Folate and depression—a neglected problem

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Researchers are not immune to fashion. A wealth of data going back several decades relating serotonin function to the regulation of mood and the current emphasis on genetics in biological psychiatry research have resulted in an increasing number of studies relating various polymorphisms of serotonin-related genes to various types of psychopathology. The assumption behind these studies is that the polymorphisms may alter serotonin function and therefore alter susceptibility to depressed mood or other symptoms. This line of research is important from a theoretical perspective but has fewer practical implications (except possibly in predicting response to drugs); practical methods to alter genes in depression patients are a long way in the future. The current explosion of work on serotonin-related polymorphisms is in sharp contrast to the much smaller number of recent studies on an entirely reversible environmental factor known to lower serotonin synthesis—folate deficiency. The purpose of this editorial is to draw attention to what is known about the epidemiology and biochemical and clinical effects of folate deficiency, to point out what studies are needed and to consider the recent recommendation that patients with depression should be treated with 2 mg of folic acid.[1]

Many studies, going back to the 1960s, show an elevated incidence of folate deficiency in patients with depression.[2] Studies vary depending on the criteria used to define folate deficiency, but often, about one-third of depression patients were deficient. Given that depression is often accompanied by decreased appetite and weight loss, the high incidence of folate deficiency in depression patients is not surprising. However, there is some evidence, though not conclusive, that folate deficiency may be involved in the etiology of depression in a minority of patients. Alternatively, depressed mood may decrease appetite, lower folate levels and thereby help to prevent recovery from depression. A recent review and metaanalysis looked at the results from the limited number of studies that investigated the effect of giving folate to depression patients and concluded that "there is some evidence that augmentation of antidepressant treatment with folate may improve patient outcome."[3] Whether the putative beneficial effect of folate is limited to those with folate deficiency is not clear.[1,3]

If folate deficiency can contribute to depressed mood and folate supplementation is beneficial in patients, a plausible mechanism implicates serotonin. In most,[4–8] but not all,[9,10] studies on patients with neuropsychiatric disorders, folate deficiency was associated with low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF). In one study, supplementation with folate restored CSF 5-HIAA levels to normal.[8] There is also a decrease in serotonin synthesis in patients with 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency, a disorder of folate metabolism.[11,12] While the mechanism relating folate deficiency to low serotonin is not known, it may involve S-adenosylmethionine (SAMe). SAMe is a major methyl donor formed from methionine. Folate is involved in a cycle that regenerates methionine from homocysteine after SAMe is demethylated to S-adenosylhomocysteine, with subsequent conversion to homocysteine. Folate deficiency decreases SAMe in the rat brain.[13] In humans, SAMe is an antidepressant[14,15] and increases CSF 5-HIAA levels.[16] Thus, there is some consistency in what is known about the interrelations of folate, SAMe and depression.

There is an important need for additional studies on folate and depression, the most pressing of which is larger studies on the ability of folate to potentiate the action of standard antidepressant therapies. Additional issues that need to be addressed are the dosage of folate needed to get the maximum effect and the possibility that the response may differ in different subgroups, such as those with and without overt folate deficiency. Meanwhile, how should clinicians act, considering what we currently know? In particular, should all depression patients be given folate supplements, and if so, how much? Is there no need for supplements in countries with mandatory or voluntary fortification of foods with

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folate? A review of the recent literature on folate supplementation provides enough information to tentatively answer these questions.

The amount of folate needed to help regulate mood, in terms of intake or serum or red blood cell levels, is not known. However, folate intake and levels have been studied extensively in relation to birth defects and plasma homocysteine levels. Low folate intake or low folate levels are associated with an increase in birth defects, whereas a metabolic cycle involving folate provides the methyl groups to methylate homocysteine to methionine. Thus, levels of folate that will minimize birth defects or homocysteine levels are sufficient to maximize folate function and are probably appropriate for patients with depression, although different metabolic systems could possibly be involved. Birth defects are obviously much more difficult to study than are homocysteine levels, but there is an extensive literature on the ability of folate supplements to lower homocysteine levels. A recent metaanalysis looked at the results of 25 randomized controlled trials of folate supplements in people who were not selected because of low folate levels. The conclusion was that daily dosages of 0.8 mg folic acid or more, in addition to dietary intake, are typically required to achieve the maximal reduction in plasma homocysteine concentrations (about 25%).[17] Vitamin B_{12} (0.4 mg/day) produced a further 7% reduction.

To lower birth defects, mandatory fortification of flour (but not whole grain flour) with 0.14 mg folate per 100 g of cereal grain product was introduced in the United States and in Canada in 1998.[18] In Chile, the level of fortification is 0.22 mg folate per 100 g of cereal grain product. In other countries, including Austria, Australia, Ireland, Portugal, Spain and the UK, voluntary fortification has been practised for several years. In Denmark, Finland and Sweden, fortification is restricted or not allowed.[18] Compulsory fortification led to an important decline in birth defects[18] and a substantial increase in serum and red blood cell folate levels. However, in the first few years of this decade, there was a small (16%) decline in serum folate levels in the United States in spite of continued fortification.[19] The reason for this is not clear, but this finding will help to intensify the debate about whether the amount of folate added to flour should be increased.[18,20,21] A recent commentary concluded that, even with the current level of fortification, most women are not getting the 0.4 mg of folate per day that is recommended.[21] The authors of the metaanalysis discussed above concluded that, even with fortification of food at the levels currently used in North America, additional supplementation with folic acid is likely to lower homocysteine concentrations by about 15%[17]; thus levels may still be suboptimal.

The above results suggest that some people with normal folate levels, including those who live in countries where there is voluntary or compulsory fortification of food with folate, may benefit from folate supplementation. Homocysteine levels can be lowered by folate supplementation, even when folate levels are normal, so it is not necessarily possible to distinguish the patients with depression who may benefit from folate by measuring folate levels. Further, some subgroups may require more folate than others. For example, people with the relatively common thermolabile variant of MTHFR have an elevated incidence of depression and require higher levels of folate.[22,23] Given the low cost of folate tablets (1 mg folic acid tablets can cost less than 5 cents each), there is no economic reason to avoid giving folate to all patients with depression, but can folate supplements have any adverse effects? Several concerns have been raised about the supplementation of food with folate.[18] The main concern relevant to the short-term use of folate supplements in depression patients is the possible masking of vitamin B_{12} deficiency symptoms. For this reason, it might be prudent to add a vitamin B_{12} supplement to the folate.

What about the recommendation that 2 mg of folate be given during the acute, continuation and maintenance treatment of depression?[1] The actual dosage may be debatable; 1 mg may suffice, particularly in countries where there is voluntary or compulsory fortification of food with folate, and the addition of a vitamin B_{12} supplement may be prudent, but the general principle is reasonable. With our current knowledge, the potential benefits seem to far outweigh any disadvantages. A recent article asked whether folate is "the ultimate functional food component for disease prevention."[20] Although the article didn't focus on depression, the question is highly relevant to its treatment.

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