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Enhancement of recovery from psychiatric illness by methylfolate

SIR: We were disappointed with Dr Procter's appraisal of the paper by Godfrey *et al* (1990) (*Journal*, August 1991, **159,** 271–272) which we felt was seriously flawed, but no criticism of the study was mentioned.

The study selected patients on the basis of borderline – low red cell folate (< 200 µg/l) although only 17 of 41 patients had actual folate deficiency (< 150 µg/l). Although the Hamilton Rating Scale for Depression was used as an outcome measure, there was no mention of baseline scores, threshold for inclusion, or the comparability of placebo-treated and methylfolate-treated groups. The overall clinical rating score, a crude four-point scale, was the major outcome measure, and no mention was made of the change in HRSD from baseline. A surprising finding that Beck scores correlated poorly with clinical outcome would suggest that the folate-treated patients were not as impressed by their folate supplementation as the researchers were.

Methylfolate was added to clinically determined 'standard' treatment, but the author's claim that depressed-folate and depressed-placebo patients received similar standard treatments is clearly not true. Lithium carbonate would not be considered by many to be a suitable first line out-patient antidepressant, meaning that six of 11 placebo-treated patients received an antidepressant (all tricyclics), while 11 of 13 folate patients did so (9 tricyclics, 2 monoamine oxidase inhibitor). Furthermore, there is no comment about dosages and whether these were similar.

By six-month follow-up, when the difference between the depressed groups was most significant, mean red cell folate of placebo patients was well in the normal range, but no comment was made as to how a normal value related to mental state.

We do not contest the view that the folate–mental disorder connection deserves further attention, but advise against overemphasising the importance of this study. We cannot agree with Drs Godfrey *et al* when they claim to have shown that replacement therapy with folate enhances the clinical response to standard psychotropic treatment or with their overstated view that the study 'provides the most compelling evidence yet' that folate and mental state are connected.

We are presently studying plasma methylfolate values in depressed patients receiving ECT, and preliminary results do not suggest a simple relationship with outcome. Twenty-seven patients with DSM–III major depression with melancholia or psychosis (mean HRSD score 33), who all received ECT, had lower plasma 5 methyltetrahydrofolate (5MeTHF) than 12 laboratory controls. Pre-ECT 5MeTHF values did not distinguish patients responding to ECT. Post-ECT folate levels were not significantly different between ECT responders and non-responders.

There are, of course, many mechanisms by which folate deficiency may influence depression (Abou-Saleh & Coppen, 1986). A metabolic connection rarely mentioned is that between folate and tetrahydrobiopterin (BH4), the essential cofactor for the formation of noradrenalin, 5-HT and dopamine. We have found evidence of impaired BH4 synthesis in severe depression which related to response to ECT (Anderson *et al*, unpublished). Tetrahydrofolate is required for BH4 synthesis, and a positive correlation has been found between plasma folate values and the urinary excretion of biopterin in euthymic patients attending a lithium clinic (Coppen *et al*, 1989). Further investigation of these associations is under way.

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