Section of Neurology

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Some Aspects of Epilepsy

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Drug Estimation in the Treatment of Epilepsy

There are a number of reasons for estimating the serum concentration of an anticonvulsant drug in the management of epilepsy, the most important of them being: (1) When it is not possible to predict the serum concentration produced by a given dose of the drug because genetic influences give rise to a wide range of rates of metabolism. (2) When the therapeutic range has been defined. (3) When this range is a narrow one and the upper limit borders on the toxic range, i.e. when the therapeutic ratio is narrow. (4) In the differential diagnosis of unusual neurological or psychiatric syndromes in a patient receiving anticonvulsant drugs. (5) When there is doubt about the patient's reliability in taking his tablets.

The measurement of serum phenytoin levels can be justified on each of these grounds. Not only is there a wide range of rates of metabolism of the drug, but, in addition, the enzyme which is responsible becomes saturated at higher serum concentrations, and this exaggerates the variation produced by genetic influences. The therapeutic range has been clearly defined (Buchthal *et al.* 1960, Lund 1973), and the upper limit, 20 μg/ml, is close to the toxic level in most patients. Although a characteristic cerebellar syndrome indicates phenytoin intoxication, atypical neurological or psychiatric symptoms occur not uncommonly and can confound the unwary (Glaser 1972). Unreliable drug taking is common in epileptic patients, and admission to hospital frequently leads to an increase in serum phenytoin concentration (Gibberd *et al.* 1970).

The indications for estimating anticonvulsant drugs other than phenytoin are less clear cut, and therefore interest will be confined to phenytoin in this paper.

Phenytoin is parahydroxylated to 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) by liver enzymes, and this substance is excreted in the urine. The activity of the hydroxylase enzyme is determined by genetic influences of a multifactorial nature (World Health Organization 1973) and therefore a unimodal distribution of serum levels is seen in a group of patients receiving a standard dose. Although a correlation is seen between the serum concentration of phenytoin and both the weight and age of the patient, these influences are small compared with genetic ones (Houghton & Richens, unpublished). Administration of the drug per kilogram of body weight in adults would achieve better control although the serum levels on a given dose would still be likely to vary from subtherapeutic to toxic from one patient to another. As a rule of thumb, increasing age and decreasing weight should demand a smaller starting dose of phenytoin, until adjustments can be made in the light of a serum phenytoin result.

Bochner *et al.* (1972) have shown that a non-linear relationship exists between the serum concentration of phenytoin and the daily dose of the drug. As the dose is increased the increments in serum level become larger. The reason for this steepening relationship is that the hydroxylase enzyme becomes saturated with phenytoin. Most drug metabolizing enzymes increase their rate of reaction in proportion to the serum concentration of the drug, and this leads to a more or less linear relationship between the concentration and daily dose. This appears to be true with phenobarbitone, where a doubling of the dose will produce approximately a doubling of the serum level. With phenytoin, however, the rate of reaction fails to increase in proportion to the serum con-

centration, and there is an upper limit to the rate of hydroxylation which is around the therapeutic range in many patients.

The development of enzyme saturation can be clearly demonstrated in two ways. The urinary excretion of p-HPPH fails to rise in parallel with the serum concentration of phenytoin, and the ratio of p-HPPH to unchanged phenytoin in the urine falls, indicating a relatively smaller increase of p-HPPH excretion than of phenytoin (Houghton & Richens 1974*a*). Furthermore, measurements of the serum half-life of phenytoin by administration of radioactive tracer doses of the drug to patients on maintenance therapy, have shown a progressive decrease in the rate of clearance of the tracer as the serum concentration of the drug rises by increasing the daily dose (Houghton & Richens 1974*a*).

The kinetics of phenytoin metabolism are best explained by the Michaelis-Menten equation. Fig 1 illustrates the change in serum phenytoin concentration produced in a 25-year-old male patient by increments of 25 mg from 200–300 mg daily. When admitted to the National Hospital – Chalfont Centre for Epilepsy he was intoxicated on 300 mg daily. An immediate reduction to 200 mg daily was made, and subsequently increases of 25 mg were made until the dose reached 275 mg. At least a month was allowed between each change, so that the serum concentration could reach steady state. The data were then analysed by a computer programmed to fit a curve according to the Michaelis-Menten equation. A good fit was achieved, and the resulting curve exemplifies the relationship which is seen between the dose of phenytoin and its serum concentration. In this patient a dose of 235 mg daily would have produced a serum concentration of 10 μg/ml (40 μM) which is the lower limit of the therapeutic range (Buchthal *et al.* 1960), whereas a dose of 290 mg would have achieved a level of 25 μg/ml (100 μM). This level is used as the upper limit of the therapeutic range in our laboratory. Thus, an increment of only 50 mg, equivalent to the smallest available tablet or capsule of phenytoin, would carry the patient's serum level from the lower limit to almost the upper limit. Obviously, a more usual increment of 100 mg, say from 200 to 300 mg, in this patient would cause intoxication when the previous level had been subtherapeutic.

The patient illustrated was a comparatively slow metabolizer of phenytoin, being intoxicated by a standard dose of 300 mg daily, but a similar relationship between serum level and dose probably exists in all patients. For a faster metabolizer the curve illustrated in Fig 1 would be shifted to the right, and larger increments in dosage could be made safely. Occasionally, however, patients metabolize the drug even more slowly than the patient illustrated, and a very steep curve might be expected in such a subject.

It is important that these kinetics be borne in mind when a phenytoin concentration in the therapeutic range is aimed at, for at these levels only small increments should be used. However, even if the physician knows what he is about, there are a number of pitfalls beyond his control. An unreliable patient does not have to forget many tablets each week to reduce his average dose by 50 mg per day. A small change in

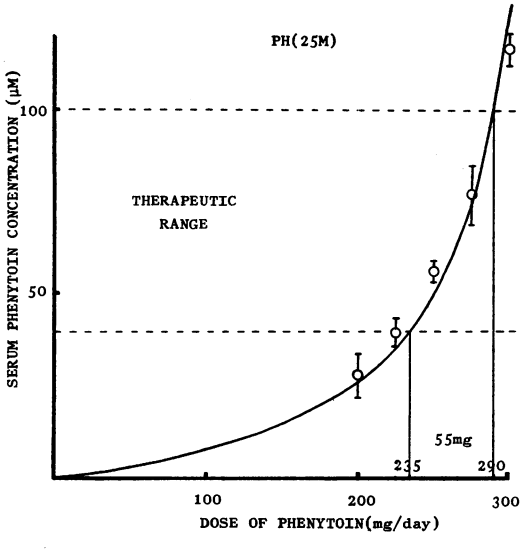

Fig 1 *Serum phenytoin concentration in a 25-year-old male epileptic patient receiving phenytoin at several different daily doses. Each point represents the mean ±s.d. of 3–8 separate estimations on a given dose. The curve drawn through the points was fitted to the Michaelis-Menten equation by computer. The horizontal dotted lines represent the upper and lower limits of the therapeutic range of the laboratory. From the computer plot it can be seen that a dose of 235 mg daily would produce a serum concentration at the lower limit of the therapeutic range in this patient, while a dose of 290 mg would be required to produce a level at the upper limit. The enzyme metabolizing phenytoin would be totally saturated at 344 mg daily*

bioavailability of phenytoin preparations could make all the difference between effective control and intoxication. A slight alteration in the activity of the hydroxylase enzyme in the liver might also lead to a marked change in the serum phenytoin level. Such an effect on the enzyme can be produced by adding other drugs such as sulthiame (Houghton & Richens 1974*b*, *c*), pheneturide Huisman *et al.* 1970), and isoniazid (Brennan *et al.* 1970), or perhaps by minor intercurrent infections or metabolic changes. These latter may well account for the occasional sudden occurrence of intoxication in a patient who has been stabilized for months or even years on the same dose of drugs.

There is no doubt that the kinetics of phenytoin create management problems and represent a great disadvantage to an otherwise invaluable drug. Perhaps what is most required is a reappraisal of the lower limit of the therapeutic range. If a level well below 10 μg/ml is compatible with adequate control in many patients, far greater stability of the serum concentration will be achieved because a greater change in enzyme activity or drug intake is allowable without too much change in serum level.

Summary
The measurement of serum phenytoin concentration in patients with epilepsy is a valuable aid to management because a wide range of serum concentrations occurs with a standard dose of the drug, many patients falling outside the therapeutic range. Phenytoin metabolism is a saturable process, and therefore a steep relationship exists between therapeutic serum phenytoin concentrations and the dose of the drug. This can result in difficulty in achieving a stable concentration.

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Field of Forel Lesions in the Treatment of Intractable Epilepsy

Encouraged by reports from Jinnai & Mukawa (1970) and Narabayashi & Mizutani (1970), and personal reports from Professor E S Watkins and from Dr C M Bertrand, we made bilateral stereotaxic field of Forel lesions in patients whose epilepsy was so frequent, and poorly controlled by drugs, as to make their lives burdensome to themselves and for those caring for them. The principal criterion in accepting patients for consideration of surgical treatment was the frequency of the attacks. Most of the patients were having 8 or 10 or even more fits daily, in spite of heavy medication given even to the point of toxicity.

The fields of Forel are situated between the thalamus above, the medial border of the internal capsule laterally, the subthalamic nucleus of Luys below, and the posterior hypothalamic nuclei medially. They are composed of the dorsal and ventral tegmental areas with the zona incerta between them. Fibres passing through the dorsal tegmental area come from the red nucleus and mid-brain, and radiate to the thalamus, striatum and cortex. The ventral tegmental area largely consists of efferent pallidal fibres to the substantia nigra, and red nucleus. The zona incerta which lies between the tegmental areas is in part nuclear and in part contains fibres radiating between the neighbouring structures. The rationale for Forel lesions in the treatment of centrencephalic epilepsy is not clear. To be successful presumably bilateral lesions would be necessary.

Preoperative investigations included IQ assessment, a number of EEG recordings, skull X-ray, pneumo-encephalography, and CSF examination.