# THE BARBITURATES IN EPILEPSY.*

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ABOUT a year ago I came to realize that my knowledge of the subject of treatment in epilepsy was far from being complete, and this paper is the outcome of efforts made to clear up some of the uncertainty which existed in my mind.

After fairly extensive reading I concluded that facts *personally* observed were most important, for inaccurate terminology may give quite wrong impressions, and often published reports are of interesting but exceptional cases rather than regular ones. Opinions are copied from one report to another, and many conclusions are derived from a fairly short observation of a few cases.

Most epileptics vary greatly from time to time; quite a number seem to be improved during the summer months, only to relapse as winter comes again. Such variations can only be appreciated by prolonged observation.

We all realize that a mere reduction in the number of attacks is no sure sign of improvement, for it may be accompanied by a worsening of behaviour and a decreasing ability to work.

I have considered large numbers of cases rather than a selected few, and they have been observed over long periods of time.

One often reads reports of some new treatment which has produced a marked improvement in a certain group of epileptic patients. A surgical operation often produces temporary benefit, but does not produce permanent improvement, except perhaps in focal epilepsy. Septic foci can always be found and surgeons to remove them. Many of my cases have lost their tonsils but retained their epilepsy. One poor fellow has lost most of his colon, retained his epilepsy and acquired peritoneal adhesions, necessitating two further operations. I have noticed marked temporary improvement after various other new treatments, such as a strict diet—recently two boys have improved greatly on a low protein diet—or by giving a new drug—four patients improved greatly after daily injections of acetyl choline for a month—or after any new regime.

This temporary improvement frequently occurs when barbiturates are given. Observers have noticed it, and have said that tolerance for barbiturates frequently sets in. I have found no true tolerance, and believe that

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these observers had cases showing this temporary improvement, so commonly found in epileptics.

This improvement, followed by a pseudo-tolerance, occurs so constantly that I think the explanation must be found, not in the particular treatment, but in the patient; possibly it is a result of auto-suggestion.

## Various Barbiturates.

During a lull in the recent battle I was asked how much barbiturate we used in a year, and I was rather surprised to find that last year I prescribed just over three stones of these drugs.

The barbitals with specific anti-epileptic qualities are all phenobarbitals and the ordinary ones are of three kinds. There are other higher members of the series, but these are still protected by French or German patents, and have not been released generally.

(1) Methyl-phenobarbital. Trade name: Rutonal. This is slow, and requires doses of 5 to 10 gr. to obtain anti-epileptic action. It is very expensive, and not so easily procurable in large quantities as are the other members. It has been used successfully, but is rarely used now, and I have not used it.

(2) Ethyl-phenobarbital. Trade names: Luminal, gardenal. B.P. name: Phenobarbitone. This is very slightly soluble in water, but by substituting sodium for one of the hydrogen atoms of the urea nucleus, soluble salts are formed, and these are called luminal sodium, gardenal sodium, and, in the B.P., phenobarbitonum solubile.

Gardenal has been used extensively at the Colony, but as it did not prove different from luminal it has not been used lately.

Luminal sodium and phenobarbitonum solubile are in general use at the Colony, and I was interested in comparing the proprietary with the official preparation.

Two hundred patients, men and women, all undergoing treatment with luminal sodium were suddenly changed to similar doses of phenobarbitonum solubile. As a comparison, a further 200 were left on their usual dose of luminal. Nobody but myself knew about this change-over. This was essential because, as I have mentioned, any obvious alteration in treatment produces a temporary effect on many epileptics. This test continued for four months, particular notice being taken of any changes, either physical or mental. The sudden change of medicine was noticed by nobody and produced no immediate ill-effects, such as rashes, nausea or alteration in temperament. Those people who were kept free from attacks by luminal remained free, and the number of attacks in the rest did not vary from the previous average. In no case did phenobarbitone produce results less satisfactory than those produced by luminal. The following points are to be noted: (1) Luminal is a foreign drug

and cannot be bought in bulk. Phenobarbitone is British. (2) There is no danger of supplies of phenobarbitone being cut off, as happened a few years ago during the luminal famine. (3) Luminal sodium costs up to 14*s.* an ounce. Phenobarbitone costs 2*s.* 6*d.* This may not be of importance where only small quantities are used, but it is worth considering in an institution or when prescribing for National Health Insurance.

(3) Methyl-ethyl-phenobarbital. Trade name: Prominal. When this was introduced in 1931 it was claimed that smaller doses would be efficacious and that there would be less hypnotic action.

Eight cases in the Colony were given prominal alone or with luminal. In no case was any improvement noticed. One case was definitely better without prominal. Three early cases of epilepsy, not in the Colony, were given prominal, and it was found that there was no sleepiness in the morning, but the effective dose is about 4 gr.—rather higher than the usual phenobarbitone dose. This absence of sleepiness was useful, as all three wished and were able to continue at work.

This prominal series is too small to give conclusive results, but it tends to show that prominal is not necessary in an institution, but may be indicated as suitable for a patient who can afford the extra expense and who is anxious not to interrupt his daily routine work.

## Treatment by Phenobarbitone.

The complete duality of the action of phenobarbitone firstly as an anti-epileptic and secondly as an hypnotic has not been recognized clearly.

It can be given as a working rule that doses above 5 gr. are hypnotic doses, and any good they do is due to the hypnotic action alone. Such doses are still used in epilepsy, particularly in *status epilepticus*, without the user always realizing that he is giving an hypnotic rather than a specific anti-epileptic drug. In such cases we, at this Colony, do not use large hypnotic doses of phenobarbitone, having found that chloral and other sedative drugs are safer and surer.

The anti-epileptic dose is less than 5 gr., usually 2 gr. Even such a small dose as 2 gr. is mildly somnifacient when first started, but after about ten days it no longer produces any drowsiness. With repeated small doses the somnifacient action passes off completely, long before any anti-epileptic action is apparent.

It has been found that 80% of the phenobarbitone taken by the mouth is decomposed in the body, the other 20% being excreted in the urine during the following nine or ten days. At present there is no simple qualitative test for detecting phenobarbitone in the urine, but probably such a test will be available shortly, as various dyes have been prepared recently from very small quantities of the drug.

We begin treatment by giving 2 gr. of phenobarbitonum solubile each morning, dissolved in ½ oz. of water. At the end of a fortnight any nausea or sleepiness has disappeared and no further ill-effect is noticed. Each case is reviewed at the end of every month, and any advisable alteration is made. Such alterations are :

(1) Phenobarbitone may be stopped at the end of six months if no change has been produced or is to be expected.

(2) If the drug has improved the patient, then an increase may be made in the dose, from 2 to 3 gr. This seldom makes any difference, and the dose is soon reduced to 2 gr., but occasionally a 3-gr. dose is better than a 2-gr. one.

(3) The time of giving the dose may be altered. If most of the attacks occur during the night it may be of benefit to take the dose in the evening rather than the morning. By taking the dose in the evening the initial morning sleepiness can be largely avoided.

(4) The daily dose may be divided into two doses each of 1 gr. This proves particularly useful in patients who get attacks of *petit mal* in the evening.

(5) The phenobarbitone may be supplemented by occasional doses of bromide. Most patients have discovered that regular doses of bromide make them dull and they object strongly to taking them. I have found that occasional doses of bromide are sometimes useful in allaying the headache and nausea which may accompany attacks of *grand mal*. Similarly an occasional dose may reduce the violence of an attack of *grand mal*.

Meerloo says that frequently an insane epileptic when given a dose of phenobarbitone will become irritable and pass readily into furor.

Several people who had been in the Colony for many years and become demented were given phenobarbitone. Two of them became very excited and the drug was stopped. Without the drug they were certainly duller and heavier mentally, and they might have improved if we had persevered. A third patient had definitely fewer attacks, but her mental condition did not alter greatly. Two cases were markedly improved, and this improvement has been maintained.

That the improvement is due largely to the phenobarbitone can be proved by stopping the drug for a time. This is never done if it can be avoided, but the result of stopping the drug is described later.

Phenobarbitone is classed as a poison under the Pharmacy Act of 1908. This means that the drug can be bought directly from a pharmacist, no doctor's prescription being needed. It is probable that under the Pharmacy and Poisons Act, 1933, this will be changed, allowing the sale of barbiturates only on a doctor's prescription. This extra precaution is strongly supported by the Home Office in England and the Préfecture in Paris.

My present practice with patients outside the Colony is to prescribe not more than eight days' medicine at a time because—

(1) It eliminates any chance of consuming a dangerous dose. If the whole

eight days' supply were taken at once it would be no more than a soporific dose.

(2) It ensures that the patient shall be seen periodically and not take a routine dose indefinitely. This eliminates any slight possibility of toxic symptoms ever becoming established.

(3) It ensures that the drug is freshly prepared.

There is a type of *petit mal* called by Gowers "jerks", which we call "jumps", and otherwise known as myoclonic or "regional" epilepsy. These terms are used to describe those attacks in which consciousness may be impaired, and in which a group or groups of muscles suddenly become tonically contracted. The attack lasts a second or two, and then relaxation occurs, but the attack tends to recur after a few minutes. Groups of these "jumps" occur either alone or with a typical attack of *grand mal*. They are very distressing to the patient, as he drops everything in his hands and he may be thrown violently to the floor.

There are several people at present in the Colony who were subject to "jumps" as well as typical attacks of *grand mal*. Two of these have been freed from all attacks by phenobarbitone. A third has found that if he takes 1 gr. of the drug when he feels the "jumps" coming on they are completely warded off.

*Serial epilepsy* is a condition in which a sequence of major attacks occurs, but there is a period of consciousness after each attack.

A regular dose of phenobarbitone is of great use in reducing the number and severity of these groups. One colonist used to have groups of seven to ten attacks before being given the drug, now he has only an occasional minor attack. In spite of being such an excellent preventive agent, I have found that a dose of phenobarbitone, given after the beginning of the group, is of little use in stopping it. A rectal wash-out and the giving of 30 gr. of chloral is the best means of aborting such a group.

*Prolonged clonic convulsions*, associated with *grand mal*, are not very common. I have met two cases, and the most successful treatment of this condition has proved to be light chloroform anæsthesia. Phenobarbitone was useless in anything below a markedly soporific dose. Hyoscine or chloral made them wildly excited.

*Status epilepticus*.—In this condition there is a sequence of attacks without consciousness being regained between them. If the patient recovers between his attacks so that he can sit up and take sips of water, we do not class the condition as *status*. Since the introduction of phenobarbitone *status epilepticus* is increasingly rare. There is no doubt that regular doses of the drug markedly diminish the liability to *status epilepticus*. Several colonists had periods of *status* before being given phenobarbitone, but they have had none since then. As a treatment for *status epilepticus* it has been proposed that phenobarbitone should be injected intrathecally, intravenously or hypodermically, or given in large doses *per rectum*. At the Colony we find the drug

is of no benefit in anything less than soporific doses. The best treatment for *status epilepticus* remains rectal lavage, followed by the administration of chloral and a solution of glucose by the mouth.

*Dangers of prolonged medication.*—Shortly after the introduction of luminal, Graeffner strongly advised an interval of two clear days after every four days' use in order to prevent any cumulative effects. Later, in this country, Mott, Pickworth and Woodhouse studied the effect on animals of very large doses of hypnotic drugs, and largely due to their work has arisen the general belief that the giving of therapeutic doses of phenobarbitone over a long period will result in degenerative changes in the central nervous system.

For instance, in 1927 Willcox affirmed that the taking of large doses or continued full therapeutic doses of barbiturates must cause definite organic changes in the central nervous system. Later he stated that the repeated daily use of barbiturates in therapeutic doses quite commonly causes symptoms such as mental depression, paralysis, etc.

The treatment of epilepsy with phenobarbitone was begun at the David Lewis Colony in 1922, and by 1925 over 250 colonists were receiving it. At the end of 1933 there were over 400 taking regular doses of barbiturates. Some of these have now been taking a regular daily dose for over twelve years, and the combined effect of epileptic attacks and phenobarbitone therapy is illustrated by a few examples.

The Colony store, which caters for 500 people, is managed entirely by two male colonists. They order, receive, check and apportion all groceries used here. The senior storekeeper is sixty-three years old and has been taking a daily dose of phenobarbitone for eleven years. He shows no sign of mental deterioration, being bright, astute and trustworthy. His assistant is thirty-six years old, and has been taking 2 gr. of phenobarbitone daily for over twelve years. This colonist is above average intelligence, and his friends say he is definitely brighter than he was twelve years ago.

Our organist, who is employed during the week as laundryman, personally attending to his horse and van, has been having phenobarbitone daily for over ten years. He still has minor attacks, but is of average intelligence and shows no sign of mental deterioration. Many more cases can be quoted who, after ten or more years of regular phenobarbitone dosage, are of normal intelligence, and even though some still have attacks, they show not the slightest sign of degeneration. Many are definitely brighter than they were before the drug was started. It can safely be asserted that therapeutic doses of phenobarbitone given daily without interruption for periods up to twelve years cause no obvious degenerative changes in patients with epilepsy. One must believe that if any degenerative change occurs in such a case it is not produced by the phenobarbitone, but by the disease itself or by some other treatment.

*Stopping the drug.*—In his book on *Epilepsy* Sir William Gowers says: " In most of these cases (of *status epilepticus*) the condition was caused by the

sudden arrest of the administration of bromides." This being so, it is interesting to see if *status epilepticus* is produced by the sudden arrest of the administration of phenobarbitone. Reports have been published describing cases where *status epilepticus* was induced by stopping the regular dose of phenobarbitone given to insane epileptics. There is not the same definite evidence if one considers sane epileptics.

A great many cases of sudden arrest of administration are found in the records of the Colony. Soon after the treatment was started here there was a luminal famine, and thirty colonists suddenly dropped it. Not one of them showed appreciable signs of harm. Those who have stopped phenobarbitone have done so without any tailing off; there has never been a slow diminution in the dose, but always a sudden arrest. These patients can be divided conveniently into four groups.

*Group 1.*—Phenobarbitone, having been taken for six months or more, seems to be doing no good. The drug is discontinued. Many cases have been investigated, and in no case has the sudden stoppage been accompanied by any appreciable result.

*Group 2.*—The drug, having been taken for six months or more, is discontinued, although it seems to be doing good. This group is very large, as all admissions to the Colony are observed for a time without any drug being given to them. In some cases phenobarbitone has been given prior to admission, but it is stopped for a time. The group also includes colonists who go with friends for a holiday but do not obey instructions to continue the drug. Cases in this group tend to relapse mentally and to have an increased number of attacks. Sometimes they seem to be worse than before phenobarbitone was started, but this rarely persists, and they quickly return to a condition at least as good as that in which they were before phenobarbitone was started. In no case has *status epilepticus* occurred.

*Group 3.*—Phenobarbitone has completely arrested the attacks, but the patient still has the epileptic mentality, being rather unbalanced and emotional. Great care is taken that the drug should not be stopped in these cases, but I have seen a few where this has happened in spite of all precautions. It is found that the sudden arrest may be followed by a worsening of the mental trait and perhaps one or two attacks of *grand mal* may occur.

*Group 4.*—Phenobarbitone has arrested the attacks and the patient is returned to normal mentality, being controlled emotionally and apparently cured. These cases are advised to continue the drug for two years after they return home; many of them continue the drug for longer than this. In my experience there is no risk of symptoms developing when phenobarbitone is stopped.

*Toxicomania.*—When a drug such as phenobarbitone is used continuously over a long period it is important that no overdose should be taken and no addiction produced. Willcox says that repeated daily doses of a barbiturate

produce a definite craving in a large number of cases, and that persons addicted to the continued daily use of these drugs not uncommonly, as a result of this habit, take a dangerous overdose, whether accidentally or otherwise.

It is generally accepted now that some constitutional predilection is the real cause of toxicomania and the addict is usually found to be cyclothymic in type.

Many colonists ask for an extra dose of phenobarbitone at times. If they feel minor attacks coming, they find that a grain of phenobarbitone frequently wards them off. This is quite understandable, but in no case is the daily dose of 3 gr. exceeded and there is no suggestion of craving for the drug.

One colonist, who had returned to work, was using more than his allowance of phenobarbitone. I concluded that he must have been taking excessive doses, but on investigating further it was found that the phenobarbitone was taken by his sister, who had discovered a remedy better than aspirin in curing her menstrual headaches. Another colonist was reported to me as having a craving for phenobarbitone and trying to steal it. I found that when phenobarbitone was denied him he tried to acquire extra doses of house mixture or anything else from a bottle. Undoubtedly he had an obsession, but it could not be described as toxicomania.

In spite of the large quantity of phenobarbitone prescribed, both to colonists and patients outside, I have no knowledge of a single case of addiction in an epileptic. Phenobarbitone has been used successfully in the treatment of people with the morphia or cocaine habit.

The only conclusion at which I can arrive is that there is no danger of establishing a craving by giving daily therapeutic doses of phenobarbitone for a period up to twelve years, and that there is no evidence of such a person taking a dangerous overdose.

*Idiosyncrasy.*—During the first few years after the introduction of phenobarbitone, cases were frequently described showing a peculiar idiosyncrasy to the drug, which usually showed itself in the production of rashes. Several colonists, on admission, have said they were not given this drug as they were liable to develop rashes.

The risk of idiosyncrasy must be very slight, for there is no record of a rash being produced in a colonist here. As mentioned elsewhere, morning sleepiness is a normal accompaniment of phenobarbitone treatment when it is started, but in every case it has been slight in degree, and it has never lasted more than a fortnight.

Wildness and excitement have been produced in a few cases, but these people have all been strange and apathetic before the drug was given, and there was merely a change from one abnormal mental state to another.

During the last twelve months two people have said that the first few doses of the drug made them feel sick, but this quickly passed off, and did not recur after about the third dose.

Willcox briefly reports two cases of jaundice, supposed to have been produced by repeated small doses of the drug. Such exceptional cases show that an idiosyncrasy must occur in a certain few cases, but this happens so rarely that the possibility can almost be dismissed if anti-epileptic doses only are prescribed. Davis says that luminal rash can be avoided by combining the drug with sodium bicarbonate. Perhaps we do not get rashes in the Colony because we always prescribe phenobarbitonum solubile, which is alkaline.

*Colony treatment.*—Within the last twelve months I have seen two cases of epilepsy in children between 13 and 16 years old, who were so retarded that neither could fasten his shoes. Whenever they went out of the house it was in a motor car. Neither had been to school or mixed with other children, and for an annual treat one was taken to a matinee at a cinema.

Several boys have been admitted to the Colony, accompanied by a fussy and overfond parent who has told us never to let her son walk alone ; yet in three months they become ardent Scouts and play cricket. With such a home life how can these young people appear or become normal ?

The best results are to be expected from phenobarbitone only if the patient's surroundings are favourable. An epileptic reacts quickly to his environment and rarely improves in spite of his surroundings. When improvement begins a return to a difficult environment does retard or even prevent further recovery. Any worry or an atmosphere of " cannot " and " must not " delays recovery, and may even induce the recurrence of attacks long after they seem to have been banished by drugs. Muskens has noticed that some trifling modification of life may be enough to raise the patient's resistance sufficiently to stop the fits. With phenobarbitone treatment it is found that colony regime may supply just this extra condition required. In a colony food and personal habits are regular. A child leads a normal life, attending school, church, dancing classes, and joining the Scouts or Guides. Any deformity is treated by exercise or advice obtained from an orthopædic surgeon. An older person is encouraged to do genuine work, not being merely occupied ; he plays football and cricket, and does his shopping in the local villages. He goes home for holidays, but is usually glad to return. Fashion is quickly followed ; clothes must be made to measure for each individual ; not bought in bulk, hoping some will fit. When an epileptic finds he can do things like an ordinary human being, he determines to do them thoroughly. Some of the boys recently formed a hiking club, and their last walk was a distance of forty miles ; their hiking club must bear comparison with those outside. Football and cricket teams are made up entirely of colonists, and play in the local leagues ; Scouts attend jamborees, and compete with other troops in tent-pitching and bridge-building competitions. In this atmosphere of normality is the real essence of colony life, and with such an environment are present the most favourable conditions for treating epilepsy with phenobarbitone.

*Summary.*—This investigation was begun to test current opinions by

personally observing a large number of cases over long periods. The material available was the cases of epilepsy who have been or are now resident at the David Lewis Colony. This has eliminated any variation due to seasonal or individual differences and exceptional cases have taken up their proper position. It is shown how an epileptic may receive temporary benefit from any new form of treatment. When this ceases, an impression is obtained that tolerance is established, but this is not true tolerance. The real explanation of this temporary improvement is found in the mental attitude of the patient himself, who responds, but only for a time, to any form of treatment. After an exhaustive test, it was shown that phenobarbitonum solubile (B.P.) is the best drug for general use in an institution. Prominal is indicated in the treatment of those who are anxious to keep at work and can afford this expensive drug. Phenobarbitone greatly reduces the incidence of " jumps ", serial epilepsy, prolonged clonic convulsions and *status epilepticus;* but, with the exception of the first, once these conditions have begun they are not benefited by the drug, unless it is given in large soporific doses. In spite of warnings against prolonged medication, cases are reported who have taken daily therapeutic doses for periods up to twelve years. No sign of mental deterioration is produced, many are markedly improved. Although it is the custom when withdrawing the drug to do so gradually, by " tailing off ", our practice of sudden complete withdrawal has never been accompanied by any unpleasant symptoms. The evidence I have obtained strongly supports the opinion of authorities in Paris and Berlin, who say no craving is established. An idiosyncrasy to phenobarbitone may occur, but we have found that it never has done to the soluble alkaline drug. Most people agree that even if idiosyncrasy occurs, ample warning is given. Emphasis is laid on the importance of suitable environment if epilepsy is to be treated successfully. The possibility of danger in phenobarbitone treatment has been greatly exaggerated, and the severity of toxic symptoms very much magnified. The drug has undoubtedly diminished the incidence of serious sequelæ, and a patient becomes brighter and more equable when under its influence.