Conclusions

This survey offers further evidence of the value of primidone as an anticonvulsant agent. The drug may be used alone, and has produced a 75% or greater reduction in the number of attacks in 21 out of 42 patients, all of whom had been treated previously with other drugs with unsatisfactory responses. Should it be desired to combine primidone with other drugs, phenytoin sodium seems preferable to phenobarbitone. The severe toxic effects are negligible, and the symptomatic side-effects tend to be transient and rarely require discontinuation of treatment. If previous treatment has been given, substitution with primidone can be accomplished in one week, building up to the optimum average daily dose of 1 to 1.5 g.

The cases described were under the care of Dr. Fergus R. Ferguson, to whom we are further indebted for helpful advice and criticism.

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PRIMIDONE IN MENTAL DEFICIENCY PRACTICE

BY

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That epilepsy is all too common a concomitant of mental deficiency is well illustrated by Tredgold (1952). He states that fits occur in 11% of the feeble-minded, 42% of imbeciles, and 56% of idiots. Thus we who devote ourselves to the care of defectives should be on the alert for newer and better therapy for our epileptic patients. Encouraged, therefore, by the reported success of Handley and Stewart (1952) and Butter (1953), using primidone ("mysoline"), it was decided to give this drug a trial with a number of epileptic patients residing in Botleys Park Hospital for Mental Defectives.

Primidone, a stable white crystalline anticonvulsant with the chemical formula 5-ethyl-5-phenyl-hexahydropyrimidine-4:6-dione, was first reported on in this country in 1952 by Handley and Stewart. They showed good results amongst epileptics at the David Lewis Epileptic Colony. This report was followed by a similar paper by Butter, dealing again with patients in an epileptic colony. Whitty (1953) and Greenstein and Saperstein (1953) have reported very comprehensively on a series of epileptics of varying types selected from out-patient practice of a neurological unit.

Clinical Trial

The aims of the trial were: (1) Primarily to discover whether grand mal epilepsy as found in the mental defective reacts favourably to primidone; (2) to observe changes, if any, occurring in petit mal, with especial reference to

changes in the E.E.G.; (3) to discover whether there was any correlation between I.Q. and results, or age and results; (4) to observe and record any toxic effects.

It should be noted that all the patients concerned had grand mal epilepsy of varying degree. Some had behaviour disorders such as would permit classification amongst the psychomotor types. Others had accompanying petit mal; these were all investigated by electroencephalography, and only those who showed characteristic spike-and-wave phenomenon were included. These totalled only six cases owing to the fact that all too frequently the patient was found to be unsuitable for any attempt at electroencephalography. It is regretted that a more extensive investigation of the effect of this drug on behaviour disorders of the psychomotor type was not possible owing to necessary limitation of expenditure.

Method Employed

The number of cases selected was 38 (15 women, 15 men, 8 children). Their ages ranged from 7 to 52 years. Seven showed focal signs in the form of a hemiplegia and were therefore classed as traumatic. One case suffered from tuberculous sclerosis. The I.Q. ranged from those who were inaccessible to 83 on the Wechsler scale.

Each subject acted as his or her own control. This was facilitated by referring to the epileptic charts recording the patient's previous attacks. Except in the case of some of the children, whose long-standing records were not available, at least three-years records were used in order to obtain a percentage of occurrence of attack prior to the survey.

The method of administration followed closely that used by Handley and Stewart. This consisted in adding 0.25 g. of primidone twice daily to the medicaments which the patient was receiving at that time. This continued for a week, when an additional 0.25 g. was given and at the same time gradual withdrawal of existing barbiturates was begun. During the third week a further 0.25 g. was added (the total being given in two daily divided doses). At this stage any other anticonvulsants such as phenytoin were also gradually withdrawn. The patients in this trial were therefore receiving only primidone, and this fact must be remembered when the results are assessed. In practice, an attempt was made to control the epilepsy with a daily dose of 1 g. of primidone. Where deterioration was serious, however, the dosage was increased up to 2 g. a day. It was found that the drug was well tolerated by children, and the average controllable dosage was about three-quarters that of an adult. As, however, the youngest child was aged 7, no assessment can be offered for infants or very young children.

It was thought advisable during the drug-substitution period to remove the barbiturates before any of the other anticonvulsants. This procedure was found to reduce any period of initial drowsiness which might take place. The total period of treatment with the drug was six months.

Toxic Effects

In common with the findings of other writers, primidone proved to be remarkably free from toxic effects of a serious nature. Drowsiness was a pronounced feature in about half of the cases initially, but soon became less so as the course proceeded. Ataxia was present in three cases, but in only one had the dosage to be reduced, and on a subsequent increase no further ill-effects were seen. Three patients became very confused and deteriorated mentally, and treatment was abandoned. No toxic skin rashes were reported. One patient developed a radial nerve palsy, but as there was a history of trauma, and as the condition subsequently cleared up without discontinuing primidone, it was thought to be coincidental to the treatment.

Results

Grand Mal Epilepsy.—The results in various age groups are given in Table I. The data are based on the percentage of grand mal attacks during the course of treatment in

TABLE I

Age Group in Years	No. of Cases	Discontinued	Worse —20%	No Change ±20%	Improved +20%	No Fits
5 to 15	10	XXT	T XXXXT	XXX X	XXXXT XXXXT	X
16 to 25	13		X XX	X X	X EXT	T
26 to 35	3		XX	XX	X	
36 to 45	7		XX	XX	X	
46 to 55	5					
Total No. of Cases	38	3	11	8	14	2
Percentage Totals		7.9	28.9	21.1	36.8	5.3

X represents one case of grand mal epilepsy.

T represents one case of traumatic epilepsy as described in text.

E represents one case of tuberous sclerosis.

comparison with previous incidence before primidone therapy. "No change" is regarded as less than 20% improvement or deterioration. "Worse" is more than 20% deterioration. "Improved" is more than 20% improvement on previous attacks of fits. The other two columns are self-explanatory. Taking the last two columns as the sum total of all improvements, we find this to represent 42.1% improvement in grand mal epilepsy. The relationship between I.Q. and the results as shown in Table I can be seen from Table II. In order to simplify the records the I.Q.s have been divided into three sections corresponding to the three classic grades of mental deficiency.

TABLE II

	I.Q. Range		
	Less than 25	25 to 49	50 to 70—
Cases discontinued	3	0	0
Cases worse	4	4	3
Cases with no change	0	3	5
Cases improved	1	7	6
Cases with no fits	0	1	1
Total cases	8	15	15
% showing improvement	12.5	53.3	46.6

Petit Mal.—Only six cases of petit mal epilepsy were included in the investigation. All showed clinical signs of typical petit mal seizures, together with varying degrees of spike-and-wave activity as shown in the E.E.G. pattern. After approximately four months' treatment with primidone all these cases were re-examined by electroencephalography. The results showed that there was a deterioration in all cases; three had grossly deteriorated, and all six had a marked increase in spike-and-wave activity. In view of the recently described "temporal lobe epilepsy," it is perhaps of interest to state that two of the six cases showed abnormality arising from the temporal lobe. The repeat E.E.G. of these cases, though showing deterioration as already stated, demonstrated also in one case that the previously seen focal abnormality was not present. The results of the E.E.G., except in one case, agree with clinical observation.

Behaviour Changes.—No objective methods were used to demonstrate behaviour changes other than observation by the nurse in charge. In the case of the children included in this report, it was found that their behaviour had deteriorated. This appeared to be irrespective of any improvement of grand mal or otherwise, and they became generally much more difficult to manage. In one adult case, which could be classified amongst the psychomotor type, behaviour became very aggressive, and treatment had to be abandoned. Generally, however, amongst the adults little change in behaviour was noted.

Psychometric Assessment.—Wherever possible, all patients accessible to mental testing were investigated both before and after the course of treatment. The tests used were the Wechsler scale and the Goodenough drawing test. The results with the Wechsler scale showed that in seven cases clinically improved there was also some improvement in I.Q.—as much as 13 points in one instance.

Discussion

The above results show that in a series of 38 mentally defective patients of varying grades an improvement in epilepsy of the grand mal type occurred in 42.1%. These results seem to be poor compared with those of Whitty and, later, of Greenstein and Sapirstein, who showed 78% improvement in focal and grand mal epilepsy. One has, however, to consider two main factors in the comparison.

First, all the cases in the above two examples were from out-patient departments in neurological units. It is just possible that such patients were less likely to have deteriorated or to be liable to deterioration than the type of institutionalized mental defective. Secondly, in Greenstein and Sapirstein's work, only two out of 30 patients were treated with primidone alone. Similarly, Whitty used a combination of primidone with sodium hydantoinate. As already stated, primidone alone was used in our own cases.

In the light of these facts, and considering also the relative lowness of I.Q. in the present series, a net result of 42.1% improvement is thought to be creditable. These results follow more closely those of Butter, who, in a series of 58 cases, found that 50% derived benefit and in only 3% were fits abolished. It would seem from the works already quoted that the improvement obtained might well have been greater if a combination of drugs had been used.

From Table I there appears to be little correlation between age groups and results, except perhaps a tendency for the children aged 5 to 15 years to show more improvement. It is therefore tentatively suggested that in primidone may be found the anticonvulsant of choice in the initial therapy of grand mal epilepsy occurring for the first time at an early age.

In considering Table II it is significant that in the class with an I.Q. of less than 25 there was much less total percentage improvement. Thus it is evident that patients of low I.Q. will be likely to respond least favourably to treatment with primidone.

That primidone is relatively free from toxic effects is again demonstrated, and it may therefore be safely used in domiciliary practice.

The effect of primidone on petit mal seizures appears from a clinical point of view to be almost uniformly bad. This observation is given support by the results of the E.E.G. examinations on termination of treatment. This is in agreement with the findings of Greenstein and Sapirstein, who quoted two cases of petit mal, both of which had a marked increase in the number, frequency, and severity of the attacks.

Though, as stated, no pure case of psychomotor epilepsy was treated, from observations of the main group little change in behaviour is to be expected.

The improvement in I.Q. reported in seven "improved" cases is not thought to be due primarily to the action of primidone on cerebral intellectual functions. Surely it is due to the removal of some of the elements of clouding and confusion of the consciousness so often evident in the chronic epileptic. They thus become more accessible to mental testing and show corresponding rise in I.Q.

Summary

A series of 38 cases of mental defective epileptics treated with primidone is recorded.

Results showed that in grand mal epilepsy 36.8% were improved, and 5.3% were much improved in that fits were abolished.

Six cases of petit mal showed very poor results, both clinically and also in E.E.G.

The dosage of primidone used varied from 0.5 to 2 g. daily according to age.

Toxic symptoms very few—mainly drowsiness and some ataxia.

In three cases treatment was discontinued owing to confusion and to deterioration of the epilepsy.

I wish to thank Dr. J. M. Crawford, physician-superintendent of Botleys Park Hospital, for his help and encouragement with the above report; Dr. J. Carse, physician-superintendent of Graylingwell Hospital, Chichester; Dr. Parsons-Smith and the staff of the E.E.G. department there for carrying out the necessary E.E.G. investigations; and Miss F. K. FitzPatrick and the nursing staff of Botleys Park Hospital for their invaluable help. I acknowledge with gratitude the financial support given by the Research Subcommittee of the South-west Metropolitan Regional Hospital Board, without which the survey could not have been undertaken.

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USE OF POLYMYXIN B IN THE EXTERNAL EAR

BY

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The polymyxin antibiotics were first described by Benedict and Langlykke (1947) and by Ainsworth *et al.* (1947). A series of antibiotic agents derived from *Bacillus polymyxa* have now been isolated and described; they are called polymyxins, and are differentiated by letters of the alphabet. The action of the polymyxins so far described—A, B, C, D, and E—seems to be bactericidal, and they all have similar antibacterial spectra, without significant differences (Brownlee *et al.*, 1952). *In vitro* experiments (Brownlee *et al.*, 1949; Pulaski *et al.*, 1949) have shown that they are effective against most Gram-negative organisms, in low concentrations. *Proteus vulgaris*, however, is an exception, and, together with the Gram-positive organisms, is sensitive only to high concentrations.

The polymyxins, chiefly B and E (the least toxic), have been used clinically, mainly by parenteral routes, in various infections due to Gram-negative organisms; the chief drawback to their use is their toxicity. A few workers have reported the use of these substances locally with some success (Jackson *et al.*, 1951; Jawetz, 1952). There do not appear to be any reports of a series of aural infections treated locally. There have also been no reports of any sensitization reactions after local use.

Present Series

Infections of the external auditory meatus, and in this group are included infected mastoid cavities, are often due to Gram-negative organisms. These infections are troublesome, since the organisms, particularly *Pseudomonas pyocyanea*, are often resistant to the commonly used antibiotics. A series of cases of otitis externa and infected radical mastoidectomy cavities have therefore been treated with polymyxin B locally. The cases chosen were those in which the infecting organisms were found to be one of the three chief Gram-negative types found in this region, *Ps. pyocyanea*, *Pr. vulgaris*, and *Bact. coli*. Infections caused by mixed organisms were not included.

The preparation used was a solution of 10% polymyxin B sulphate in propylene glycol, acidified with acetic acid. It was supplied to the patients in a bottle, with a dropper, for use at home. They were instructed to fill the ear with the solution, placing the head on one side, with the affected ear

uppermost, morning and evening, and then to insert a plug of cotton-wool. A swab was taken from the ear for laboratory examination before treatment was begun and another after seven days' treatment. In most cases in which organisms were sensitive the ear was found to be dry at the end of this period. The results are shown in the Table. In a

Results

Organisms	Type	No. of Cases	Dry	Failed	% Dry
<i>Pr. vulgaris</i> .. {	Otitis externa	8 (2c)	1	7	10
	Radical cavity	12	1	11	
<i>Bact. coli</i> .. {	Otitis externa	7 (3c)	5	2	65
	Radical cavity	13	8	5	
<i>Ps. pyocyanea</i> .. {	Otitis externa	11 (3c)	10	1	90
	Radical cavity	9	8	1	

c = Cases with bilateral infection in which a control solution was used in one ear.

small number of cases the infection was bilateral, and the infecting organisms were the same on both sides. In these cases the polymyxin solution was instilled into one ear and a control solution, consisting of solvent only, was instilled into the other. At the end of the seven-days period the control solution was stopped, a swab taken for culture, and treatment with the polymyxin solution begun. In no case did the control solution alter the infecting organisms. The number of cases suitable to act as controls is small. No sensitivity or reaction to the solution was noted.

It would seem that the polymyxin B solution is effective in a large proportion of cases against infections of the external ear caused by *Ps. pyocyanea*. To a less extent it may clear up infections caused by *Bact. coli*. It is ineffective against *Pr. vulgaris*. These results conform to the *in vitro* sensitivity of the organisms concerned, except that *Bact. coli* appears to be less effectively controlled in the ear than one might expect from its *in vitro* sensitivity. Since *Ps. pyocyanea* infections are often resistant to other antibiotics and other forms of treatment, it is suggested that polymyxin B sulphate solution has a place in their local treatment.

Summary

A series of cases are reported in which polymyxin B sulphate was used in the treatment of otitis externa and infected mastoid cavities.

Polymyxin B sulphate appears to be effective against infections caused by *Pseudomonas pyocyanea*.

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The 1954 *Yearbook* of the British Standards Institution, recently published (12s. 6d.), lists the British Standards current at March 31, 1954, and gives a brief description of each. They cover every field of industry and technology, and the standards laid down may be concerned with design, physical properties, methods of testing, limit tolerances, and so on. Many articles commonly used in hospitals and laboratories are manufactured in accordance with these standards, which are agreed only after discussion with all the parties concerned. The British Medical Association is a member organization and appoints representatives to committees of the B.S.I. when a medical opinion is required. Individuals are also eligible for membership of the B.S.I., and particulars as well as the *Yearbook* may be obtained from it at 2, Park Street, London, W.1.