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EFFECT OF PHENYTOIN ON SERUM PHENOBARBITONE LEVELS

DEAR SIR,

Although the clinical importance of the observations is still unclear, the influence of phenobarbitone on serum phenytoin levels in epileptics is well documented, e.g. Kutt *et al.* (1969) and Sotaniemi *et al.* (1970). However, the converse relationship has received little attention. I wish to report some preliminary findings on the relationship between serum phenobarbitone levels and dose during long-term phenobarbitone administration, with and without the concurrent administration of phenytoin.

Steady-state anticonvulsant levels were determined, using the isothermal gas liquid chromatographic procedure of Toseland *et al.* (1972). The estimations were performed on serum samples from male mentally retarded epileptic in-patients of Stoke Park Hospital, Bristol. The patients fell into two groups: Group 1 consisted of 54 patients receiving phenobarbitone for anticonvulsant therapy, and Group 2 consisted of 21 patients receiving phenobarbitone with phenytoin. The mean ages of the patients in the two groups were 35·5 years (range 15–68) and 33·4 years (range 16–56) respectively. All patients had been receiving anticonvulsant therapy for a number of years. Two patients in Group 1, and three patients in Group 2 were receiving drugs for disorders other than epilepsy.

The results of a total of 106 estimations are displayed graphically in the accompanying figures. It was found that for a given dose of phenobarbitone the mean serum phenobarbitone concentration was significantly greater in patients receiving this drug in combination with phenytoin than it was in patients receiving phenobarbitone alone. The relationships between serum levels and dose of phenobarbitone are given by the regression equations $y = 7{\cdot}14\,x + 2{\cdot}14$ for Group 1, and $y = 9{\cdot}58\,x + 6{\cdot}70$ for Group 2. The correlation coefficients for the two groups were respectively 0·79 ($p < 0{\cdot}001$) and 0·74 ($p < 0{\cdot}001$), validating the claim of Buchthal and Lennox-Buchthal (1972) that serum phenobarbitone levels correlate reasonably well with dose of the drug. The serum levels of phenobarbitone in the patients on combined therapy could not be related either to the serum levels or to dosage of phenytoin.

The elevation of serum phenobarbitone concentrations by methylphenidate has been described by Garrettson *et al.* (1969), and Rizzo and co-workers

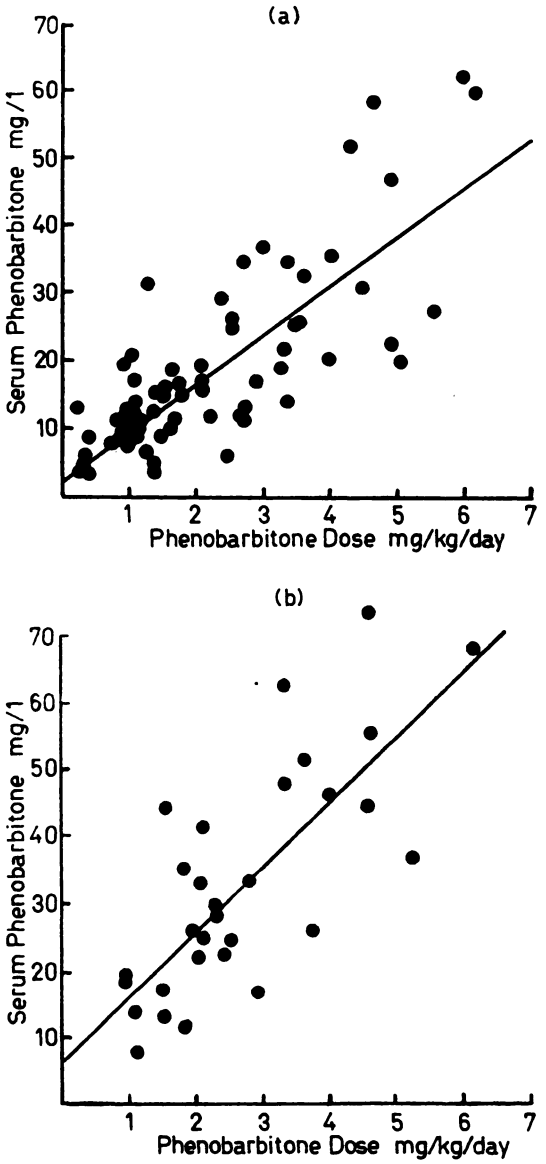

FIG.—Serum phenobarbitone concentrations plotted against the phenobarbitone dose in epileptic patients receiving phenobarbitone (a) and phenobarbitone and phenytoin (b) anticonvulsant therapy.

(1972) have shown, in acute experiments, that phenytoin enhances plasma phenobarbitone levels in rats. Morselli *et al.* (1971) showed that administration of phenytoin to five children who had been receiving phenobarbitone 'for at least 15 days' caused a 1·5 to 4-fold elevation of plasma phenobarbitone levels 'after several days of combined treatment'. The findings presented here show that a similar effect occurs during long-term combined phenobarbitone and phenytoin therapy. The biochemical mechanism underlying this effect remains to be clarified, as does its relation to seizure control. The findings would indicate the necessity of monitoring serum phenobarbitone, as well as phenytoin, levels in epileptic patients receiving combination anticonvulsant therapy.

I should like to thank Dr. J. Jancar, Consultant Psychiatrist, Stoke Park Hospital, for permission to study his patients.

J. D. Cameron.

Department of Pathology,
Frenchay Hospital,
Bristol, BS16 1LE.

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TEMPERATURE FALL AFTER ECT

Dear Sir,

Has anyone noticed a fall in temperature in those patients who have had ECT? I have found a fall in temperature in all of ten patients who have been receiving ECT for depression. The fall in temperature varied from a 2 °C–5 °C and lasts for about one to two hours. A fall begins within fifteen to thirty minutes of receiving ECT. The anaesthetic used was methohexitone sodium (Brietal) and the relaxant used was suxethonium bromide (Brevidil).

I am postulating that one of the temperature-regulating centres in the hypothalamus is interfered with by ECT—either as a direct action of the electrical current or indirectly through the fronto-hypothalamic pathways. It may be that the alteration of body temperature after ECT results from stimulation of the anterior centre rather than being part of the normal body homeostasis.

It is interesting to note that the hypothalamus is an important area for mood change in animals. This hypothesis would suggest that possible mood centres in the hypothalamus are influenced by ECT as well as the temperature regulation centres, and would thus account for the remarkable way in which ECT alters a depressed patient's affect for the better in such a short time.

P. V. F. Cosgrove.

Barrow Hospital,
Barrow Gurney,
Near Bristol.