THE RELATIVE ANTIBACTERIAL ACTIVITY OF FOUR PENICILLINS

BY

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When an antibiotic with important new properties is discovered it is apt to be introduced into clinical use before the full range of its antibacterial activity has been ascertained. This is particularly true of penicillins, because it has sometimes been assumed that their action is identical, or nearly so, with that of penicillin G. Phenoxymethylpenicillin (penicillin V) was not only introduced but widely used for six years before this assumption was shown to be incorrect (Garrod, 1960a); phenethicillin (alpha-phenoxyethylpenicillin; "broxil"), introduced as another acid-resistant penicillin, which is better-absorbed than penicillin V, shows similar differences.

An extension of these observations is reported here: they are extended by including both more bacterial species and another penicillin, 6-(2,6-dimethoxybenzamido)penicillanate monohydrate (BRL 1241; "celbenin"), the outstanding property of which is resistance to staphylococcal penicillinase. Information about the activity of this penicillin against bacteria other than staphylococci is given by Knox (1960) and by Rolinson *et al.* (1960), but some of this refers only to single strains, and in the second of these studies no comparison was made with other penicillins.

Methods

The plate dilution method with twofold differences was used as in the earlier study. Blood or heated blood was included for species requiring it. All strains used were recently isolated in this department except those of *Corynebacterium diphtheriae, Bacillus anthracis, Salmonella* spp., and some of *Proteus morgani,* which were stock cultures.

Results

The results are presented in a detailed but condensed form, as recommended in a Report (1960) of W.H.O., in the accompanying Table. The majority are as already reported elsewhere (Garrod, 1960b), but some are new, and those for *Neisseria gonorrhoeae* refer to a fresh set of strains, the earlier ones not having been preserved.

Staphylococci.—It must be emphasized that all the strains tested were penicillin-sensitive. Had a separate category of resistant (penicillinase-forming) strains been included, the findings for celbenin would have been the same, but the concentrations of other penicillins required to inhibit their growth would have been greater, the degree of difference depending largely on the size of the inoculum, although, owing to differences in the rate of inactivation by penicillinase, the order of their activity would have been broxil>penicillin V>penicillin G. Because of the effect of inoculum size, absolute figures, although frequently quoted, seem meaningless in this connexion.

Streptococci.—The descending order of activity of the four penicillins against all species of streptococcus studied (*Str. viridans* was omitted as being too variable in its characters) is the order of their discovery, the usual differences being 2-, 4-, and 16-fold.

Neisseria spp.—Penicillin G has four times the activity of penicillin V against the gonococcus, and the newer penicillins are rather less active still. Meningococci behave similarly.

Gram-negative Bacilli.—Only the less highly resistant species were examined: it seems improbable that *Aerobacter* and *Pseudomonas* spp., which are very resistant to penicillin G, would be any less so to others. The diminution in activity with later discovery is more pronounced among these organisms. No other penicillin can compare with G in its action on *Haemophilus influenzae, Escherichia coli,* or *Salm. typhi.* The single exception to this, although of little therapeutic significance, depends on the fact that celbenin is alone in resisting the penicillinase formed by *P. morgani* and *P. rettgeri,* although not that formed by other *Proteus* spp. (Garrod, 1960b).

Minimum Inhibitory Concentration of Four Penicillins for Different Species of Pathogenic Bacteria*

	No. of Strains	Penicillin G	Penicillin V	Broxil	Celbenin
Staph. pyogenes (sensitive)	36	–6,**–5**,–5	–6,**–5**,–5	–6,**–5**,–4	**0, 1, 2**
Str. pyogenes ..	11	–7,**–7**,–5	–7,**–6**,–5	–5,**–5**,–4	–3,**–3**,–1
,, *faecalis* ..	13	**0, 1**, 1	**0, 2**, 2	**0, 2**, 2	**4, 5**, 6
,, *pneumoniae* ..	12	–6,**–6**,–5	–6,**–5**,–5	**–5**,–4,–4	–2,**–2**,–1
C. diphtheriae ..	7	–4,**–4**,–2	–5,**–5**,–3	–4,**–3**,–1	**0, 2**, 2
B. anthracis ..	14	–7,**–6**,–6	–7,**–6**,–6	–5,**–4**,–4	–4,**–3**,–3
N. gonorrhoeae ..	17	–8,**–7**,–3	–6,**–5**,–2	–5,**–3**,–2	–5,**–4**, 0
N. meningitidis ..	7	–6,**–5**,–4	–3,**–1**,–1	–1, **0**, 0	–2, **0**, 0
H. influenzae ..	8	–2,**–1**, 0	**1, 2**, 4	**1, 2**, 5	**2, 2**, 4
E. coli	11	**5, 6**, 6	**7, 8**, 8	**9, 9**,>9	>9
Salm. typhi ..	7	**1, 1**, 2	**6, 7**, 7,	**8, 8**, 9	**8, 9**, 9
Salm. paratyphi B	2	**1**	**7**	**9**	**9**
P. mirabilis (sensitive)	8	**2, 2**, 4	**5, 7**, 9	**7, 9**,>9	**7, 8**,>9
P. mirabilis (resistant)	8	>9	>9	>9	9,>9,>9
P. vulgaris ..	7	**6, 9**,>9	>9	>9	**8, 9**,>9
P. morgani ..	6	>**9**	>**9**	**8, 9**,>9	**8, 9**,>9
P. rettgeri ..	6	>9	**9, 9**,>9	**8, 8**,>9	**6, 8**,>9

* 0 denotes 1 μg./ml. Other figures are the $\log_2$ of the difference from this—that is, 1, 2, 3, 4 denote 2, 4, 8, 16 μg./ml. etc. –1, –2, –3, –4 denote 0·5, 0·25, 0·125, 0·062 μg./ml. etc. The first figure given is the *lowest* inhibitory concentration for any strain. The second (heavy type) is the *usual* inhibitory concentration. The third figure is the *highest* inhibitory concentration for any strain.

Discussion

Antibacterial activity demonstrable *in vitro* is only one property determining the therapeutic value of an antibiotic, and one should beware of exaggerating its significance. It is no true guide, for instance, to the treatment of enteric fever: several antibiotics are as active as chloramphenicol against typhoid bacilli in the test-tube, but not in the body. Nevertheless, in comparing antibiotics so otherwise similar as different penicillins, such comparisons as these must have some validity. Five years ago there was a discussion at the Antibiotics Symposium in Washington (Report, 1955–6) about reasons for the failure of a large dose of penicillin V to cure a substantial proportion of cases of gonorrhoea: no one suggested that the penicillin itself might be at fault, and the fact that penicillin V has indeed a lesser activity than penicillin G against the gonococcus has emerged only in the study reported here.

The resistance of celbenin to penicillinase places it in a class apart for the treatment of resistant staphylococcal infections, and clinical experience has confirmed its value for this purpose (Douthwaite and Trafford, 1960; Stewart *et al.*, 1960). When this infection is of a less serious nature, and treatment with celbenin is impracticable, the slower inactivation of broxil (and to some extent of penicillin V) by staphylococcal penicillinase, recommends its use in preference to penicillin G.

The place of the newer penicillins in the treatment of any other infections than staphylococcal is more doubtful. Penicillin G exceeds all other penicillins in activity against all other bacteria (except two uncommon species of *Proteus*), the differences being often wide. The nearest approach to the activity of penicillin G against important pathogenic organisms such as haemolytic streptococci and pneumococci is that of penicillin V, which may therefore reasonably claim to retain its place in the oral treatment of sufficiently sensitive infections.

Summary

The minimum concentrations of four penicillins inhibiting the growth of a variety of pathogenic bacteria have been determined, and the differences in activity so revealed are briefly discussed.

I am indebted to Beecham Research Laboratories for kindly furnishing supplies of broxil and celbenin; to Eli Lilly and Co. for supplies of pure potassium penicillin V; to Dr. C. S. Nicol for the specimens from which the strains of gonococci were cultivated; to Dr. Patricia Carpenter for some strains of *P. morgani*; and to Miss Pamela M. Waterworth for her skilled execution of the tests described.

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FURTHER NEUROPSYCHIATRIC OBSERVATIONS IN NIGERIA

WITH COMMENTS ON THE NEED FOR EPIDEMIOLOGICAL STUDY IN AFRICA

BY

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The present study is a supplement to the preliminary survey of neuropsychiatric problems in the Western Region of Nigeria (Lambo, 1955, 1956). Intensive studies (*British Medical Journal*, 1956) have been made in various parts of Nigeria, and the present article is an attempt to present a review of our work.

The need for epidemiological study in Africa, using small but effective samples, is urgent. The field for research in this direction, which has not yet been exploited, remains difficult, yet it is of first and ever-increasing importance (W.H.O., 1959; Lambo, 1959a).

Clinical Findings

I shall attempt to appraise briefly the most important types of neuropsychiatric disorders seen over a five-year period at Aro Hospital, the University Psychiatric Clinic, and the villages around Aro, a rural suburb of Abeokuta town, 60 miles from the Federal capital. In addition, patients have been referred to us from various parts of West Africa. We have therefore been well placed to see neurological, psychotic, psychosomatic, and neurotic patients of various types and in various subcultural and social settings. A supplementary rural survey (native treatment centres), the first of its type to be carried out in Nigeria, has also proved valuable, while many acute and episodic types have been admitted for study in the hospital (Tables I and II).

In respect of the usual terms "recovered," "improved," and "not improved," in the light of our experience among the rural and semi-primitive population of Africa, it is almost impossible to find any definable criterion on which to base the distinction. Consequently, we have deliberately dropped the term "recovered," as a result of which our "improved" group includes those who have recovered.

TABLE I.—*Aro Hospital, Other Mental Health Centres, and Native Treatment Centres (N.T.C.). Admission Data, 1954–8 (Western Nigeria)*

Diagnostic Classification	Treated at Aro		Treated at N.T.C.	
	Total	No. Improved	Total	No. Improved
Schizophrenia	960	486	635	452
Schizophreniform reactions	138	93	230	220
Anxiety states	250	210	330	317
Drug addiction	18	1	—	—
Chronic alcoholism	16	3	—	—
Endogenous depression	184	53	280	90
Organic brain syndrome	62	20	28	3
Manic-depressive	117	70	109	—
Psychopathic personalities	39	3	—	—
Involutional disorders	66	42	29	3
Obsessive-compulsive neuroses	10	2	23	21
Hysteria (conversion)	82	29	67	35
Psychoneuroses of ill-defined patterns	1,236	843	1,807	1,434
Puerperal and post-puerperal psychoses	315	34	211	6
Epilepsies with or without psychosis	219	102	36	2
Mental deficiency	83	53	64	54
Excito-motor syndrome and other unclassified psychoses (e.g., periodic psychosis)	180	146	122	120
Total	3,975	2,190	3,971	2,757

TABLE II.—*Classification of Cultural Backgrounds*

Diagnostic Categories	Treated at Aro			Treated at N.T.C.		
	Urban and Literate	Urban and Illiterate	Rural	Urban and Literate	Urban and Illiterate	Rural
Schizophrenia	370	320	270	363	180	92
Schizophreniform reactions	49	59	30	72	124	34
Anxiety states	71	93	86	94	170	66
Drug addiction (pethidine and hemp)	15	3	—	—	—	—
Chronic alcoholism	16	—	—	—	—	—
Endogenous depression	100	63	21	127	82	71
Organic brain syndrome	32	27	3	15	10	3
Manic-depressive	63	41	13	47	28	34
Psychopathic personalities	15	23	1	—	—	—
Involutional disorders	29	35	2	13	11	5
Obsessive-compulsive neuroses	5	3	2	14	9	—
Hysteria (conversion)	19	57	6	13	46	8
Psychoneurosis of ill-defined pattern	643	379	214	206	1,489	112
Puerperal and post-puerperal psychoses	173	110	32	127	63	21
Epilepsies with or without psychosis	41	72	106	4	18	14
Mental deficiency	11	18	54	2	14	48
Excito-motor syndrome and other unclassified psychoses (e.g., periodic psychosis)	—	72	108	2	10	110
Total	1,652	1,375	948	1,099	2,254	618

The mean age of the group of 960 schizophrenic patients at the time of onset of the illness was 23.45 years. There was no appreciable difference between the sex distribution of the major psychoses and well-known psychoneuroses. Excito-motor syndrome and malignant anxiety are, however, exclusively confined to men in rural and primitive areas. On this and other observations it seems that patients from rural, non-literate communities of Africa recover much more readily and quickly from the major mental disorders than the urbanized Africans.