Anticonvulsant Osteomalacia and Vitamin D

SIR,—Controversial data concerning the effect of vitamin D on anticonvulsant osteomalacia have recently been reported in the *B.M.J.*[1-3]

In 1971 we reported a preliminary study using photon absorptiometry in which we found decreased bone mineral content (B.M.C.), decreased serum calcium values, and increased alkaline phosphatase activity in nine epileptic patients treated with anticonvulsants as compared with 10 psychiatric patients resident in the same epileptic colony.[4 5] Six months' treatment with 50 000 IU vitamin D_2 daily was unable to affect the mean values of B.M.C. in any of the groups.[6] In the following year both groups were given a reduced dose of 2400 IU vitamin D_2 daily without dietary calcium supplements, but the B.M.C. values remained constant. In the following six months a dietary calcium supplement of calcium lactate 3 g/day was added to the vitamin D treatment, B.M.C. values remaining unaltered. The serum calcium values gradually returned to normal and have remained normal since the eighth month of vitamin D treatment. Serum alkaline phosphatase levels remained elevated in the epileptic patients during the whole period of treatment.

Our results of long-term treatment with varying doses of vitamin D and calcium intake in a small group of epileptic patients are in some respects in disagreement with those of Christiansen *et al.*,[1] who were able to demonstrate a 4% increase in B.M.C. following three months' treatment with 2000 IU vitamin D_2 and calcium supplements in a large group of epileptics.

Our finding of unaltered serum alkaline phosphatase values for more than two years of treatment seem to support the assumption of Rowe and Stamp[2] that the elevated levels in adult epileptics are mainly due to increase in the hepatic isoenzyme.

We have been unable to relate variations in serum calcium to B.M.C. values, but we agree with the statement of Christiansen *et al.* that prophylactic vitamin D supplements might prove to be beneficial to antiepileptic-treated patients.—We are, etc.,

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Possible Hazard of Nitrous Oxide for Hysteroscopy

SIR,—It is now our practice to use nitrous oxide rather than carbon dioxide for laparoscopy, the reason being that the use of carbon dioxide may lead to a rise in arterial P_{CO_2} and subsequent cardiac irregularities.[1 2]

Recently we have been studying changes in arterial P_{CO_2} using arterialized capillary samples. During hysteroscopy when carbon dioxide was used as the insufflating gas the arterial P_{CO_2} either fell or was unchanged in artificially ventilated patients. However, when nitrous oxide was used arterial P_{CO_2} rose and in two patients this rise was of the order of 1·6 kPa (12 mm Hg) in the first five minutes. One of these patients, who was apparently in good health, developed a profound bradycardia some eight minutes after hysteroscopy was started and required resuscitation.

We are at a loss to explain this apparent difference between hysteroscopy using carbon dioxide and nitrous oxide but feel that we should publish our preliminary findings as a warning to others.—We are, etc.,

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Plasma Levels of Antidepressants and Anticonvulsants

SIR,—The discussion in your correspondence columns (30 November, p. 533 and 11 January, p. 91) about the value of plasma concentrations of nortriptyline (or other tricyclic antidepressants) and the possible existence of a "therapeutic" range below and above which there is no clinical response might usefully be extended, and perhaps illuminated, by reference to plasma anticonvulsant levels, for which some similar problems and questions exist.

Following the initial studies of Buchthal *et al.*[1] it seems to have been widely accepted that the "therapeutic" range for phenytoin is 40-80 μmol/l (10-20 μg/ml).[2] But the fact remains that it is not uncommon to find epileptic patients whose seizures are controlled with plasma levels of phenytoin below 40 μmol/l (10 μg/ml) as well as others with continuing attacks despite a plasma level within the recommended range. Furthermore, several studies have failed to demonstrate significant differences in plasma levels of phenytoin in patients with well-controlled or poorly controlled epilepsy, or have even found higher levels in the latter group.[4] However, it is also true that many other patients with continuing seizures and low plasma levels of phenytoin benefit considerably by elevation of the plasma level into the 40-80 μmol/l (10-20 μg/ml) range.

Probably the major factor in understanding these observations is the severity of the underlying epilepsy. Well-controlled groups include some patients with relatively mild epilepsy responding to small doses of the drug, while poorly controlled groups usually include patients receiving large doses in an unsuccessful attempt to control severe epilepsy. Therefore, though there is no universal "therapeutic" range applicable to all patients, most benefit to most patients of the moderate to severe type is achieved with blood levels within the range recommended by Buchthal *et al.*, but obviously this will not improve or control all patients. One advantage of this knowledge for the patients is that it should not be necessary to add or substitute a second drug unless and until it has been shown that phenytoin has failed despite a plasma level in what may be properly called the "optimum range."

Above 80 μmol/l (20 μg/ml) there is an increasing prevalence of clearly recognizable toxic effects of phenytoin (nystagmus, ataxia, confusion), but though other patients apparently tolerate such high levels, another advantage of the plasma level determination has been the detection of previously unrecognized toxicity, especially mental symptoms.[6] Whether plasma levels above 80 μmol/l (20 μg/ml) confer any additional protection against epilepsy is uncertain, but those who have argued that there is an upper level of plasma nortriptyline above which antidepressant effects are not seen may be interested to know that there is some evidence that toxic plasma levels of phenytoin may actually aggravate seizures.[3]

The usefulness of blood levels of phenytoin as well as other anticonvulsants (for which similar considerations are applicable) have been emphasized by many,[2 3] especially in view of the increasing recognition of the hazards of chronic polypharmacy in epilepsy.[7]—I am, etc.,

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Poisoned Children

SIR,—We have been interested in the comments by Dr. J. R. Sibert (26 October 1974, p. 231) and Drs. A. W. Craft and R. H. Jackson (11 January, p. 95) on the study of suspected poisonings in children carried out by the Medical Research Division of the Health Education Council. May we restate our personal propositions?

(1) That cases of suspected poisoning in children can be divided into two groups, which we may call "poisoning scares" and "true poisoning." Poisoning scares are those cases where medical care has been sought but where the substance has not been taken, or is non-toxic, or too little has been taken to hurt, or it has been spat out or removed before it has been swallowed. True poisonings are those cases where the ingested substance produces undesirable symptoms or where prompt medical treatment arrests their development.

(2) That an epidemiological survey[1] carried out in a defined population of 23 000 children showed that of the 183 cases of suspected poisoning in the study period over 65% were poisoning scares as defined above.

(3) That in assessing the effects of any preventive measures or treatment poisoning scares and true poisonings must be distinguished. Changes in the incidence of one may be independent of changes in the incidence of the other; and the consequences of one are different from the consequences of the other.