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Acute effect of phenytoin on serum folate concentration

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Many epileptic patients have subnormal serum folate concentrations, which have been attributed to long-term anticonvulsant therapy. Klipstein (1964) reported that the highest incidence of subnormal serum folate concentrations occurred in epileptic patients who had been treated with phenytoin for long periods, but found no correlation between drug dose and the concentration of serum folate. The present

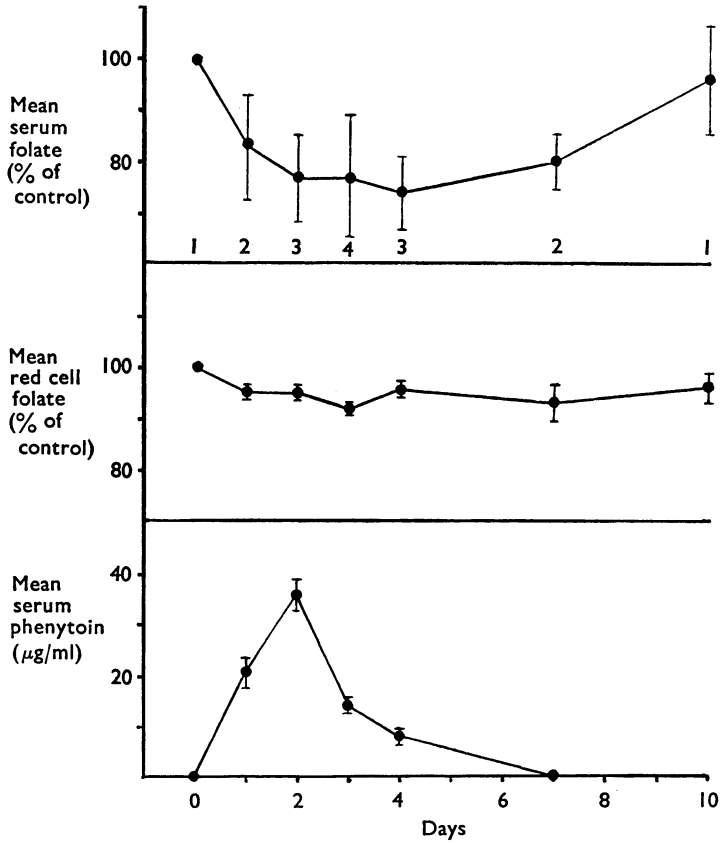

FIG. 1. Mean (±S.E.) values of the concentration of folate in serum, and red cells, and of phenytoin in serum of six subjects receiving 1,600 mg of phenytoin sodium orally during the first 4 days of the experiment. The folate concentrations have been expressed as a percentage of the control before treatment. The figures below the serum folate curve represent the number of subjects having a subnormal serum folate on the respective days.

experiment investigates the effect on concentrations of folate in serum and red cells of a short course of phenytoin in normal subjects. Six subjects each took 1,600 mg of phenytoin sodium orally over 4 days as follows: 600 mg on day 1, 400 mg on day 2, and 300 mg on day 3 and day 4. Folate estimations were performed using an automated assay with a chloramphenicol resistant strain of *Lactobacillus casei* (Millbank, Davis, Rawlins & Waters, 1970).

Five of the six subjects showed a gradual fall in concentration of serum folate during the 4 days of treatment (Fig. 1), and four subjects had developed subnormal values (<4·0 ng/ml) by day 3. Six days after stopping the drug, serum folate returned almost to control concentration. Red cell folate concentrations fell only slightly. Phenytoin had only a slight, if any, effect on the assay system in a concentration of 100 μg/ml (L. Millbank, personal communication), which is higher than the peak serum phenytoin levels in the subjects studied (Fig. 1).

These findings suggest that the acute fall in serum folate concentration is due to a disturbance of folate metabolism caused by the administration of phenytoin. The mechanism of this effect is still unexplained. Phenytoin may inhibit intestinal 'conjugase' (polyglutamate hydrolase) and thereby impair the absorption of polyglutamates in food (Hoffbrand & Necheles, 1968; Rosenberg, Godwin, Streiff & Castle, 1968; Rosenberg, Streiff, Godwin & Castle, 1969), but conflicting results have subsequently been reported (Baugh & Krumdieck, 1969; Bernstein, Gutstein, Weiner & Efron, 1970). However, recent observations (Hepner, Brown, Cohen, Herbert & Janowitz, 1970; Hepner, Aledort, Gerson, Cohen, Herbert & Janowitz, 1970), show that phenytoin impairs the absorption of pteroyl-glutamic acid, and that this may be due at least partly to inhibition of intestinal ATP-ase activity. Another possibility is that phenytoin induces liver enzyme systems which are important in folate metabolism, by analogy with the disturbance of vitamin D metabolism by anticonvulsant drugs which has recently been reported (Richens & Rowe, 1970; Dent, Richens, Rowe & Stamp, 1970). The observed time course would be compatible with such an explanation.

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