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DRUG TREATMENT IN EPILEPSY

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SOLUBLE phenytoin (epanutin) has been extensively used in the treatment of epilepsy for about seven years and nearly all observers have testified to its efficiency and to the excellent results obtained in many cases. Most of its limitations and the precautions to be observed in its use have probably also been discovered. Conflicting reports of its usefulness compared with other drugs have, however, appeared in the medical literature since, following the original work of Putman and Merritt (1938), the American Council on Pharmacy and Chemistry in 1939 voted that dilantin sodium be accepted for inclusion in the N.N.R.

Critchley (1939) regarded soluble phenytoin as showing no promise of surpassing or even equalling phenobarbitone. Putnam and Merritt (1939) concluded that it was the most effective drug that they had used, and they advised its use for patients who are not free from symptoms with other forms of treatment. Williams (1939) obtained the best results using it alone in 52 cases, combined with phenobarbitone in 9 cases, with bromides in 16 cases, and with phenobarbitone and bromides in 6 cases. Doltolo and Bennett (1940) concluded that for severely deteriorated institutional patients, the drug should be combined with phenobarbitone, while Blair (1940) doubted the general usefulness of the drug as compared with phenobarbitone. Robinson and Osgood (1942) found that in 56 patients who failed to benefit greatly from increased doses of phenobarbitone, 21 per cent had great, and 30 per cent. had moderate improvement from soluble phenytoin. In some patients, a combination of phenobarbitone and soluble phenytoin was better than either alone. Dickerson (1942) treated 211 patients with soluble phenytoin and considered that 47 per cent. were more than 75 per cent. benefited, 12 per cent. had from 50 to 74 per cent. benefit, 14 per cent. from 25 to 49 per cent. benefit, 6 per cent. from 1 to 24 per cent. benefit; 14 per cent. were not improved, and 7 per cent. were worse. The drug was not effective alone in 34 cases, and was supplemented with phenobarbitone. Robinson (1942) treated 221 patients and obtained marked

reductions in the number of seizures in the following proportion of patients:—15 per cent. taking phenobarbitone, 39 per cent. taking soluble phenytoin, and 29 per cent. taking a combination of the two.

Merritt and Brenner (1942) treated 100 patients who had not responded satisfactorily to phenobarbitone or to soluble phenytoin used alone, and found that 34 per cent. improved on giving both drugs together. Tullidge and Fox (1942) came to the conclusion that soluble phenytoin should never be prescribed unless phenobarbitone and the bromides have first been given a thorough trial, and that every patient taking soluble phenytoin required close and continuous supervision.

Material

The authors own impression in 1945 supported the caution expressed by Critchley, Blair, and Tullidge and Fox, rather than the views of other workers. In order to confirm or modify that impression an examination was recently undertaken of the records of 713 cases of non-psychotic idiopathic epilepsy treated as in-patients in St. David's Hospital (an epileptic colony) during the five years, 1940 to 1944 inclusive.

The patients, all males, varied in age from fifteen to eighty-five years, and the drugs most commonly used were the bromides, phenobarbitone, epanutin (soluble phenytoin), rutonal (phenyl-methyl malonylurea), belladonna, chloral hydrate, and pilocarpine nitrate. In some cases one of these drugs alone was found to produce the optimum effect in a patient, but more frequently a combination of drugs was required, and altogether twenty-two different combinations were tried.

Of the 713 case-records, 323 were set aside because they referred to patients who had been in residence for less than six months; most observers would agree that in many cases a longer time is needed to discover the most satisfactory treatment. All of the remaining 390 cases had been in-patients for periods varying from six months to five years and of these 15 required no drug treatment. The remaining 375 form the subject of this investigation.

Method

In order to avoid a mass of details, it may be sufficient to say that the criterion of treatment was an assessment of what drug, or drugs, appeared in each case to reduce the number of fits most successfully without obvious toxic reactions. The average dosage of phenobarbitone was four and a half grains daily, and of soluble phenytoin, four and a half grains daily.

Most patients on admission to St. David's Hospital had been taking either bromides or phenobarbitone, or both. After a short period of observation, if the patient had several fits, the dosage of phenobarbitone was increased up to six and even up to nine grains daily. When this appeared to produce no reduction of fits or made the patient drowsy, one capsule (grs. $1\frac{1}{2}$) of soluble phenytoin was added twice daily, and cautiously increased to three, four, five, or even six capsules daily. This dosage was again regulated according to the reduction of fits or the production of toxic symptoms. In practice it was found that very few patients could take more than three capsules (grs. $4\frac{1}{2}$) daily without toxic reaction sooner or later. Blair (1940) came to the same conclusion. Where complete or almost complete relief was obtained, the dose of epanutin was reduced until what was considered the optimum dose for that particular patient had been reached. Thereafter, if the patient's condition continued to be satisfactory, other drugs, such as bromide or phenobarbitone which he might be taking, were gradually withdrawn.

Again, in cases where soluble phenytoin appeared to produce no effective improvement other drugs were added, and soluble phenytoin in its turn was slowly withdrawn. The choice of drug in such cases was largely one of trial and error but certain principles derived from previous experience were followed. For example, many writers have found that a combination of drugs in relatively large doses proves beneficial in severe cases.

(1) Fifteen of the very worst cases, some of whom had several hundred fits in a year, were very much helped by the old but useful mixture referred to in Table 1 as Mist. 2 B.C., viz:—

Sod. brom.	..	..	grs. x
Chlor. hydrat.	..	..	grs. v
Tr. bellad.	..	..	m. xv
Aq. ad.	..	..	℥js

Despite the high dosage of belladonna, no instance of poisoning occurred. In a separate investigation into the effects of this mixture, undertaken several years ago, in a series of 47 cases, it was discovered that the addition of $7\frac{1}{2}$ grains of sodium bichlorate appeared to confer further benefit in only three cases. This tends to confirm the findings of numerous writers that either alone or in combination with other drugs, sodium bichlorate need have no great claim on our attention in the treatment of epilepsy.

(2) The patients deriving benefit from rutonal had previously been taking phenobarbitone, but were given a change because of complaints of drowsiness

and lethargy. In almost all such cases, 3 grains of rutonal were found to be less soporific than $1\frac{1}{2}$ grains of phenobarbitone, and slightly more anti-convulsant.

(3) A change of drug, or an increased dose of the same drug, may confer benefit for an indefinite time, but in about 8 per cent. of cases, particularly in younger adults, adjustment of the dosage was found to be necessary at least once a year.

(4) In some cases, complete remission of fits does not prove to be an unqualified blessing, and perhaps should not be aimed at, whatever drug is being taken. Disorders of conduct and occasionally a frightening excursion into status epilepticus may follow absence of fits.

Results

The following table shows the number and percentage of cases treated with a single drug, or with the combination of drugs which appeared most efficacious. In each case the drug or combination finally chosen, appeared to be the most suitable for that particular individual. In some cases as many as seven combinations of drugs were tried. In all cases the particular drug or combination referred to had been taken for at least six months, and, in many cases for as long as five years. In compiling the table cognisance was taken not only of the reduction in the number and severity of the patient's fits but also of the patient's behaviour and his general health. Practically all cases showing great improvement in the decrease of *grand mal* also had rather fewer observed attacks of *petit mal*, but several of the men stated that they experienced more "sensations." In addition, all those who improved on soluble phenytoin, alone or in combination with other drugs, appeared to improve psychologically, being brighter and more intelligent, and less introspective, hypochondriacal, and irritable.

TABLE I

Drug	Number of cases	Percentage of cases
Phenobarbitone, alone	141	37.60
Phenobarbitone and soluble phenytoin	46	12.26
Phenobarbitone and sodium bromide	43	11.46
Various other combinations of drugs (15 in all)	42	11.20
Phenobarbitone, sodium bromide, and pilocarpine nitrate ..	16	4.26
Phenobarbitone and "Mist. 2 B.C."	15	4.00
Soluble phenytoin and sodium bromide	14	3.73
No pre-eminently satisfactory combination of drugs discovered	13	3.46
Sodium bromide, alone	11	2.93
Rutonal, alone	11	2.93
Soluble phenytoin, alone	10	2.60
Rutonal and sodium bromide ..	9	2.40
Soluble phenytoin and rutonal ..	4	1.06
TOTAL	375	100.09

Two outstanding facts revealed by this table are (1) that phenobarbitone, used alone, had been found to be more generally useful than any other drug or combination of drugs, and (2) that soluble phenytoin had been regarded as sufficient by itself in only ten cases.

Table II, however, puts a different complexion on the relative usefulness of the four principal drugs, showing the number and percentage of cases in which each was used:—

TABLE II

Drug	Number of cases	Percentage of 375 cases
Phenobarbitone, used alone or in combination with other drugs	278	74.1
Sodium bromide, used alone or in combination with other drugs	150	40
Soluble phenytoin, used alone or in combination with other drugs	85	22.6
Rutonal, used alone or in combination with other drugs ..	36	9.6

As will be seen, phenobarbitone again leads the field, nearly three-fourths of the patients having benefited most from that drug taken alone or in combination with other drugs.

It is disappointing to find that soluble phenytoin, despite its universally admitted value as an anti-convulsant, takes such a relatively low place in the list, and that in fewer than one-fourth of the patients did it appear to be an appropriate drug. Various factors account for this. Nearly fifty per cent. of the patients had been given soluble phenytoin at one time or another during the five years under review. In nearly half of these cases the drug was withdrawn, the efficient anti-convulsant dose having been found to produce toxic symptoms or signs at intervals varying from a week to fourteen months, or because even in non-toxic cases other drugs were proved to be more effective in reducing the number of fits.

An explanation of these relatively disappointing results may be ascribed to excessive caution in using this drug. No patient was allowed to suffer for more than a short time from what appeared to be early toxic symptoms or signs. Thus, if a patient were observed to be slightly tremulous or if he complained of slight nausea or giddiness or persistent anorexia, or if hypertrophic gingivitis caused any discomfort, the dosage of soluble phenytoin was immediately reduced, and where this did not amelio-

rate the symptoms or signs the drug was completely withdrawn. Other observers who have obtained better results have in most instances been dealing with cases of psychotic epileptics, and such patients are on the whole less articulate about their symptoms.

Toxic symptoms and signs may develop, without increase in dosage, after a few days, a few months, or, for all one knows, after a few years. This fact suggests that even greater caution should be used in prescribing soluble phenytoin when strict supervision is not possible. Undoubtedly the drug is more suitable for epileptics under institutional care than for those living at home.

One final point should be mentioned about the figures in the tables for the large number of patients shown as deriving benefit from phenobarbitone may give a misleading impression. Many patients had been taking it with good effect for years before the advent of soluble phenytoin, and there appeared to be no good reason for altering the treatment. In several of these cases, fits might have been equally well controlled by soluble phenytoin. The same applies to those taking bromides. An analysis of treatment five years hence might therefore yield a different picture, showing a smaller percentage of patients taking phenobarbitone or bromides.

Summary

Drug treatment in 375 cases of non-psychotic idiopathic epilepsy is analysed.

Phenobarbitone, used alone or in combination with other drugs, was found in both instances to be by far the most generally useful anti-convulsant (74.1 per cent. of cases).

Soluble phenytoin (epanutin), used alone or in combination with other drugs, was shown to be suitable in only 22.6 per cent. of the cases.

Several other practical points emerging from the investigation are discussed.

REFERENCES

- Blair, D. (1940). *J. ment. Sci.*, **86**, 888.
 Council on Pharmacy and Chemistry (1939). *J. Amer. med. Assoc.*, **113**, 1734.
 Critchley, M. (1939). *Practitioner*, **143**, 491.
 Dickerson, W. W. (1942). *Amer. J. Psychiat.*, **98**, 515.
 Doltolo, J. J., and Bennett, C. L. (1940). *Psychiat. Quart.*, **14**, 595.
 Merritt, H. H., and Brenner, C. (1942). *J. Nerv. ment. Dis.*, **96**, 245.
 — and Putnam, T. J. (1938). *J. Amer. med. Assoc.*, **111**, 1068.
 — — — (1939). *Arch. Neurol. Psychiat.*, Chicago, **42**, 1053.
 Robinson, L. J. (1942). *Amer. J. Psychiat.*, **99**, 231.
 — and Osgood, R. (1940). *J. Amer. med. Assoc.*, **114**, 1334.
 Tullidge, G. M., and Fox, J. T. (1942). *Lancet*, **2**, 6.
 Williams, D. (1939). *Ibid.*, **2**, 678.