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ABRUPT WITHDRAWAL OF ANTIPARKINSONIAN DRUGS IN CHRONIC SCHIZOPHRENIC PATIENTS

DEAR SIR,

Dr. Peter Hall (*Journal*, July 1974, p. 110) has made a number of pertinent comments on our article (*Journal*, Feb. 1974, p. 151). We would like to discuss these and draw the attention of readers to some recent publications.

(1) Our trial excluded patients aged over 70 years, and this does indeed limit the practical application of our findings. We could have emphasized this in our discussion. (2) We did not find that an increased number of patients on depot injections 'developed' extrapyramidal symptoms when AP drugs were withdrawn. The table heading and the text make it clear that there was a one point *deterioration* on the rating scales. In the discussion we note that EPS have been found to be very common in patients on neuroleptic drugs, whether or not receiving AP medication. The 'deterioration' in our patients was found on careful neurological examination and did not cause patient discomfort or warrant AP resumption. Such deterioration was therefore statistically and clinically non-significant. It should be distinguished from the overt clinical relapse in a small minority of our patients. (3) Our low relapse rate compared with other studies from the U.S.A. could well be a reflection of the lower neuroleptic dosage regimes used in this country, and we discussed this very point. (4) We accept that the peripheral side effects are more marked with benzhexol. The central side effects do occur with other AP drugs (El-Yousef, *et al.* 1973; Meyler and Herxheimer, 1972).

While our article was in press two further investigations on chronic schizophrenic patients have been published. A double-blind cross-over study by Mindham *et al.* (1972) showed no difference in parkinsonian side effects in 35 patients on fluphenazine decanoate (25 mgm. every four weeks) irrespective of whether they were taking amantidine, orphenadrine or placebo. Chien *et al.* (1974) studied 41 patients on fluphenazine enanthate (average dose 37·5 mgm. every 13·2 days) and found that the incidence of EPS was similar whichever one of three AP drug regimes were in use (one regime entailed AP medication only at the time of occurrence of acute EPS), but that severe EPS were less frequent in the maintenance AP medication groups. These authors concluded that the routine prophylactic use of AP drugs with depot injections was questionable, but further research was necessary. Their more equivocal findings compared with the studies of other investigators, including Mindham and ourselves, are probably due to their use of the enanthate preparation in higher doses.

The development of tardive dyskinesia in patients on neuroleptics causes considerable concern. Articles by Klawans (1973), Fann *et al.* (1974), Gerlach *et al.* (1974), implicate the anticholinergic action of AP drugs in accentuating a dopaminergic-cholinergic imbalance that is believed to be responsible for the dyskinetic movements. If confirmed, this makes the cautious use of AP drugs imperative.

We feel that the weight of evidence is against routine long-term prescribing of antiparkinsonian medication with neuroleptics. That some patients continue to need AP drugs we do not deny, but the clinician should actively determine which patients are in such need. We have had no difficulty in doing this on an out-patient basis by careful dosage reduction.

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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

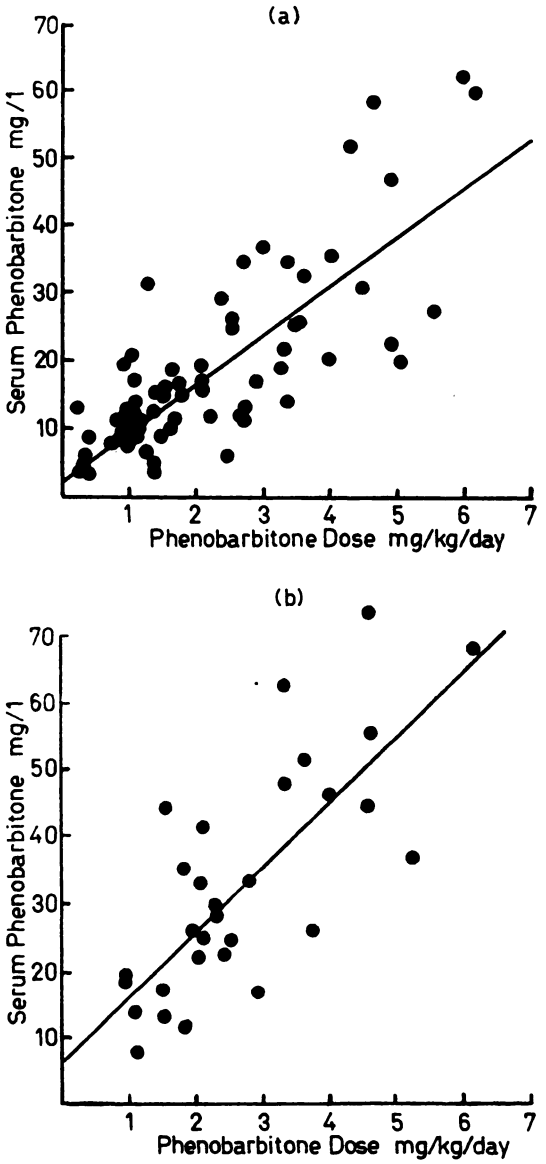

FIG.—Serum phenobarbitone concentrations plotted against the phenobarbitone dose in epileptic patients receiving phenobarbitone (a) and phenobarbitone and phenytoin (b) anticonvulsant therapy.