



Folic acid to prevent neural tube defects

SIR,—As the MRC Vitamin Study team (July 20, p 131) points out, their results can be applied directly only to women with a previously affected pregnancy. About 95% of NTDs occur in pregnancies with no such history. Such women could take the 4 mg folic acid per day used in the trial during the years when they might become pregnant. Although this would ensure protection, it would not be without risk because of the very high dose of folic acid involved. One can derive little comfort from the long-established safety of such doses when taken later in pregnancy; the risk during early embryonic development is not comparable.

We suggest an increased risk apart from that from a high level of circulating folate. The normal daily median intake of dietary folate for British women is 209 µg.¹ At these levels the various forms of dietary folate are converted, during their passage through the intestine and liver, to the single circulating form of 5-methyltetrahydrofolate (5-MTHF).² This process is easily saturated and at higher levels of synthetic folic acid progressively more of it appears unmetabolised in the urine.³ After an oral dose of 500 µg a small but detectable level of unmetabolised folic acid appears in the urine but at levels of 4000 µg urinary folic acid amounts to more than one-quarter of the dose administered.^{3,4} This excess has to pass through the systemic circulation to get from the gut to the kidney. Thus a developing embryo would probably be exposed to unmetabolised folic acid—a form of the vitamin which it would not normally encounter. Folic acid is a neurotoxin⁵ and convulsant⁶ in laboratory animals. Although the blood/brain barrier normally restricts access of folic acid so that very high doses are required to produce these effects, similar toxicity occurs at much lower doses if the blood/brain barrier is damaged.⁷ In epilepsy, treatment with doses of folic acid of the order of those used in the trial increased seizure frequency.⁸ Whilst the normal fully developed brain may be protected from the neurotoxic effects of synthetic folic acid, we do not know whether neural tissue during early embryonic development is similarly protected.

Women with no obstetric history of an NTD who may become pregnant may be advised to protect themselves by taking a lower dose of folic acid or more food that is rich in or fortified with folate—but would such a regimen be effective? Perhaps it is folic acid itself rather than 5-MTHF that is effective. Yates et al⁹ found significantly lower red-cell folate levels in women with a history of two or more NTD pregnancies, compared with controls matched for age, obstetric history, and social class. The serum folate status and that of a range of other nutrients were the same. Low red-cell folates in the face of normal serum folates is usually associated with an inability to demethylate circulating 5-MTHF, a step necessary for its retention by all cells. This happens, for example, in vitamin B₁₂ deficiency. While the women in Yates' study and in a larger one¹⁰ had normal vitamin B₁₂ status, another study revealed accumulation of plasma homocysteine in NTD pregnancies,¹¹ perhaps indicating a metabolic block of demethylation. This could mean that folic acid would be effective whereas its methylated reduced counterpart would not.

There is thus a conflict between the option of taking high-dose folic acid known to be beneficial but which may have some neurotoxic or other risk, or a smaller dose (or increased dietary folate) that would reduce or eliminate the risk of toxicity but might be ineffective. We suggest that the trial of primary prevention now underway in China should be modified to contain a high-dose arm (to confirm the effect found in the MRC trial) and a low-dose arm of

400 µg or 200 µg folic acid. Almost all of a 200 µg or 400 µg dose of folic acid would be converted into 5-MTHF. An alternative would be to include an arm with 200 µg or 400 µg 5-MTHF: if that prevented NTD one would be reasonably confident that a woman contemplating pregnancy could avoid NTD in her baby by taking either low-level folate preparations or improved or even fortified diet high in folate.

Biochemistry Department,
Trinity College,
University of Dublin,
Dublin 2, Ireland

Health Research Board, Dublin

St James's Hospital, Dublin

Trinity College, Dublin

J. M. SCOTT

P. KIRKE

S. O'BROIN

D. G. WEIR

1. Gregory J, Foster K, Tyler H, Wiseman M. The dietary and nutritional survey of British adults. London: HM Stationery Office, 1990.
2. Rosenberg IH, Godwin HA. The digestion and absorption of dietary folate. *Gastroenterology* 1971; 60: 445-63.
3. Scott JM, Weir DG. Excretion of folates, pterins and their metabolic products. In: Blakley RL, ed. Folic acid and pterins. New York: Wiley, 1966: 297-324.
4. Saleh AM, Phemant AE, Blair JA, Allan RN. The effect of malignant disease on the metabolism of pteroylglutamic acid in man. *Biochem Soc Trans* 1980; 8: 566-67.
5. Olney JW, Fuller TA, de Gubareff T, Labruyere J. Intrastriatal folic acid mimics the distant but not focal brain damaging properties of kainic acid. *Neurosci Lett* 1981; 25: 185-91.
6. Baxter MG, Miller AA, Webster RA. Some studies on the convulsant action of folic acid. *Br J Pharmacol* 1973; 48: 350-51.
7. Hommes OR, Obbens EAMT, Wijffels CCB. Epileptogenic activity of sodium-folate and the blood-brain barrier in the rat. *J Neurol Sci* 1973; 19: 63-71.
8. Strauss RG, Bernstein R. Folic acid and dilantin antagonism in pregnancy. *Obstet Gynecol* 1974; 44: 345-48.
9. Yates JRW, Ferguson-Smith MA, Shenkin A, Guzman-Rodriguez R, White M, Clark BJ. Is disordered folate metabolism the basis for the genetic predisposition to neural tube defects? *Clin Genet* 1987; 31: 279-87.
10. Molloy AM, Kirke P, Hillery I, Weir DG, Scott JM. Maternal serum folate and vitamin B₁₂ concentrations in pregnancies associated with neural tube defects. *Arch Dis Child* 1985; 60: 660-65.
11. Steegers-Theunissen RP, Boers GH, Trijbels FJ, Eskes KA. Neural-tube defects and derangement of homocysteine metabolism. *N Engl J Med* 1991; 324: 199-200.

SIR,—The outcome of the MRC study will be an increase in the consumption of folic acid by all women planning pregnancies, as advocated by the MRC group. Women planning several pregnancies may continue to take the vitamin for a long time. As the study team and your editorial point out, the risks of such a policy whether at high or low dose of folic acid are not yet known.

It remains possible that excess folate as well as folate deficiency harms the developing nervous system (as for the adult nervous system), as has been reported, for example, with vitamin A excess.¹ Another possibility is the precipitation of subacute combined degeneration (SCD) in women with incipient or unrecognised vitamin B₁₂ deficiency. SCD can occur at childbearing age; I have recently seen an example in a 26-year-old. In the avoidance of this complication the serum vitamin B₁₂ level is not entirely reliable. Vitamin B₁₂ deficiency is occasionally present at serum B₁₂ levels above 200 pg/ml.² My colleagues and I have described a 31-year-old man with vitamin B₁₂ deficiency in whom SCD was precipitated by prolonged inappropriate treatment with folic acid.³ The correct diagnosis had been overlooked because he had a high serum vitamin B₁₂. Another very rare complication of excess folate therapy that I have observed is hypomania in patients vulnerable to manic-depressive illness, as has also been reported with the closely related metabolite S-adenosylmethionine.⁴