SODIUM DIPHENYL HYDANTOINATE IN THE TREATMENT OF EPILEPSY: PRELIMINARY OBSERVATIONS IN SEVERE CASES.*

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THE present communication is a preliminary report on 12 certified cases suffering from insanity with epilepsy treated with solantoin, a preparation of sodium diphenyl hydantoinate. This paper also discusses the site of action of the drug, and the possible relationship between its excretion and toxic effects.

Procedure.—Following Putnam and Merritt (1), who first announced the new drug, my first few cases were put on 0·1 grm. solantoin two or three times a day. Later cases were given a preliminary course of vitamin C (as a safeguard against sore mouth and tender gums—a possible complication reported by Kimball (2)). Included in my preparatory measures was the exhibition of nicotinic acid as a possible protection against toxic disorders of the skin. No case so prepared developed skin or gum complications subsequently.

All the cases under review were previously on phenobarbitone sodium; this drug was gradually discontinued, in some cases completely, and in other cases the patients were given a ½-gr. dose each night.

In cases where the unit of epileptic activity recurs at fairly short intervals, it seems possible to give the drug for brief spells and then to withdraw it in accordance with the pre-existing rhythm. For example, in two cases where the epileptic cycle recurred every 4 and 7 days respectively, the drug was given for corresponding periods and then withdrawn for slightly shorter periods to anticipate the forthcoming cycle (in the cases cited 3 and 6 days respectively) with no ill effects. This seems to me a way to prevent cumulative and toxic sequelæ.

CLINICAL RESULTS.

So far observations have extended for two to three months, and in consequence it is not yet possible to speak in terms of complete cure. Nevertheless, striking improvement was noted in 9 out of the 12 cases, whose fit incidence ranged from 6 to 87 a month.

The table herewith indicates that 6 out of these 9 cases have had no fit in

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the past month. One case has had only 1 fit in the past month, another 4, and yet another 7. The charts appended graphically illustrate the daily progress of some selected cases.

A point to emphasize is the striking alertness and cheerfulness of the patients, which stood in great contrast to their previous dullness and apathy. From being confused, helpless and " touchy ", they had on the whole become accessible, co-operative and agreeable. Nevertheless, in the case of two patients who had always suffered from violent episodes (epileptic equivalents), though the solantoin favourably influenced the major convulsive attacks, the phases of excessive excitement recurred as before.

Two cases are described in some detail, and five charts are reproduced herewith.

Number of Fits.

Case No.	Monthly average before treatment.	First month after treatment.	Second month after treatment.	Third month after treatment.
1	87	4	2	0
2	10	1	0	..
3	9	0	1	0
4	17	0	2	0
5	6	0	0	0
6	17	4	0	..
7	16	4	5	1
8	13	4	7	..
9	12	9	4	..

CASE 1.—R. W—, aged 29, single ; admitted August 22, 1930.

Family history negative. His fits began at 11 years of age. Very intelligent, reaching the top standard at 12 years. When he was 21 he had a fit in a swimming-bath and was nearly drowned. Pneumonia supervened and he had 100 fits in five days, and was certified shortly after, being hallucinated, deluded, violent and confused.

On admission fits occurred almost daily, reaching a total of 60 major attacks a month. He has steadily become worse, having an average of 87 fits a month, i.e., over 1,000 fits a year. In the 18 months preceding the new treatment he has never been free from fits for more than two days at a time on four occasions.

Treatment with solantoin was begun on April 12, 1939, the dose being worked up gradually to 0·1 grm. four times daily. The dose was subsequently reduced to 0·1 grm. twice daily. He had previously had phenobarbitone sodium, ½ gr. three times a day. This was reduced to one dose of ½ gr. at night.

In the first month following treatment he had 4 fits ; in the second month 2 fits ; in the third month *nil*. He has now been completely free from fits for over five weeks. From being a confused, helpless wreck physically and mentally, confined to bed, he is alert, cheerful and occupied.

On May 6, 1939, he developed tremors and pyrexia and the drug was discontinued for a fortnight. However, he remained free from fits during that period, (having only the pheno-barbitone sodium, ½ gr., at night). It seemed that the sodium phenyl hydantoinate had broken the " cycle " of fits. Treatment with the new drug was recommenced on May 20, 1939, at a reduced level of 0·1 grm. twice daily, with completely successful results so far.

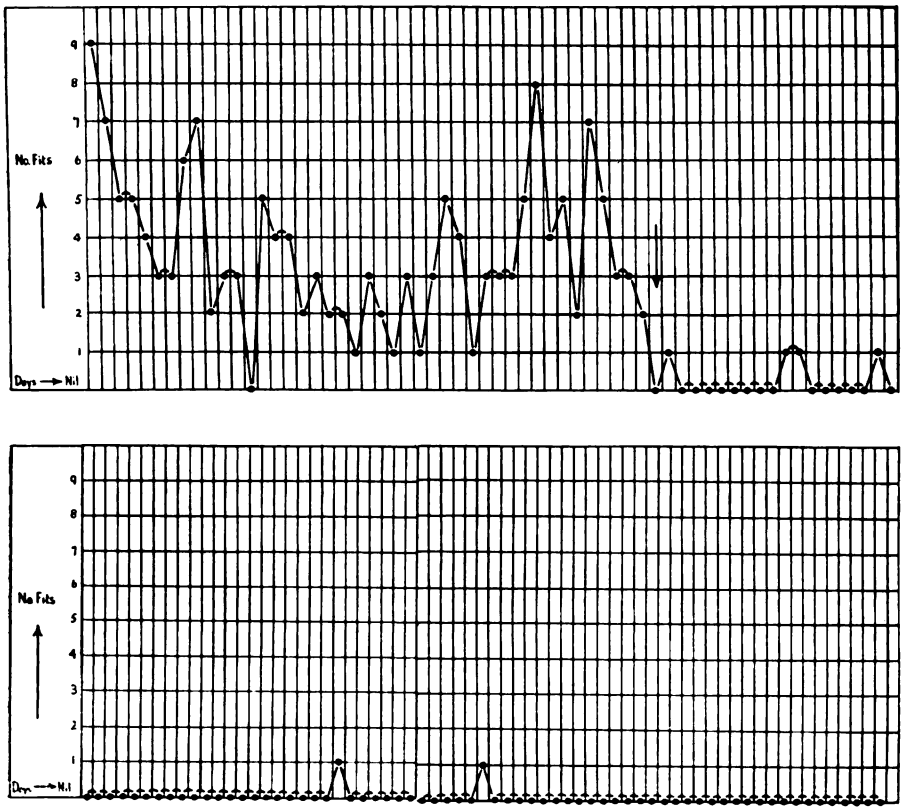

CHART 1.*

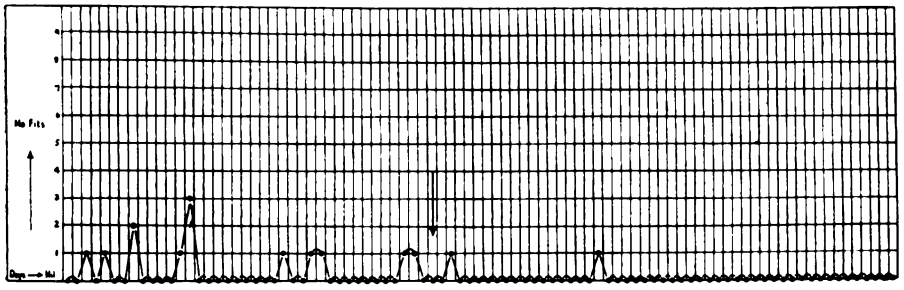

CHART 2.

* The arrows indicate where treatment commenced.

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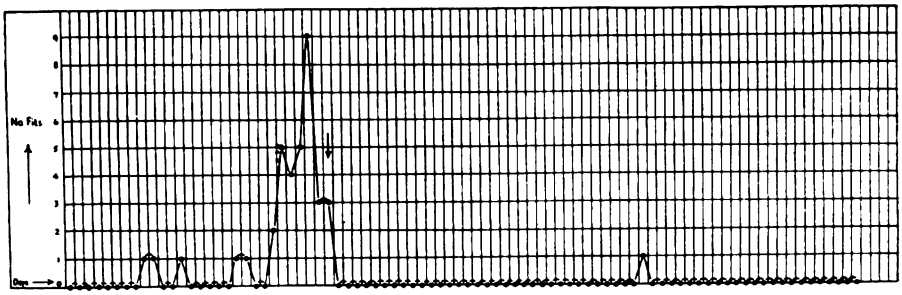

CHART 3.

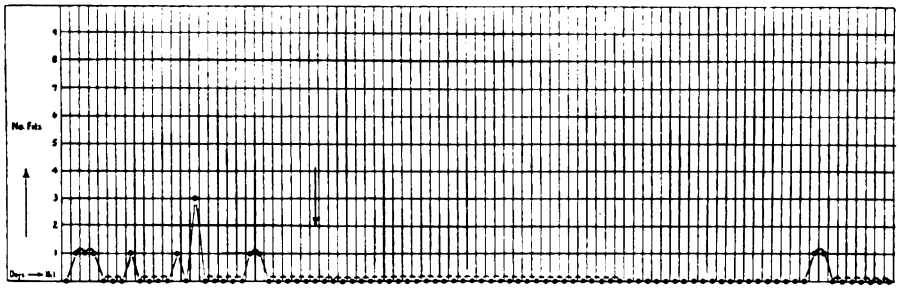

CHART 4.

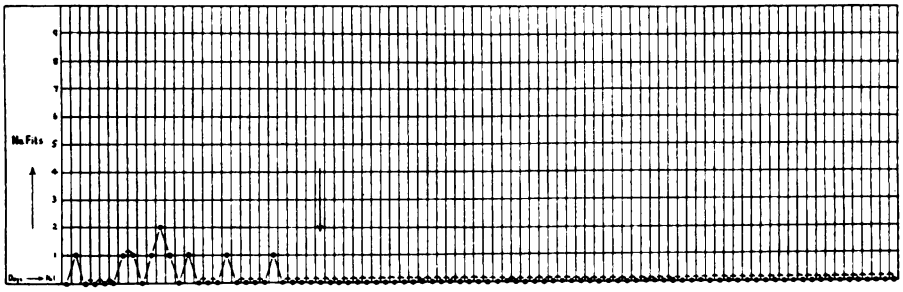

CHART 5.

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CASE 2.—R. L—, aged 34, single; admitted November 17, 1933.

Family history negative. Fits began at the age of 5; entered Chalfont Epileptic Colony at 12 years of age, and had to be withdrawn from there at the age of 26 because he was too dull. He was certified at the age of 28 because he became confused and violent.

The patient has had a steady average of about 10 fits a month (about 120 a year) since admission.

Treatment with solantoin (0·1 grm. three times a day) began in the middle of May, 1939. He had one fit 10 days later, but has been free from fits for nearly seven weeks since.

New Toxic Symptoms Noted.

In addition to the tremors, pyrexia and skin eruptions originally noted by Putnam and Merritt, I observed epistaxis as a previously unrecorded toxic symptom. In each instance the nose-bleeding was associated with a rise in blood-pressure. (Vitamin C apparently affords no adequate protection against this complication, as both cases had received preliminary treatment with ascorbic acid.) In addition, isolated myoclonic twitches were observed in two cases. It was, of course, difficult to say how far these twitches were toxic in origin, or merely signs of minor epilepsy. In two other instances nodding of the head occurred, but this may have been only a localized form of tremor.

Excretion and Accumulation: Creatinin-like Substances an Index?

The close similarity in chemical structure makes it probable that sodium diphenyl hydantoinate is excreted as a creatinin-like substance if not as hydantoinate. At any rate following upon administration of the drug there is an increase in the amount of creatinin-like substances in the urine. In two cases I observed a falling off in this additional apparent creatinin in urine, using the di-nitro benzoic acid test described by Benedict and Behre (3). It may be that this falling off of apparent creatinin excretion may be an index of the accumulation of the drug in the tissues of the body. Further details of these investigations will be given in a subsequent paper.

Site of Action of the New Drug.

In an attempt to find evidence as to the site of action of the new drug, I took advantage of the fact that I had patients whose threshold to fits artificially induced by cardiazol was known to me. In one case the patient was a schizophrenic (undergoing shock therapy) whose cardiazol threshold was 0·4 grm. After a fortnight of 0·3 grm. sodium diphenyl hydantoinate daily the patient's threshold to cardiazol remained unchanged. (That is to say, on one occasion 0·5 grm. cardiazol was needed, but on the next 0·4 grm. sufficed.)

In two other cases which were epileptics the cardiazol threshold was very low—0·1 grm. (This has been discovered in an unsuccessful attempt to raise the threshold to cardiazol as a form of treatment.) In neither of these cases did sodium diphenyl hydantoinate raise the threshold to fits induced by cardiazol. It seems therefore that the two drugs act at different sites.

Conclusion.

Preliminary results on 12 certified cases of insanity with epilepsy show that sodium diphenyl hydantoinate can be used with strikingly favourable effect. Epistaxis is herewith reported as a previously unrecorded toxic symptom. Nodding of the head may occur as distinct from generalized tremor, and isolated myoclonic twitches are also noted. Excretion of creatinin-like substance in urine may serve as an index of cumulation of the drug in the tissues.

The drug does not raise the threshold to convulsions induced by cardiazol.

Wherever there is a short regular rhythm of epileptic activity, it seems possible to exhibit the drug for brief periods and then to withdraw it before recommencing in accordance with the previously established cycle.

From clinical evidence it appears that sodium diphenyl hydantoinate has no effect upon the threshold for cardiazol when used for inducing fits, and that therefore the site of action of the former drug is different from that of the latter.

On the whole it may be said that so far as they go the clinical results of the use of sodium diphenyl hydantoinate in the treatment of epilepsy confirm the original findings of Putnam and Merritt.

Acknowledgments.

I wish to thank Dr. J. Brander, Medical Superintendent of Friern Hospital, for permission to conduct this investigation.

References.

(1) Merritt and Putnam.—*Journ. Amer. Med. Assoc.*, September 17, 1938, p. 1068.
(2) Kimball, O. P.—*Ibid.*, April 1, 1939, p. 1244.
(3) Benedict, S. R., and Behre, J. A.—*Journ. Biol. Chem.*, 1936, cxiv, p. 515.

Discussion.

A letter from Dr. Friedländer to the President was read before the discussion.

Bad Aussee,
Ostmark;
July 9, 1939.

DEAR COLLEAGUE,—I sincerely regret that I cannot attend the meeting. You are discussing the question of "Epilepsy" on July 13, and I should have liked to be present. Allow me to give you a brief sketch of observations which I have made during forty years. They refer to those illnesses which are combined with fits.

My statements *here* only refer to the genuine hereditary epilepsy with the major and minor attacks, the absences and equivalents which often lead to dementia.

In my younger days the bromide treatment stood in the first line. Flechsig introduced the opium-bromine therapy, Richet and Toulouse the saltless or salt-poor diet. The bromine-arsenic-*wine*-therapy of Szabó has a certain historic interest. Many other measures, including operations, are known.

I was not satisfied with any of these treatments, least of all with the bromine treatment, where up to nearly half an ounce was given and the attacks were replaced by a bromine poisoning.

The results were quite different when I introduced *luminal* into the treatment of epilepsy (1912). In the beginning of the year 1912 the firm Bayer sent me a new remedy for trial. They had called it "Hyp". In trying it myself I noticed a curiously strong sedative effect. By chance I had two patients in my sanatorium (Hohe Mark, near Frankfurt/M.), who, although they were treated by existing methods, fell into *status epilepticus*. In consideration of the danger to life I decided to make use of "Hyp". Both patients were cured and went back to their families. The unexpected and stupefying success induced me to have these cases published by my assistant (September, 1912). "Hyp" received the name "Luminal" later on.

The recovery from epileptic dementia was especially striking. The father of my patient thought her quite cured, but this was not the case. A far-reaching amelioration could be seen after one-and-a-half years' treatment without any other remedy, and without a special diet.

After this I only used luminal, later luminal sodium and then prominal.

A Tokio colleague wrote to me: "Since I have treated my patients in the way you describe, *epilepsy has lost its former terror*". I published these prescriptions under the title: "Die Behandlung epileptischer Anfälle: die Luminal-Therapie der Epilepsie," December, 1919, im XXXIII *Jahrgang der therapeutischen Monatshefte*, Berlin, Verlag Julius Springer.

It is unnecessary, gentlemen, to call your attention to the importance of the right diet, hydrotherapy, massage, the careful training of right breathing and psychical treatment. I only emphasize the following: the doses must be carefully considered, especially the night doses. Good results are often attained by minimal doses (luminaletten). How *small* the dose, how frequent the doses—all belong to the sphere of medical art. Schematical instructions and prescriptions, including some for children and babies are given in my publication, 1919.

Special attention must be given to the daily opening of the bowels. In case of constipation (and if a diet with salad, fruit, etc., is insufficient) luminal can be combined with a mild purgative. I had proposed to Bayer's a certain combination, but they did not accede to my suggestion. For more than twenty years I have

treated my epileptic patients in the aforesaid manner. It has not been necessary for me to change my directions, which I laid down in 1919.

Perhaps this short retrospect has some interest. I beg to excuse my cumbrous style, as I am not a master of the English language.

I wish your meeting very good success.

An old colleague sends his kindest greetings.

Hofrat Professor Dr. A. A. FRIEDLÄNDER,
Foreign Member
(Dr. med. Austriacus et Germanicus).

Prof. WOLFSOHN (San Francisco) said he had just come from a meeting of the American Neurological Association at Atlantic City, where Dr. Merritt had read a paper on the second year's results of the use of sodium diphenyl hydantoinate, which in America was called dilantin; these results had substantiated the results obtained in the first year. There was complete cessation of all attacks in about 55 to 60 % of cases. The speaker thought it essential to emphasize the fact that the drug should be used predominantly in major epilepsy; it had very little effect on the minor disease. He had treated 60 cases in the last thirteen months, and he did not think there was any case in which one could not eliminate all major attacks if enough of the drug was given. But the patient had to be seen frequently, because of the delayed reactions of wl ich Dr. McCartan had spoken. He was afraid to allow the patient to continue the drug while he was away because he had seen 12 cases of severe ataxia after three months' use of the drug. One patient, the sister of a doctor, played tennis up to the day before she began to take the drug. Within four weeks, when she was taking 4·5 gr. per day, she became so ataxic that she could not walk. He had had two cases of swollen gums which the patient did not notice and the swelling disappeared on cutting down the drug.

In conclusion he thought with a patient suffering from major epilepsy it was flying in the face of Providence to cut out the luminal. He would cut out the bromide, but he thought it a good plan to give a nightly dose of luminal and use the sodium diphenyl hydantoinate during the day, and grade it so that the patient would get the optimum response with the minimum of toxic doses. The patient should be under observation at least once a week.

Dr. D. BLAIR (Cane Hill) wanted to make a few observations on 35 cases he had treated. With regard to toxic effects of the drug, they were very important, and he confirmed what had been said already. As regards the early effects he found one or two cases had mental changes, they felt the kind of fear that occurred during cardiazol treatment—upset and agitated. He had also had a patient who had subjective symptoms, who felt he had lockjaw and loss of vision, and complained that he had no use in his arm. The patient was taken off epanutin and appeared to be all right, but some days later he had two very severe fits and died. There was another point regarding the question of control of fits on a change-over from luminal; 3 cases were controlled by 3 gr. per day for four or five weeks, and then suddenly had as many as 16 fits in three days. He decided that it would be better to take them off, but it did not make much difference. He had 3 patients with ataxia; the dose was increased and they had very bad attacks and marked confusion.

Another case was completely controlled on epanutin; for the first six weeks he had no fits and his temperament markedly improved—in many psychotic cases the temperamental outlook was improved tremendously—but he then went in a state of confusion which lasted for about a month. The number of capsules was reduced, the patient had a fit, and was better.

Dr. McCARTAN referred to the point raised by Dr. Frost with regard to the use of ascorbic acid. They had been using it for three months and the complication of hyperplasia of the gums was not known when they started, although they might have thought of it by analogy with nirvanol. There was no suggestion that this hyperplasia was due to vitamin C deficiency. The gums were slightly swollen and hyperplastic, and the patient had no discomfort. They considered the advisability of using the drug in combination with other drugs and decided not to do so. He might be wrong from his patient's point of view, perhaps he had been looking at it too exclusively from the scientific point of view, but he felt it was a pity to complicate the position by introducing other medicines. He did not see the slightest objection to using luminal at night, because, as Dr. Frost had pointed out, one was able to give a smaller dose of epanutin and therefore avoid possible toxic effects.

Referring to the name " epanutin " Dr. McCartan said he felt they were getting far too many names in medicine that meant nothing. He had suggested D.P.H. on the spur of the moment, and he thought it would be a nice gesture to their American colleagues, Putnam and Merritt, if they called the drug P.&M. 108. He was not sure that the number was right ; he knew it was well over a hundred before they discovered the best one for their purpose, but they would probably go on to try to discover something better.

Dr. FROST said he had asked if a preparation could be made that could be injected, but apparently the solution was far too alkaline, and at the moment no means was known of overcoming this difficulty.

Dr. FRIED asked Dr. McCartan what method he used for his blood sedimentation tests and whether he found any change.

Dr. McCARTAN said that Dr. Carson and he had used the Windrop method, and, as he had mentioned, on the series as a whole they found a very definite drop in the blood sedimentation rate. He did not know what that meant ; it was certainly not due to the withdrawal of luminal.

Dr. MOFFATT (Caterham) said his experience of the drug was 11 cases over two months. He had a suspicion that if new drugs were given to epileptics, some of them would always show encouraging results. The 11 cases he had were very regular " major-fitters ", they were having phenobarbitone. Out of the 11 he stopped 7, 1 because it did no good, and the other 6 for toxic symptoms—2 for ataxia and diplopia, 3 for nystagmus, tremors, nausea, and 1 for a condition of irritability which went on to excitability and delusions. In every case the toxic symptoms cleared up within two or three days of the drug being stopped. He had not seen a rash and only one hyperplasia of the gums.

He concluded that it was a drug to be careful with and that the margin between therapeutic efficiency and toxicity was very narrow ; it was not suitable for out-patients unless they came up twice a week, because these serious ataxias came on out of the blue.

Dr. CHISLETT (Glasgow) wished to associate himself with the last speaker. He had treated 12 cases over three months, and 6 showed no improvement whatever ; the other 6 certainly showed some, but in 3 of them the minor fits were increased, which was rather a peculiar effect. One case of *status epilepticus* which had not responded to any other form of treatment was given three capsules and the fits ceased altogether, but the patient unfortunately died thirty hours after the last fit. The patients certainly became bright—one had been in a semi-somnolent condition for years.

Dr. K. C. BAILEY (Warlingham Park) wished to emphasize the occurrence of mental clarity in psychotic epileptics by replacing bromides and luminal by epanutin. This clearing of mentation was, however, followed in some cases by an increase of psychotic symptoms of hallucinations and delusions, and for this reason he had re-introduced bromide in association with epanutin in these cases. He thought that it was useful to administer bromide or luminal with epanutin to control the psychotic symptoms in these cases

He wished to recall one case with toxic symptoms—a rash of a morbilliform character with a temperature of 105°—which occurred ten days after starting epanutin. The epanutin was stopped for two days and the condition cleared up. After another three days epanutin was given again and there was no more trouble. He had used epanutin with out-patients; they did not come up every week, and if it was used cautiously and carefully there was no reason why it should cause any trouble. He had not seen any toxic symptoms in the out-patients.

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