12	1	32	32	0.5
1	2	0.12	0.12	1	32	32	2
1	2	0.12	0.5	1	32	32	8
1	2	0.5	0.12	1	128	32	0.5
1	2	0.5	0.5	1	128	32	8
1	8	0.03	0.12	1	128	128	8
1	8	0.12	0.12	1	128	512	32
1	8	0.12	0.5	1	512	128	8
2	8	0.5	0.5	2	512	512	32
3	8	2	0.5	1	512	>512	32
1	32	0.5	0.5	1	>512	>512	32
1	32	2	0.12	1	>512	512	128
2	32	8	0.5				

in order of diminishing sensitivity to G. The first eight produce so little penicillinase that they are reasonably sensitive to all three penicillins, and the last nine so much that they are too resistant to all of them for therapy of any such infection to have any prospect of success. Without exception they are more sensitive to V or B than to G, and these differences are very large among strains of intermediate degrees of resistance to G, amounting in several instances to 256-fold. Many are considerably more sensitive to B than to V, though in a few strains this position is reversed.

Streptococci.—The order of activity against *Str. pyogenes* (group A), *Str. faecalis*, and *Str. pneumoniae* (pneumococcus) is consistently $G > V > B$, (Table II), but the differences are not great, being only twofold—where they exist—between G and V, and at maximum fourfold between G and B.

Gram-negative Bacilli (Table III).—Two species less resistant to penicillin than most other Gram-negative

TABLE II.—Minimum Inhibitory Concentrations of Three Penicillins for Three Species of Streptococci

	No. of Strains	M.I.C. ($\mu\text{g./ml.}$)		
		G	V	B
<i>Str. pyogenes</i> (11 strains)	4	0.007	0.007	0.03
	5	0.007	0.015	0.03
	1	0.015	0.015	0.03
	1	0.03	0.03	0.06
<i>Str. faecalis</i> (11 strains)	1	1	1	2
	2	2	2	4
	8	2	4	4
<i>Str. pneumoniae</i> (12 strains)	3	0.015	0.015	0.03
	1	0.015	0.015	0.06
	3	0.015	0.03	0.03
	4	0.015	0.03	0.06
	1	0.03	0.03	0.06

TABLE III.—Minimum Inhibitory Concentrations of Three Penicillins for Two Species of Gram-negative Bacilli

	No. of Strains	M.I.C. ($\mu\text{g./ml.}$)		
		G	V	B
<i>H. influenzae</i> (7 strains)	1	0.25	2	2
	1	0.25	2	4
	1	0.5	2	8
	2	0.5	4	4
	1	1	4	2
	1	1	16	32
	2	4	32	256
<i>Proteus mirabilis</i> (10 strains)	2	4	64	256
	1	4	64	512
	2	8	128	512
	1	8	128	>512
	2	16	128	>512

bacilli were examined. *H. influenzae* is very much more sensitive to G than to V, the difference being usually eightfold, and B has the same order of activity as V. *Proteus* was examined because treatment with penicillin V, in dosage which, according to the result of a sensitivity test (with G), should have been fully effective, had not been entirely successful in preventing the recurrence of a urinary infection due to this organism. The 10 strains in Table III are *P. mirabilis*; one of *P. vulgaris* behaved similarly and one of *P. rettgeri* quite differently. Against this organism G is 8–16 times as active as V, and 64 or more times as active as B.

Discussion

These observations reveal considerable differences in antibacterial activity *in vitro* between the new penicillin (B) and penicillin G. They also show greater differences between the activities of penicillins G and V than have hitherto been generally recognized. They might with advantage be extended to other species. The existence of such differences raises the question whether sensitivity tests performed as a guide to treatment can continue to be carried out solely with penicillin G, as at present. When another penicillin may or may not be many times more active, a further test with it may seem to be called for, at least in a difficult or critical case. In testing staphylococci, the degree of penicillin resistance of which varies so greatly, some such standard as that proposed by Abboud and Waisbren (1959) may be found helpful.

In so far as *in vitro* tests are an indication of therapeutic activity, the following conclusions may be drawn. B is decidedly the penicillin of choice for treating resistant staphylococcal infections, and might indeed be preferred for all such infections when facilities are not readily available for determining whether they are resistant or not. It is somewhat less active than G against streptococci and pneumococci, but the higher blood levels attained may compensate for this. It has a relatively very poor activity against the two Gram-negative species tested, and is to that extent less likely to be effective in bronchial and urinary-tract infections.

Summary

A comparison has been made between the antibacterial activity *in vitro* of benzylpenicillin (G), phenoxymethylpenicillin (V), and the potassium salt of 6-(α -phenoxypropionamido) penicillanic acid (B).

The usual order of activity against penicillin-resistant staphylococci, in a form of test which measures resistance to penicillinase, is $B > V > G$, with wide differences.

The order against streptococci and pneumococci is $G > V > B$, with only small differences.

The order against *H. influenzae* and *Proteus* is also $G > V > B$, with considerable differences between G and the other two.

For the skilful and rapid execution of this work, and for devising the method used for resistant staphylococci, I am indebted to Miss Pamela M. Waterworth. I am also indebted to Beecham Research Laboratories Ltd. for a supply of "broxil," and to Dr. J. S. Murrell for many strains of staphylococci isolated during a current study of antibiotic resistance in septic lesions in out-patients.

REFERENCES

- Abboud, F. M., and Waisbren, B. A. (1959). *A.M.A. Arch. intern. Med.*, **104**, 226.
 Garrod, L. P., and Waterworth, Pamela M. (1956). *Brit. med. J.*, **2**, 61.
 Knudsen, E. T., and Rolinson, G. N. (1959). *Lancet*, **2**, 1105.
 Lund, Erna (1957). *Acta path. microbiol. scand.*, **40**, 168.
 Martin, W. J., Nichols, D. R., and Heilman, F. R. (1955). *Proc. Mayo Clin.*, **30**, 467.
 Report (1959). *Brit. med. J.*, **2**, 1090.
 Zischka, W. (1956). *Zbl. Bakt., I Abt. Orig.*, **166**, 173.

ANTERIOR PITUITARY DEFICIENCY IN DISORDERS ASSOCIATED WITH STEATORRHOEA

BY

J. N. MICKERSON, M.D., M.R.C.P.

Senior Registrar, Charing Cross Hospital, London

Intestinal absorption may be impaired by a variety of disorders which, despite their diversity, often evoke a pattern of symptoms and signs which conforms to a characteristic clinical picture. Furthermore, these patients have a number of features in common with those of Addison's disease (Salvesen, 1956; Cooke and French, 1958). Prominent among these similarities are asthenia, pigmentation, intermittent diarrhoea, disturbances of water and sugar metabolism, disordered gastric secretory function, and the occurrence of macrocytic anaemia.

It is the purpose of this paper to show that defective intestinal absorption may be associated with decreased anterior pituitary activity and to relate this state to certain metabolic abnormalities which may occur in patients with steatorrhoea.

Material

Seven female patients whose ages ranged from 16 to 64 years were studied; each had steatorrhoea with a

24-hour excretion of faecal fat which averaged 6 g. or more (Cooke, 1956). Two patients had idiopathic steatorrhoea, two had adult coeliac disease, one coeliac disease, one chronic relapsing pancreatitis, and one steatorrhoea following a partial gastrectomy (Table I).

All seven patients had clinical evidence, in varied degree, of endocrine deficiency; especially prominent were features reminiscent of Addison's disease. Investigations included estimation of the 24-hour urinary 17-ketosteroid excretion before and after corticotrophin administration, determination of the serum electrolyte and serum protein levels, examination of the peripheral blood and sternal marrow. With one exception (Case 2), routine urine tests for albumin and sugar were negative, and all had normal liver-function tests. Some patients were further investigated with water-loading and glucose-tolerance tests, a fractional test meal, and radioactive-iodine studies of thyroid function.

The influence of steroid therapy upon the water load and glucose-tolerance tests was studied in one patient (Case 1) over a period of five months. Water-loading tests were repeated four years later, when this patient reattended hospital, having ceased all therapy during the interval. In five patients the effect of treatment upon the blood-picture was also assessed.

Assessment of Endocrine Activity

Clinical Evidence

Pigmentation of the skin was present in five patients, three of whom had buccal pigmentation also. In one (Case 3) asthenia, abdominal discomfort, vomiting, and diarrhoea associated with extensive buccal pigmentation, and a low blood-pressure (100/50) would have justified a clinical diagnosis of Addison's disease.

A deficiency of both growth and gonadal stimulating hormones seemed probable in the youngest patient (Case 4), who had had coeliac disease since early childhood. She was physically retarded—height 53 in. (134.5 cm.), weight 65 lb. (29.5 kg.)—and lacked secondary sexual characteristics; her physical and bone age (assessed radiologically) were comparable with those of a girl aged 9, though her intelligence corresponded with her real age, 16 years.

The skin was smooth and atrophic in four patients; in one it had a semitranslucent appearance with an easily discernible vascular pattern. Some had fine "hair-lines" radiating from the angles of the mouth and eyes.

TABLE I.—Patients with Intestinal Malabsorption

Case No.	Age	Diagnosis	Associated Conditions	Fat Excreted in Faeces in 24 Hours (g.)	Anaemia (Hb g. per 100 ml.)	Fasting Blood Sugar (mg./100 ml.)	Blood Electrolytes (mEq/l.)				Blood Urea (mg./100 ml.)	Plasma Proteins (g./100 ml.)		
							Sodium	Potassium	Chlorides	Alkali Reserve		Total	Alb.	Glob.
1	47	Adult coeliac disease	Bronchiectasis	16	Normocytic (11.3)	30	147	4.4	102	36.0	32	6.5	3.4	3.1
2	54	Chronic pancreatitis	Chronic nephritis	6	Macrocytic (6.8)	—	144	5.9	112	—	77	6.5	4.2	2.3
3	26	Idiopathic steatorrhoea	—	6.5	Macrocytic (5.3)	95	140	5.1	100	—	45	6.8	4.4	2.4
4	16	Coeliac disease	—	14	Normocytic (9.3)	80	137	5.1	105	26.4	21	6.7	4.3	2.4
5	55	Adult coeliac disease	Pulmonary sarcoidosis	7.2	Normocytic (13.3)	—	140	5.0	103	28.3	—	6.9	4.3	2.6
6	64	Idiopathic steatorrhoea	Diverticulitis. Prolonged thyroid medication (20 years)	14	Macrocytic (12.0)	—	125	3.0	112	—	27	7.4	4.7	2.7
7	58	Partial gastrectomy (1952)	—	8.3	Normocytic (12.9)	83	130	4.9	102	30.0	30	6.7	4.9	1.8