acidity, and especially because, in my experience, if a patient has any sort of discomfort after a gastro-enterostomy he has almost certainly a stomal ulcer, and the sooner the anastomosis is undone the better. He declined this.

He returned in October, 1946, when he was "not feeling too good." He still had the pain, and his appetite was only fair. A third fractional test meal showed that the highest total acid and free acid were 70 and 52 respectively in contrast to the previous figures of 60 and 45 (see Fig. 1). Operation was again advised, and this time it was accepted.

Second Operation, November, 1946.—An enormous gastric ulcer was found, beginning on the stoma and passing widely up on to the lesser curvature, perforating into the pancreas as shown in Fig. 3, which is taken from the artist's painting of the

FIG. 3.—Findings at re-operation, Nov. 19, 1946. Lines A—B and C—D indicate area of stomach excised. The size of the ulcer is also shown.

specimen. It was approximately 3 by 3½ in. (7.6 by 8.9 cm.). A partial gastrectomy was performed (Fig. 4) and he made a good recovery.

FIG. 4.—Operation (Nov. 19, 1946) completed.

Comment

The points I wish to present in reporting this case are: (1) This is the largest anastomotic ulcer I have seen in a personal series of 40 cases and certainly the quickest to develop after a gastro-enterostomy (twelve months). (2) The progressive increase in the acid content of the gastric juice is the opposite to that for which the operation is designed. (3) I have performed the Somervell operation for several patients with unimpressive results, and therefore offer the conclusion that, for London patients at any rate, the Somervell method offers no advantage. (4) Finally, in my experience, if a patient after a gastro-enterostomy is not completely comfortable, but needs to diet or to take powders, then the sooner the gastro-enterostomy is undone the better. A stomal ulcer is likely to be present, and in my patients it was seldom shown by the radiographs.

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THE COMBINED ACTION OF PHENOBARBITONE AND EPANUTIN

BY

DONALD BLAIR, M.A., M.D., D.P.M.

Deputy Medical Superintendent, St. Bernard's Hospital (L.C.C.), Southall; Consultant Psychiatrist, Paddington, St. Mary Abbots, and Western Hospitals, L.C.C.

The two most important drugs in the modern treatment of epilepsy are phenobarbitone (5-phenyl-5-ethylbarbituric acid, "luminal," "gardenal") and "epanutin" (soluble phenytoin, sodium diphenylhydantoinate, "soluble dilantin"). It is only when the pharmacology, toxicity, etc., of these drugs are appreciated that they can be used with the maximum efficiency; I have dealt with this matter fully elsewhere (Blair, 1940). For the present it suffices to say that the chief disadvantage of the former is the drowsiness it may produce in adequate anticonvulsant doses, and of the latter the toxic effects (particularly those of a neurological, mental, or dermatological nature) when administered in doses of over three or four capsules (1½ gr.—0.1 g.—each) daily. A number of authors have tried these two drugs in combination in the hope that a synergistic action might occur.

The reports published to date (see Bibliography) have varied in their findings; some claim that in nearly all cases the use of epanutin and phenobarbitone together is more efficient than when these drugs are administered separately, but others find that in combination they are seldom better than when one or other is given alone. Moreover, little has been said regarding the frequency of toxic symptoms when they are combined, the optimum dosage in which they may be administered, etc.

In my experience there is a definite place in anti-convulsant therapy for the combined use of epanutin and phenobarbitone, and the present work was undertaken* to try to throw some light on the proportion of cases in which the combination of the drugs is more efficient than either administered separately (a) in controlling the number of fits and (b) in improving behaviour; the optimum dosage in which the two drugs may be combined; what toxic effects or other complications occur during their administration; and their pharmacological action.

Method and Results of Investigation

All patients concerned in this series were epileptic psychotics, mostly of long standing. For purposes of description the work may best be considered in three different categories: (1) the effect of adding epanutin in patients previously on phenobarbitone; (2) the effect of adding phenobarbitone in patients previously on epanutin; (3) a clinical trial of the two drugs combined in capsule form (referred to throughout this article as "E and P capsules").

Patients Previously on Phenobarbitone

In this group 30 chronic psychotics (whose ages ranged from 32 to 67 and averaged 42 years) had been on phenobarbitone for at least twelve months previously. Epanutin was added and the results observed. In a few cases previously on 3 or 4 gr. (0.2 or 0.26 g.) of phenobarbitone the dosage was reduced for control purposes to 2 gr. (0.13 g.) after epanutin had been combined with the former dose for several months.

* At Cane Hill Hospital in 1940-1 and not previously published owing to my absence on service in the R.A.M.C.

At first epanutin was added in a dosage of $1\frac{1}{2}$ gr. (0.1 g.) twice a day. This produced no noticeable reduction in the number of fits. None of the patients showed any noteworthy change in behaviour or any digestive upset, but there was evidence of toxicity in one case which took the form of typical ataxia and confusion, and which cleared up as soon as epanutin was withdrawn. After three months on $1\frac{1}{2}$ gr. of epanutin twice a day the dosage was increased to $1\frac{1}{2}$ gr. three times a day, and this combination of drugs was continued for six consecutive months, at the end of which time epanutin was again gradually withdrawn. The results obtained were as follows. In five cases there was a definite decrease in the number of fits,* but in the rest the total number of fits remained, broadly speaking, unchanged. In eight cases an improvement in behaviour was noted (three in association with a diminution of fits and five with no change in their frequency). In each of these cases the diminished frequency of fits or improved behaviour ceased when the epanutin was withdrawn.

Five of the cases had toxic symptoms, but these were confined to the nervous system and took the following form: ataxia, 1 case; confusion, 1; ataxia and confusion together, 2; paraesthesia, 1. All cleared up on withholding the epanutin.

In one of the two control cases in which the phenobarbitone had been reduced from 3 to 2 gr. (0.2 to 0.13 g.), and in all three cases in which it was reduced from 4 to 2 gr. (0.26 to 0.13 g.) (all cases being on $4\frac{1}{2}$ gr. (0.3 g.) of epanutin), there was an increase of fits compared with the combination of drugs or of phenobarbitone alone in the doses prior to reduction.

Patients Previously on Epanutin

Unfortunately only six patients who had previously been on epanutin for over a year were available, and these now also had 1 gr. (65 mg.) of phenobarbitone twice a day, after food. As this produced no effect on the frequency of fits or on the behaviour of the patients, at the end of three months the dosage was in each case increased to 1 gr. three times a day and continued for a period of six months, at the end of which time the phenobarbitone was withdrawn, the patient thus being put back on epanutin alone.

The results of this step were as follows. Two patients who had had their fits well controlled by epanutin alone did not experience further improvement on the addition of phenobarbitone, either in frequency of fits or in quality of behaviour. Two cases not so well controlled by epanutin showed no improvement when the two drugs were combined. In the fifth case there was a marked reduction of fits and an improvement in behaviour, due apparently to the combined action of the two drugs. The sixth patient developed toxicity in the form of dullness, apathy and general lethargy, and wretchedness, which cleared up when phenobarbitone was omitted. In the fifth case withdrawal of epanutin led to a return of frequency of fits and quality of behaviour to their previous levels.

Use of Epanutin and Phenobarbitone Combined in Capsule Form

One of the chief drawbacks to the combined method was the numerous doses of medicine required (e.g., epanutin three times a day before meals, and phenobarbitone three times a day after meals). It was therefore decided to try the administration of these drugs together. Capsules were made up containing $1\frac{1}{2}$ gr. (0.1 g.) of epanutin and $3\frac{1}{4}$ gr. (50 mg.) of phenobarbitone, and the following clinical trial was carried out on two different groups of patients.

Eighteen female patients of the type previously described (part of the group of 30 chronic patients), already on epanutin $1\frac{1}{2}$ gr. thrice daily and phenobarbitone 1 gr. thrice daily, were put on to one E and P capsule three times a day immediately after meals, and the other drugs were withdrawn. In the absence of any contraindications this medication was in each case continued for eight weeks. The five of the eighteen patients whose fits had been diminished on epanutin capsules and phenobarbitone tablets separately had them equally well controlled following the administration of the combined drugs in capsule form, and in nine of those cases where the fits had been unchanged on epanutin and phenobarbitone separately they remained similarly unchanged in frequency on the E and P capsules. In the four remaining cases no untoward occurrence took place until they had been on the capsules of the combined drugs for a number of weeks, when they each had a batch of several fits in the course of a few days. It is probable that the increase in the number of fits was associated with a reduction in the total dose of phenobarbitone involved in changing to the E and P capsules.

There was no digestive upset of any kind, but one patient who had been on E and P capsules for a month had four severe fits and for a few hours ran a temperature of 100.2° F. (37.9° C.). This woman had always been subject to fits in batches, so that the occurrence of these and the concomitant temperature could obviously not be proved to be the result of any change in medication. Nevertheless, it was thought advisable to discontinue the E and P capsules. Another patient who had developed a typical ataxia and confusion on epanutin and phenobarbitone separately was among those tried on the combined drugs, and she soon developed similar toxic symptoms.

Fifteen suitable male patients were also tried on one E and P capsule thrice daily, and during the three weeks they were on these capsules no toxic manifestation whatsoever was observed in any of them. The period was too short for any conclusions concerning frequency of fits.

Conclusions

1. *Frequency of Fits and Improvement in Behaviour.*—In five (16.6%) of the 30 cases treated by the addition of epanutin to phenobarbitone there was a marked reduction in the number of fits, and in eight (22%) a definite and consistent improvement occurred in behaviour. The decrease in frequency of fits and the simultaneous improvement of behaviour in only one of the six cases treated with the combination of the two drugs (as opposed to epanutin alone) also represents a percentage of 16.6. The figures of certain authors (Pratt, 1939; Williams, 1939) support these percentages, and some claim higher percentages (Pullar-Strecker, 1945). Others (Butter, 1940) have formed lower estimations but do not deny that in certain cases the combination of these drugs is the most effective form of therapy that can be administered.

2. *Toxicity.*—(a) Of the 30 cases in which epanutin was added to previous phenobarbitone medication only one showed toxicity (in the form of ataxia) when it was added in doses of $1\frac{1}{2}$ gr. twice a day, but a further five developed various toxic nervous symptoms when the dose was increased to $1\frac{1}{2}$ gr. thrice a day, and in every case the symptoms cleared up after epanutin was withdrawn. From a survey of the literature (Blair, 1940) it is plain that the toxic symptoms were similar to those which may be experienced when epanutin is given alone, and it seems definite that the combination of epanutin with phenobarbitone does not add to its toxicity. Thus the more severe manifestations seen when epanutin is given in 4 or more capsules per day

* The term "fits" in this paper refers to major epileptic fits only.

(=6 gr., or 0.4 g., total) were not observed. (b) Of the six patients previously on epanutin one developed toxic symptoms. She became dull, retarded, lacking in powers of concentration, devoid of energy, and generally miserable, and on withholding the phenobarbitone these symptoms cleared up. The symptoms are those that might be expected from phenobarbitone alone (Blair, 1940), and again it seems that the combination with epanutin does not produce increased toxicity. (c) Only one of the 18 female cases and none of the 15 males treated with E and P capsules showed any toxic symptoms during the time they were on this therapy (over 5,000 capsules were used in all). It is interesting to note that Pullar-Strecker (1945) maintains that the drugs given in combination (in E and P capsules) are less toxic than when given alone. This has not yet been established, but the present work does seem to show that they are at least not more toxic in combination than separately.

3. *Dosage.*—It is obvious from the foregoing that the addition of $1\frac{1}{2}$ gr. of epanutin twice a day to those patients previously on phenobarbitone produced no effect on the incidence of their fits, but when the dosage was increased to $1\frac{1}{2}$ gr. three times daily better results were obtained. Similarly the addition of phenobarbitone, 1 gr. (0.65 mg.) twice daily, to patients previously on epanutin produced no noticeable effect, but when the dose was increased to 1 gr. thrice daily it caused a marked decrease in the number of fits and an improvement in behaviour in one of these six cases. The number of cases in the present series was of course too small to offer any definite conclusions. Nevertheless, from my experience of other cases I have found that the dosage in which epanutin is most frequently used with success is $1\frac{1}{2}$ gr. three times a day (Blair, 1940), and similarly the dosage of phenobarbitone most often used in this type of case is 3 gr. (0.2 g.) daily. However, in view of the fact that the cases dealt with here were confirmed psychotics, it was thought that for general use a more suitable dose of phenobarbitone would be $\frac{3}{4}$ gr. (0.05 g.) thrice daily. I therefore wondered if capsules containing both drugs could be made up in these doses, and consulted Parke, Davis and Co. regarding such a possibility. After pharmaceutical investigation they reported favourably and produced the E and P capsules for trial. Since 1941 the capsules have been on the market and been used quite extensively. Pullar-Strecker (1945) described very good results from their use and stated that he now uses them exclusively in place of epanutin alone.

It is to be noted that a few patients showed an increase of fits after being on these capsules for a few weeks. This was probably associated with a reduction in the total dose of phenobarbitone in capsule form as opposed to the previous dose when given alone. In such cases it may be necessary to administer phenobarbitone alone once or twice a day to increase the total dose to the original value.

Pharmacology

Unfortunately, comparatively little is known of the exact mode in which phenobarbitone and epanutin achieve their anticonvulsant effects. The principal seat of action of phenobarbitone is probably the diencephalon, but it is thought that it also affects the cortex and thus produces its hypnotic action. In therapeutic doses it has been recovered from the above areas only, whereas in large doses it may be found in every part of the nervous system in equal amounts (Keeser and Keeser, 1928).

The exact site of action of epanutin is unknown, although it is probable that it acts differently from phenobarbitone. In large doses it has a depressant effect on the whole central nervous system. It differs from phenobarbitone in chemical composition, hydrogen-ion

concentration, and anticonvulsant effect on electrically produced convulsions in animals; it has a greater anticonvulsant effect than phenobarbitone (on certain patients) and a greater toxicity; and there is an absence of hypnotic effects. It has been suggested that epanutin may produce its effect by (a) alteration of permeability of the cortical cells (Putnam and Merritt, 1941), (b) some metabolic effect (Hemphill and Walter, 1941), or (c) raising the electrical threshold of the cortical cells (Naffziger *et al.*, 1942). Observations made on the differing effects of epanutin and phenobarbitone in inhibiting convulsions produced by cardiazol (leptazol) (Blair, 1940; Fröst, 1939) may also indicate different modes of pharmacological action. Taking everything into consideration it may at least be said that epanutin almost certainly has a completely different anticonvulsant effect from that of phenobarbitone (Blair, 1940; Williams, 1939; Putnam and Merritt, 1941).

Synergistic action of these drugs has been claimed by Cohen *et al.* (1940). In my opinion the present work indicates that the fundamental difference in the modes of action of these drugs persists when they are used in combination—that is to say, the one drug does not reinforce the other, but two entirely different effects are present instead of one. This is shown by the fact that the beneficial effect of the second drug is not obtained unless it is given in sufficiently high doses to produce an effect in itself. For instance, the addition of one or even two capsules ($1\frac{1}{2}$ –3 gr.) of epanutin produced no beneficial effect, and I have shown previously (Blair, 1940) that these doses are very seldom effective in this type of case. It is only when epanutin is given in three capsules ($4\frac{1}{2}$ gr.) that some cases benefit. Again, some cases on 3 or 4 gr. (0.2 or 0.26 g.) of phenobarbitone, to which had been added $4\frac{1}{2}$ gr. (0.3 g.) of epanutin daily, later had the phenobarbitone reduced to 2 gr. (0.13 g.). In four such cases reduction of the phenobarbitone led to an increase in fits. All these observations indicate that epanutin did not replace the phenobarbitone. This was further instanced in the cases placed on E and P capsules exclusively. In a few cases a batch of fits occurred several weeks later, and, as I have already pointed out, this was probably due to the reduction of the total dosage of phenobarbitone involved. I was not able to observe these cases long enough to see the effect of adding phenobarbitone to restore the original level. It is to be noted that in not a single case did combination of the drugs produce an increase in fits. Also, the toxic effects of one drug are apparently neither diminished nor enhanced by the second drug.

Epanutin is soluble in water and has a reaction in solution of about pH 11.7. Phenobarbitone is practically insoluble in water, but in suspension gives a reaction of approximately pH 5.6. When the two compounds are mixed in a capsule the effective reaction in solution is essentially that of the dissolved epanutin, and is again approximately 11.7. This admixture in capsules (E and P capsules) appears from the present work to be a convenient and innocuous means of administering them together, despite its marked alkalinity.

Summary

Several previous articles have claimed a synergistic action between phenobarbitone and epanutin. The present investigation confirms that this synergism exists in not less than 16% of cases.

It is indicated that when the drugs are used in combination the toxicity of one is neither enhanced nor diminished by the presence of the other.

Knowledge of the pharmacological action of these drugs is still sparse, but it is here shown that they probably produce their anticonvulsant effects in entirely different ways, and that used in combination they act by summation of two different processes.

It is considered that the optimum dosage for combining these drugs is $1\frac{1}{2}$ gr. (0.1 g.) of epanutin to $\frac{3}{4}$ gr. (0.5 mg.) of phenobarbitone.

Capsules ("E and P") containing these doses were given a successful initial trial. The capsules have now been placed on the market and very good results have been reported from their use (Pullar-Strecker, 1945).

I have to thank Dr. G. Lilly, medical superintendent of Cane Hill Hospital (where these researches were made) for his interest and encouragement in carrying out this work, and Messrs. Parke, Davis and Co. for their co-operation in producing the E and P capsules.

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NOMOGRAMS FOR RELATIVE HUMIDITY

BY

G. H. BELL, M.D., B.Sc.

AND

J. B. de V. WEIR, M.A., M.B., B.Sc.

(From the Institute of Physiology, Glasgow University)

Wynne (1947) has recently given simplified formulae for calculating the relative humidity and drying capacity of the atmosphere. These values can be read off direct on the accompanying nomograms and no calculation is required. A stretched black thread or a ruler placed so as to lie on the readings of the wet-bulb and dry-bulb thermometers cuts the third scale (relative humidity or saturation deficiency) at the required value.

The basic formula is $P = S^w - f\Delta$, where P is the partial pressure of water vapour in the air (in millibars), S^w the saturated water-vapour pressure at the temperature of the wet bulb, f a constant depending on the barometric pressure and the velocity of the air, and Δ the difference in Fahrenheit readings between the two thermometers. The relative humidity H is given by $H = 100 \frac{P}{S_d}$, where S_d is the saturated water-vapour pressure at the temperature of the dry bulb, and the drying capacity or saturation deficiency of the air in millibars by $S_d - P$. The charts are based on the exact values of the partial pressure of water vapour under saturated conditions, and have the additional advantage that

both Fahrenheit and Centigrade scales have been incorporated. The nomograms are designed for use in calm conditions such as exist in buildings where f can be taken

FIG. 1.—Nomogram for finding the relative humidity of the air from the dry-bulb and wet-bulb temperatures.

FIG. 2.—Nomogram for finding the drying capacity or saturation deficiency of the air from the dry-bulb and wet-bulb temperatures.

as 0.5. They do not apply accurately to observations made in the Stevenson screen or with the sling psychrometer, where the value of f is lower.

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