If we are to succeed in reducing the number of pregnancies in which the fetus has a neural tube defect we must adopt a policy of fortification of food. This approach is both simple and cheap and most likely to serve those at risk.

CATHERINE BOON
Trainee in general practice
SALLY HULL
General practitioner

Jubilee Street Practice,
Steels Lane Health Centre,
London E1 0LR

1 Wald NJ, Bower C. Folic acid and the prevention of neural tube defects. *BMJ* 1995;310:1019-20. (22 April.)
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Folate has potential to cause harm

EDITOR,—Nicholas J Wald and Carol Bower favour a population strategy rather than a selective strategy to prevent 1000 neural tube defects annually in the United Kingdom, with compulsory fortification of flour with folic acid.[1] They could perhaps have strengthened their case by referring to other potential benefits of their proposal—for example, in mental health, especially in psychiatric and geriatric populations.[2] Instead, however, they rather undermine their case by inaccurately minimising the disadvantages of their policy.

Their statement that "even in large doses folic acid has not been shown to cause harm" should not pass unchallenged. Although they acknowledge that folic acid may mask the anaemia of pernicious anaemia, they fail to emphasise that it may precipitate neurological complications in this context, as colleagues and I have shown.[3] This can occur in the absence of anaemia, macrocytosis, or even a low serum vitamin B-12 concentration. The authors suggest that the problem of masking pernicious anaemia could be resolved by education, but apparently they do not favour a selective educational approach to prevent neural tube defects.

The risk that seizures may increase in patients with epilepsy[4] is rather casually dismissed by the suggestion that higher doses of antiepileptic drugs might be needed, as if this in itself did not carry any risk.

A wider and more detailed consideration of all the advantages and disadvantages of the authors' proposals would be appropriate.

E H REYNOLDS
Consultant neurologist

Maudsley Hospital,
London SE5 8AZ

1 Wald NJ, Bower C. Folic acid and the prevention of neural tube defects. *BMJ* 1995;310:1019-20. (22 April.)
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Evidence based medicine

Example was flawed

EDITOR,—While I admire the intended efforts of evidence based medicine to reinforce clinical practice with up to date research, the article by William Rosenberg and Anna Donald highlights the flaws in this system.[1] The example that the authors cite—of an elderly woman with non-rheumatic atrial fibrillation—is interesting. The risk-benefit analysis outlined makes no mention of therapeutic reference ranges, which are inextricably linked to any analysis of outcome measures associated with management with oral anticoagulants. Thus, after it has been established that the patient would be more likely to benefit from treatment with warfarin, the clinical decision to have a target international normalised ratio of 1·5-2·0 is apparently picked out of thin air. This therapeutic range is too narrow to be of practical use and does not agree with the British Society of Haematology's current guidelines.[2] If strong advocates of evidence based medicine make such experientially based decisions, what chance do the rest of us have?

DAVID A FITZMAURICE
Lecturer

Department of General Practice,
University of Birmingham,
Medical School,
Birmingham B15 2TT

1 Rosenberg W, Donald A. Evidence based medicine: an approach to clinical problem solving. *BMJ* 1995;310:1122-6. (29 April.)
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Megatrials are subordinate to medical science

EDITOR,—Evidence based medicine started life as a flawed but marvellously refreshing approach to clinical practice and continuing education.[1] Unfortunately, it has recently been taken up by politicians and managers and is currently being packaged and promoted as a panacea, at the expense of medical science.

The main defining feature of evidence based medicine is its assertion that randomised controlled trials, especially "megatrials," should serve as the basis for clinical practice. For instance, William Rosenberg and Anna Donald deplore "the gaps between research evidence and clinical practice,"[2] as if megatrials told clinicians what to do and the job of clinicians was simply to do it.

But this whole notion of a gap between research and practice is misconceived. The results of megatrials—even in the rare circumstances that they are available and have been replicated—offer knowledge only at the population level.[3] To apply this to the care of individual patients would be a classic example of the ecological fallacy: group averages tell us nothing about causal processes in the individuals who compose that group.

Furthermore, the population sampling achieved by a megatrial is non-random and subject to large selection bias. Megatrials are typically performed in specialised research settings. Despite this, some trials have included fewer than 10% of eligible patients.[4] Even after admission, drop outs and crossovers between the comparison groups inevitably occur.[5]

The result of a megatrial cannot be extrapolated to a target population without substantial adjustments being made, and these adjustments will need to be based on contextual scientific knowledge. The epidemiological emphasis of evidence based medicine is mistaken. Science provides the innovations, the causal hypotheses, and the framework within which megatrials have their function.

Megatrials have an important role, but it is subordinate to medical science and consists mostly of checking predictions and refining protocols. If we needed to make a choice between medical science and megatrials as the basis of clinical practice then we would have to choose science.[5]

BRUCE G CHARLTON
Lecturer

Department of Epidemiology and Public Health,
University of Newcastle upon Tyne,
Newcastle upon Tyne NE2 4HH

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Must be applied critically

EDITOR,—William Rosenberg and Anna Donald make a clear case for evidence based medicine.[1] Logically one would assume that there could be no case against such an approach. They describe a relatively tedious method of gathering evidence to answer a clinical question. Their method entails performing appropriate searches from scratch. Developments in systematic reviews—particularly in maternity care—have led to the gathering of evidence being simplified. In short, someone else's meta-analysis has already answered your question. Problems can arise when results of meta-analysis are not viewed critically and in an informed manner. I am aware that one purchaser refused to fund ultrasound scanning for anomalies in the second trimester because meta-analysis had shown that it detected only largely lethal anomalies.

In the development of a policy for induction of labour in our unit I suggested routine "cervical stretch and sweep" for pregnancies proceeding beyond term. I was challenged because a recently published book, summarising several meta-analyses, states that "there is too little evidence to assess the effectiveness of this technique."[2] This statement is supported by reference to a meta-analysis in the *Cochrane Database of Systematic Reviews*.[3] This review was performed in 1989 and last amended more than three years ago. Since then a well conducted randomised controlled trial has been published,[4] accompanied by a favourable review article.[5] The compilers of the Cochrane database have not yet updated their meta-analysis to take account of these publications, and the book[2] has not been updated either, leading to a false interpretation of the value of a useful clinical intervention.

Purchasers and other decision makers should avoid adopting the findings of incomplete or out of date meta-analysis uncritically. Is there scope for a trial of evidence based medicine, assessing all outcomes and with full economic data?

MALCOLM GRIFFITHS
Consultant obstetrician and gynaecologist

Department of Obstetrics and Gynaecology,
Luton and Dunstable Hospital NHS Trust,
Luton LU4 0DZ

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Many questions cannot be answered by evidence based medicine

EDITOR,—We envisage that databases for evidence based medicine would answer the question "What is best practice?" and that hospital based audit would check that best practice is being achieved. Our audit programme has examined pain relief for tonsillectomy. In the 58 children audited, nine tonsillar blocks were performed; additional oral