aggravate the situation; whether it plays any significant role in lowering the plasma level is very doubtful.

The second point is more important—the suggestion that epileptic women on anticonvulsant drugs should not be given folic acid supplements during pregnancy unless "megaloblastic anaemia actually occurs," because of a risk of increased fits. The clinical evidence for an increase in fits following folic acid supplements in epilepsy has been disputed. But on the other hand there seems no doubt that anticonvulsants can provoke a measure of folate deficiency, which may not necessarily develop into overt megaloblastic anaemia. The dilemma becomes particularly acute with anticonvulsant therapy during pregnancy. The possibility of a lower fit threshold must be balanced against the potential hazards to mother and fetus of some insidious disturbance of folate metabolism. Until we know much more about the complex metabolic inter-relations of folate and anticonvulsant drugs, particularly in pregnancy, Dr. Hall's advice seems a little injudicious.—We are, etc.,

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1 Landon, M. J., and Hytten, F. E., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1971, **78**, 769.

Death during Dental Anaesthesia

SIR,—Dr. J. G. Bourne (16 March, p. 516) has undoubtedly done a useful service in drawing attention to the dangers of fainting in the dental chair. I have given between 400 and 800 dental anaesthetics annually, the great majority in the 45° sitting position, for the past 30 years. In this time, however, I have only once observed a faint before or during anaesthesia, and this, as in Dr. W. N. Rollason's case (25 May, p. 444), occurred on venepuncture and before the injection of an intravenous anaesthetic. The occasional patient has, of course, shown a vasovagal response to a postoperative nausea or vomit, but none has proceeded to unconsciousness and all have responded promptly to treatment.

This experience prompts me to ask why I have been more fortunate than some others. It may be that the circumstances of private practice are, in some respects, more favourable than outpatient clinics. The patients generally know the dentist well and may also know me, the anaesthetist, personally. The sessions are short, usually three to five cases, and by having them in the early morning the patients are not hanging about a large part of the day with nothing in their bellies. It is unusual for them to be kept longer than a few minutes in the waiting room. Consequently it is rare for them to come to operation looking pale and frightened, and when they do extra care is taken.

In short, what strikes me most about these difficult cases is the presence of pathological fear. If this is protracted (and, maybe, aggravated by pain and toxic absorption) we have a situation in which the patient's adrenocortical response mechanism is exhausted before it is confronted with anaesthetic or surgical insults. This, I believe, is of greater significance than either the particular anaesthetic technique, or the agents used—provided of course that they are correctly applied—or indeed the exact position of the patient in the dental chair.

While not disputing the potential added safety of the horizontal position, therefore, I wonder whether stressing it is not putting the accent in the wrong place. Would it not be as well to teach (1) that greater efforts should be made to protect patients from the stresses which lead to a fainting reaction and (2) that pale and frightened patients are very special risk patients who need extra care in their management?—I am, etc.,

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Cremophor EL as a Diluent for Diazepam

SIR,—Diazepam has proved a safe and reliable drug though there have been many reports of minor sequelae after intravenous administration. Pain during injection has been reported in 15% to 22% of patients[1 2] and a 3·5% to 30% incidence of postoperative venous thrombosis or thrombophlebitis has been found.[1 3] There seems to be no correlation between pain during injection and postoperative venous sequelae.[3]

Dilution of diazepam with water or saline reduces the incidence of these side effects[4] but an emulsion of fine particles is produced.[5] We have found that, if freshly prepared, these emulsions will clear when mixed with an equal volume of serum. However, if the emulsion is allowed to stand for a short time solid crystals which are insoluble in serum gradually form. It would therefore seem that the intravenous injection of such emulsions presents a potential hazard. Cremophor EL has the ability to take into solution a variety of agents which themselves are only sparingly soluble in water, a 20% solution being used in preparations of both propanidid and Althesin. We have found that when diazepam is diluted with a 1% solution of cremophor EL no clouding or precipitation occur. The mixture is stable for some time and it does not form a precipitate when added to serum. Though cremophor EL appears to be a safe organic solvent[6] possibly it may very occasionally be responsible for adverse reactions in susceptible subjects. In view of this we are at present studying the use of a 10% mixture of ethanol in saline as an alternative diluent.

Over the past two years we have used a 1% solution of cremophor EL in saline as a diluent for diazepam given intravenously in over 400 patients. Before use the cremophor solution was filtered, put into ampoules, and autoclaved: 8 ml of the solution was used to dilute 2 ml of diazepam, giving a mixture containing 1 mg/ml. Use of this mixture has practically eliminated the incidence of pain during injection, even when into small veins on the back of the hand. Postoperative venous thrombosis and thrombophlebitis occurred in fewer that 1% of patients.—We are, etc.,

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Flupenthixol Decanoate and Some Aggressive States

SIR,—There is no reference in the English medical literature to the use of flupenthixol in remote reactions. Because neuroleptic drugs as a group have sedative properties of a special order I gave flupenthixol decanoate to six patients in doses of 10-12 mg fortnightly by deep intramuscular injection. The patients all had a common factor—extremely low tolerance to frustration. Their reaction to this was either a sudden outburst of rage or the development of sullen hate with a later manifestation of aggression against the object that had induced the complex mood.

They all benefited with a marked reduction of the underlying anxiety and cessation of this form of aggression. There was an improvement in concentration, no lessening of drive, and no evidence of anergia. The relief occurred within three weeks of commencing treatment. No anticholinergic drugs were required. Naturally, they were happier people and their rapport with friends and family improved.

I lay no claim to having found a universal panacea for aggressive behaviour but the straws in the wind do seem to indicate that there is a place for the use of this drug or its oral form, flupenthixol dihydrochloride, outside the treatment of the schizophrenias. I would be very interested to hear if others using this drug have noted any like reaction. —I am, etc.,

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Measurement of Side Effects of Drugs

SIR,—Drs. E. C. Huskisson and J. A. Wojtulewski (29 June, p. 698) suggest that when assessing the proportion of patients with side effects from drug therapy the interviewing doctor should not consult a check list. They found that direct questioning increases the number of positive responses in a group not receiving the treatment and reduces the number of positive responses to questions not on the check list.

They suggest that the doctor should ask, "Have you noticed any new symptoms which might be related to the treatment?" This method of collecting information suffers from a lack of standardization. The exact question asked may vary, and the "sympathetic" doctor receives more positive responses. The results thus obtained may not be reproduced by another observer, and may account for the wide variation in the prevalence of side effects reported in different publications. An example is given by methyldopa and sleepiness. In well-designed and conducted studies the proportion complaining of sleepiness while taking this drug varies between 12%[1] and 83%.[2] Research workers investigating symptoms and side effects require to know the prevalence of these complaints in the general population