Folic acid or folate is an essential nutrient found in a variety of foods. Since folic acid cannot be made endogenously, humans rely completely on dietary intake. Though present in leafy green vegetables, liver, eggs, yeast, and citrus fruits, prolonged cooking and even ultraviolet light can destroy much of the folate content in these foods. Primary folate insufficiency is most common among pregnant and lactating women in less-developed countries. Though severe folate deficiency is rarer in North America, the risk for moderate folate deficiency among adults is up to 10% (1).

The biological importance of folic acid lies in its role as a coenzyme in several key biosynthetic pathways. For example, folic acid is important for the maturation of both red and white blood cells, and for maintenance of epithelia. In addition, it is essential in reactions leading to nucleic acid synthesis, which highlights its fundamental role in fetal growth and development (2).

Interest in vitamins and health is hardly new. Doctors and health officials have worked to correct problems such as scurvy and pellagra for centuries. However, in the past few decades folate has come under increasing scrutiny for its associated role in preventing neural tube defects (NTDs) in newborns. There are a variety of NTDs, disorders of neural development that can be crippling or even fatal. The most common are spina bifida, and anencephaly, which occur at rates as high as 4 per 1000 live births in North America (3).

With increasing evidence that folate can prevent a great deal of morbidity and mortality due to these birth defects, a medical and public policy debate over vitamin supplementation has begun in earnest. As more and more data show the possible benefit of delivering adequate folic acid to women of childbearing age, one of the prime questions has become, should American staple food such as bread or flour be fortified with folic acid?

Neural Development and Folic Acid

Neural tube defects include a wide variety of problems, but the two most common are spina bifida, and anencephaly, as mentioned above. In the former, the caudal end of the embryonic neural tube fails to develop properly, leaving either meninges, spinal nerves, or both outside of the spinal column. With anencephaly, there is a complete failure of normal brain development, ultimately incompatible with life. Development and closure of the faetal neural tube is normally initially completed by day 28 following conception (4).

The causes of NTDs are multifactorial. The epidemiology of NTDs shows a varying rate depending on race, genetics, the use of certain medications, and geographic location (5). What is clear, however, is that a sizable number of cases can be traced to a simple folate insufficiency. While this could be the result of faulty folate metabolism in some cases, several studies have shown that simple, periconceptional supplementation with folic acid can significantly decrease both first-time and repeat NTD births (6). Approximately 2,500-3,000 children with NTDs are born each year in the United States: any significant inroads into prevention of these debilitating defects would be a very welcome step. To date there have been at least four studies on the reduction of risk among women with a

previously affected pregnancy, and five studies on primary prevention of NTDs with folic acid supplementation (7). These investigations have included case-control studies, prospective cohorts, and randomized controlled trials. Almost every study has demonstrated a significant protective effect associated with the use of periconceptional vitamins, independent of other vitamins or related dietary changes. Folic acid is not associated with any protective effect after the time of closure of the neural tube, usually completed by the end of the fourth week of embryonic development (8). Presumably, then, folic acid supplementation would have to begin before conception to be maximally effective. Though the exact mechanism of action is not known, and the minimum dose required for significant effect has not been determined (studies have included supplementation from 0.36 mg/day up to 5 mg/day, or ten times the US RDA), these studies typically do show a 60% to 70% reduction in risk. It has been estimated that universal supplementation of women of child-bearing age in the U.S. would reduce the risk of spina bifida by 50% (9).

Adequate Dietary Folic Acid and How to Achieve It.

Recall that US RDA for adult men is 200 micrograms per day, for women 185 micrograms per day and an additional 300 micrograms if pregnant. Since neural tube development begins early in faetal life and is virtually complete by the 28th day of development, it is essential that adequate folic acid intake begin before conception. In 1991, the United States Centers for Disease Control released recommendations that folic acid supplementation be provided to women planning a pregnancy who had had a previous pregnancy complicated by the presence of a neural tube defect (10). The recommended dose was 4 mg/day. In 1992, the Public Health Service expanded that recommendation to all women of childbearing age who are capable of becoming pregnant. In 1993, the Teratology Society Public Affairs Committee recommended that the PHS take whatever action necessary to ensure that American women of reproductive age receive sufficient daily folic acid to assist in preventing NTDs (11).

While women receiving prenatal care are routinely offered vitamins that include folate, not all women receive early prenatal care. Moreover, approximately half of all American pregnancies are unplanned (12). How, then, do we ensure that all women get adequate folate intalce in time? One major policy recommendation has been to supplement staple foods such as bread or flour with extra folate, just as most milk is fortified with vitamins A and D.

The objections to this intervention are twofold. First, folate intake can mask pernicious anemia while allowing neurological degeneration to continue unnoticed. This disease, related to B12 deficiency occurs somewhat commonly in older, Caucasian Americans (13). Secondly, there is some concern that the fortification of staple foods might actually lead to too much folate intake by non-target groups (ex., young men, who consume large amounts of grain products.

The Teratology Society found that "no scenario could provide 75% or more of the target population with at least 400 micrograms of folic acid per day without also providing in

excess of 1 mg at the upper intake levels for most age/gender subgroups," but that " three scenarios could provide between 200 and 300 micrograms without exceeding a safe upper intake level" (14).

In short, then, a risk/benefit analysis should be done, comparing the potential risks of folate intake and the covering-up of pernicious anaemia with the known benefits of folic acid intake in the prevention of NTDs. Clearly one area of study should be to monitor and expand the number of clinical markers for folate/B12 status (perhaps staple foods could be fortified with both vitamins, to pre-empt the problem?). Any policy shift so fundamental as to include fortification of American bread would also require cooperation and input from consumer groups, the food industry, government, and medical organizations.

Given the one acceptable scenario provided by the Teratology Society, and the continuing debate over how much folate is actually necessary to achieve the desired reduction in NTDs, perhaps the best interim policy would be to fortify foods at those acceptable levels while ongoing studies determine how best to fine-tune the situation. The benefits to society and the individual children could be invaluable.

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