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Jeanne I. Rader and Barbara O. Schneeman

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# Prevalence of Neural Tube Defects, Folate Status, and Folate Fortification of Enriched Cereal-Grain Products in the United States

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The authors have indicated they have no financial relationships relevant to this article to disclose.

**I**N THEIR RECENT report, Williams et al<sup>1</sup> examined data from 21 population-based birth defect surveillance systems for trends in prevalence of spina bifida and anencephaly for specific racial/ethnic groups from 1995 to 2002. Data were stratified into pre-, optional, and mandatory fortification intervals, coincident with the authorization of folate fortification of enriched cereal-grain products by the Food and Drug Administration (FDA) in 1996. Williams et al<sup>1</sup> found prevalence values per 10 000 births for spina bifida for Hispanic, non-Hispanic white, and non-Hispanic black women of 4.18, 3.37, and 2.90, respectively, for the mandatory fortification interval versus corresponding values for the same groups of 6.49, 5.13, and 3.57, respectively, for the prefortification interval. These results suggested that folate fortification was associated with significant decreases in the prevalence of spina bifida among non-Hispanic white and Hispanic births (34% and 36% decreases, respectively). The 19% decline in the prevalence of spina bifida among non-Hispanic black births was borderline statistically significant.<sup>1</sup> This failure to find a statistically significant decline among non-Hispanic black births may have been attributable to smaller samples examined (total cases were 515 for non-Hispanic black births, 2672 for non-Hispanic white births, and 1281 for Hispanic births).

In their editorial on the article by Williams et al,<sup>1</sup> Brent and Oakley<sup>2</sup> argued that folic acid fortification levels in the United States are too low. They have inappropriately generalized the data of Williams et al<sup>1</sup> into a broad criticism of the current folic acid fortification program and a call for increased fortification. This warrants our response. Consideration of whether increases in fortification are warranted depends a number of complex issues. For example, are the residual neural tube defects (NTDs) in all racial/ethnic groups folate sensitive? If so, then would increasing the levels of folic acid in enriched cereal-grain products be effective in reducing the remaining NTDs? Can increased fortification, if appropriate, be achieved without unduly increasing risk for people in the nontarget population? These issues are considered next.

## FOLATE FORTIFICATION

Mandatory fortification of enriched cereal-grain products with folate became effective in the United States on January 1, 1998. This fortification program was

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### Key Words

public health, public policy

### Abbreviations

FDA—Food and Drug Administration  
NTD—neural tube defect  
NHANES—National Health and Nutrition Examination Survey  
RBC—red blood cell  
IOM—Institute of Medicine

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undertaken to assist women of childbearing age in increasing their intake of folate to reduce their risk for having a pregnancy affected by an NTD. Cereal-grain products are consumed on a daily basis by >90% of women of childbearing age.<sup>3</sup> Therefore, the fortification program that now is in place has the potential to reach most such women. The prevalence of spina bifida and anencephaly, the 2 most common types of NTDs, varies by race/ethnicity, with the highest rates occurring among Hispanic women and the lowest among black and Asian women. Because of the observed higher rates of NTD-affected pregnancies among Hispanic women, it is important to determine whether the benefits of folate fortification are being realized in this group.

### NEW DATA ON PREVALENCE OF NTDs

Williams et al<sup>1</sup> noted the statistically significant decreases during the mandatory fortification period in the prevalence of spina bifida and anencephaly among Hispanic and non-Hispanic white births but not among non-Hispanic black births. The reasons for the disparity in the rates of NTDs by race/ethnicity are unknown, as are the reasons for the disparity in declines in the prevalence of NTDs since folic acid fortification. Important questions that arose from the analyses of Williams et al<sup>1</sup> are whether the higher rates of NTDs in Hispanic women and the apparent folate-unresponsiveness of rates of NTDs in non-Hispanic black women are attributable to inadequacy in the current fortification program or to other factors. Brent and Oakley<sup>2</sup> argued that the FDA should require at least a 2-fold increase in the amount of folic acid added to enriched cereal-grain products and also should require that vitamin B<sub>12</sub> be added to flour to achieve an average daily consumption of at least 2.4 μg of vitamin B<sub>12</sub>.

### SIGNIFICANT CHANGES IN FOLATE STATUS OF THE US POPULATION AFTER FORTIFICATION

Recent data on the vitamin B status of the US population are now available and are essential for understanding the current situation. Pfeiffer et al<sup>4</sup> recently published the largest documentation of folate status since mandatory folic acid fortification of enriched cereal-grain products was initiated in 1998. These new data provide a comprehensive biochemical assessment of folate status in a representative sample of the American population in the National Health and Nutrition Examination Survey (NHANES). Pfeiffer et al<sup>4</sup> also compare data from NHANES III (1988–1994) with the newer data from NHANES 1999–2000.

Geometric mean concentrations of serum folate (nmol/L) for Mexican American, non-Hispanic black, and non-Hispanic white women in NHANES 1999–2000 were 265%, 244%, and 251%, respectively, of values measured in NHANES III. Geometric mean concentra-

tions of red blood cell (RBC) folate (nmol/L) for Mexican American, non-Hispanic black, and non-Hispanic white women in NHANES 1999–2000 were 161%, 164%, and 161%, respectively, of values measured in NHANES III. The prevalence of low serum folate concentrations (<6.8 nmol/L) in women of childbearing age (12–49 years) decreased from 20% in NHANES III to 0.8% in NHANES 1999–2000, and the prevalence of low RBC folate concentrations (<317 nmol/L) in women of childbearing age decreased from 38% in NHANES III to 5% in NHANES 1999–2000.<sup>4</sup> Therefore, currently available folate status data do not provide evidence that the level of fortification is too low.

Although overall prevalence of low RBC folate concentrations decreased significantly after the introduction of folate fortification, pronounced ethnic differences in folate status remain: 2% of Mexican American, 4% of non-Hispanic white, and 11% of non-Hispanic black women of childbearing age had RBC folate concentrations <317 nmol/L.<sup>4</sup> NHANES 1999–2000 data do indicate that significant improvements in folate status have occurred across all population groups since mandatory fortification began. However, because dose-response data relating indices of folate status to occurrence of NTDs are not available, it is not possible to determine whether these values are sufficiently high to protect all women who are at risk.

### ASSESSMENT OF THE EFFECTIVENESS OF FORTIFICATION IS INFLUENCED BY COMPLETENESS OF NTD CASE ASCERTAINMENT

A major issue in determining the success of fortification with respect to its goal of assisting women in reducing their risk for NTDs by increasing their folate intake is the identification of all NTDs that occur. This requires the identification of prenatally diagnosed NTDs. Mills and Signore<sup>5</sup> reviewed studies from the United States and Canada that compared rates of NTDs before and after the fortification programs began in both countries. Health Canada required the addition of 150 μg of folic acid/100 g to specific grain products by November 1, 1998. Therefore, the Canadian fortification program is similar to the US program. Mills and Signore<sup>5</sup> found a strong correlation between the completeness of case ascertainment and the percentage decrease in NTD rates. Studies that had more complete case ascertainment showed that folic acid fortification was preventing ~50% of NTDs versus smaller decreases of 19% to 26% in studies with partial ascertainment (see Mills and Signore<sup>5</sup> for review). Therefore, at current fortification levels in the United States and Canada, we may be close to achieving the estimated maximum level of protection against NTDs.

Williams et al<sup>1</sup> also considered this issue, noting that only 9 of their 21 participating birth defects surveillance systems were able to ascertain prenatally diagnosed

cases. When they analyzed data only among programs that conducted prenatal surveillance, they found that the prevalence of NTDs among Hispanic births was only 10% higher than the prevalence of NTDs among non-Hispanic white births; this value was of borderline statistical significance. However, the apparent difference in prevalence between Hispanic and non-Hispanic white births was 42% among programs that did not conduct prenatal surveillance. This suggests that in this study, some of the observed difference in rates among racial/ethnic groups could be attributable to differences in access to or use of prenatal diagnostic services. Therefore, the data of Williams et al<sup>1</sup> agree with the findings of Mills and Signore<sup>5</sup> about the importance of case ascertainment.

### **MIGHT INCREASING FORTIFICATION LEVELS BE EFFECTIVE IN REDUCING THE REMAINING CASES OF FOLATE-SENSITIVE NTDs?**

#### **Failure to Select Fortified Foods or Dietary Supplements**

In analyzing strategies to reduce further the risk for an NTD-affected pregnancy, it is important to distinguish between increased risk that results from failure to consume folate-containing fortified foods or dietary supplements and increased risk that results from inadequate levels of folate in such products. Brent and Oakley<sup>2</sup> noted that not all products are fortified (eg, corn tortillas). Members of different ethnic groups may prefer or have access only to unenriched products. An FDA action to increase fortification would have no impact on such individuals. Rather, if this is a problem, then greater education for women about the importance of selecting fortified products or dietary supplements and/or campaigns by the public health community to encourage manufacturers to fortify cereal-grain products may help to resolve the issue.

#### **Other Factors That Affect the Prevalence of NTDs**

Williams et al<sup>1</sup> reviewed literature on a number of other factors that may be affecting the higher rates of NTDs among Hispanic women and considered factors such as eating habits and multivitamin supplement use practices as unlikely causes for the observed higher rate of NTD-affected pregnancies among Hispanic women and lower rates among non-Hispanic black or white women. Williams et al<sup>1</sup> noted that findings from NHANES III showed that black women had lower dietary folate intakes than women in the other 2 groups. As noted above, if these lower intakes are the result of a failure of women to choose fortified foods, then increasing the level of fortification in fortified foods will not affect the rates of NTDs.

Information on other factors that are associated with NTD risk (eg, maternal diabetes, obesity, intake of other nutrients) was not available from the study of Williams

et al.<sup>1</sup> Williams et al<sup>1</sup> reviewed recent literature and concluded that variation in such factors does not explain the prevalence of NTDs by race/ethnicity.<sup>1</sup> For example, vitamin B<sub>12</sub> levels vary by racial and ethnic groups, and several studies have suggested that low vitamin B<sub>12</sub> levels may be associated with an increased risk for NTDs.<sup>1</sup> The most recent data for serum vitamin B<sub>12</sub> for Mexican American, non-Hispanic black, and non-Hispanic white women show values (pmol/L) of 385, 400, and 327, respectively, for participants in NHANES 1999–2000.<sup>4</sup> The variation of this possible risk factor does not seem to explain the prevalence of NTDs by race/ethnicity.

The study of Williams et al<sup>1</sup> lacked the power to control for confounders such as polymorphisms that are associated with folate metabolism, other known risk factors, and folate status of women with or without NTD-affected pregnancies. Until data on folate status from women who have had NTD-affected pregnancies are correlated with their intakes of folate-containing foods and dietary supplements, it will not be possible to determine whether increasing the level of fortification in enriched cereal-grain products will actually have an impact on NTDs that are still occurring in the United States. Such retrospective data are not yet available; they would be invaluable in determining whether higher fortification levels would be likely to have an impact on the remaining NTDs among US women. It is possible that the remaining NTD-affected pregnancies among black women are not folic acid sensitive or that higher levels of folic acid consumption would be required to prevent NTD cases in this population. Currently available data do not provide information that might resolve this uncertainty.

#### **SAFETY OF INCREASED FORTIFICATION**

Fortification is nonspecific: it affects both the target group (women of reproductive age) and all nontarget groups (all other age/gender groups). For this reason, fortification must be safe for all groups, particularly those for whom no benefit is likely to occur.

The current US fortification program has brought about a rapid population-wide improvement in folate status in a relatively short time. It is not possible at this time to determine which proportion of NTDs in the United States are folate responsive; lacking such information, it is premature to call for increased fortification.

The discussions that preceded fortification covered many issues, including those of current folate intake from all sources, bioavailability, minimum effective dose for reducing NTDs, risk of excessive folate intakes, nutrient interactions, possible benefits for other diseases of increased folate intake, other factors that affect risk for NTDs, safety concerns and need for monitoring. Some of these issues have been addressed in the recent literature, whereas others represent areas in which more research is needed.

### Cardiovascular Disease Risk

One proposed additional benefit of the fortification is a reduction in risk for cardiovascular disease, possibly as a result of a folate-mediated lowering of serum homocysteine levels. Recent data show clearly that such a lowering has occurred in the population.<sup>4</sup> In addition, a number of clinical trials that are designed to determine whether use of a multivitamin (eg, folic acid, pyridoxine, and vitamin B<sub>12</sub>) to lower total homocysteine levels might reduce the incidence of recurrent cerebral infarction and coronary heart disease have been in progress. A review of the extensive literature in this area is beyond the scope of this commentary. However, at least 1 major clinical intervention trial has found no effect on vascular outcomes during 2 years of follow-up.<sup>6</sup> The large NORVIT trial also found no causal link between homocysteine levels and vascular disease and concluded that use of B vitamins cannot currently be recommended for post-myocardial infarction patients.<sup>7</sup> Similarly, Liem et al<sup>8</sup> recently reported that a trial using 0.5 mg of folic acid daily in patients with stable coronary artery disease showed no benefit with respect to a composite of vascular events during 42 months of follow-up. Therefore, there is still considerable uncertainty in this area of proposed fortification-related benefit.

### High Intakes of Folic Acid in Specific Subgroups of the Population

The US Institute of Medicine (IOM)<sup>9</sup> has expressed concern about potential adverse effects of high doses of folic acid in specific subgroups in the population (eg, individuals who are treated with anticonvulsants and antifolate therapeutics such as methotrexate). In addition, there are no data regarding effects of long-term exposure of, for example, young children to several times their daily recommended intake of folic acid. This is of some importance because the daily recommended intake for children is 200 to 300  $\mu\text{g}$ , and the IOM has established a tolerable upper limit of folic acid intake of 300  $\mu\text{g}/\text{day}$  for children aged 1 to 3 years and 400  $\mu\text{g}/\text{day}$  for those aged 4 to 8 years.<sup>9</sup> Estimates of folic acid intakes in several US population groups suggest that some people may already be consuming quantities that approach or exceed the IOM's upper limit for folic acid.<sup>9</sup> In their analysis of the most recent NHANES 1999–2000 data on B vitamin status, Pfeiffer et al<sup>4</sup> defined high serum folate concentrations as  $\geq 45.4$  nmol/L, which reflected the upper end of the Bio-Rad Quantaphase II assay calibration range. Beyond this concentration, samples need to be diluted and reanalyzed to obtain a valid result.<sup>4</sup> Using this value, the prevalence of high serum folate concentrations increased from 7% in NHANES III to 43% in NHANES 1999–2000 for children who were aged  $\leq 5$  years and from 7% in NHANES III to 38% in NHANES 1999–2000 for elderly individuals.

### Co-fortification With Vitamin B<sub>12</sub>

Brent and Oakley<sup>2</sup> argued that the FDA should require that vitamin B<sub>12</sub> be added to flour so that the average person consumes at least 2.4  $\mu\text{g}$  daily. The issue of co-fortification with vitamin B<sub>12</sub> arose early in the FDA's discussions regarding folic acid fortification. Because there was interest in raising the proposed folate fortification level of 140  $\mu\text{g}/100$  g enriched cereal-grain product to levels of 350  $\mu\text{g}/100$  g or 700  $\mu\text{g}/100$  g, proponents of higher levels of fortification suggested that considerably higher folate fortification could be implemented safely if simultaneous fortification with vitamin B<sub>12</sub> at a level of 1 mg also were required. These suggestions were based on assumptions that the greatest potential for adverse effects with high folate intakes (which would occur frequently with the higher fortification levels) is its masking of the anemia of vitamin B<sub>12</sub> deficiency, with continued progression of neurologic damage and that provision of oral vitamin B<sub>12</sub> would negate this concern.

In its 1993 proposed rules for folic acid fortification,<sup>10</sup> the FDA requested comments, specifically data, on the appropriateness, potential effectiveness, and safety of use of simultaneous fortification with high levels of vitamin B<sub>12</sub> for the purpose of minimizing adverse effects of high folic acid intakes. The FDA did not receive any data addressing the issue of co-fortification with vitamin B<sub>12</sub>. Although several comments recommended requiring the addition of vitamin B<sub>12</sub> in a 1:1 ratio with folic acid, they provided no data regarding the potential effectiveness of such a proposal. Therefore, the FDA had no basis on which to determine whether co-fortification proposals were appropriate. In addition, proposals to fortify enriched cereal-grain products with vitamin B<sub>12</sub> failed to recognize the potential for other adverse effects of increased folate intakes in population groups such as pregnant women, children, those who are taking anti-epileptic medications, or those who are taking anti-folate medications.

Perhaps the most serious concern regarding suggestions about co-fortification with vitamin B<sub>12</sub> has to do with how little is known about how this might actually be accomplished. Technical issues surrounding proposed fortifications are of major importance but are rarely considered. Unlike the B vitamins, which now are added back to enriched cereal-grain products, vitamin B<sub>12</sub> is not found naturally in cereal-grain products. Therefore, the extensive vehicle suitability and stability testing that was performed for the B vitamins that are added to enriched cereal-grain products was not performed for vitamin B<sub>12</sub>. As a result, virtually no information is available regarding recommended levels, appropriate vehicles, and the stability and the bioavailability of this vitamin when added to cereal-grain products.

### Chronic Exposure to Unmetabolized Folic Acid in Plasma

Recent data show that there have been significant improvements in folate status in the US population in a very short period of time. Recent reports indicate that the program is providing approximately twice as much folic acid as was originally estimated.<sup>11,12</sup> Therefore, Brent and Oakley's argument that the original fortification levels should be doubled<sup>2</sup> may have already been achieved.

The issue of significantly increased folic acid intakes is of some consequence because such intakes may overload the body's metabolic capability and lead to the appearance of unmetabolized folic acid in plasma.<sup>13</sup> The consequences of the chronic presence of unmetabolized folic acid in plasma are unknown, and its effects on normal homeostatic mechanisms (eg, those that regulate cellular retention and metabolic function of folate) remain to be determined.<sup>14</sup>

### Other Safety Issues

The FDA's earlier conclusion that fortification with folic acid was unlikely to affect those who are taking anti-folate or other drug therapies was based on the limited data that were available at the time and on estimations that the fortification program would provide an additional 100  $\mu\text{g}/\text{day}$  folic acid. This earlier conclusion may need to be reexamined in light of the higher estimated current intakes and newer data on interactions among folic acid, anti-folate drugs, and specific disease states.<sup>13,15-17</sup> For example, 1 recent report involving the use of methotrexate<sup>17</sup> seems to be the first evidence that high serum folate levels may block the action of anti-folate drugs. Because anti-folate drugs are used to treat a variety of illnesses, this interaction warrants continued attention.

### CONCLUSIONS

There is an absence of systematic studies of the safety of high doses of folic acid. It is axiomatic that absence of data does not equate with assurance of safety. Rosenberg<sup>18</sup> noted that at the time the decision was made to mandate the addition of folic acid to enriched cereal-grain products, there was no coherent plan to monitor the effects on NTD births or on actual changes in folate status or to assess the possible occurrence of untoward effects in the population. Currently, no single agency is assigned the responsibility of monitoring the long-term or overall safety of the fortification program. Despite initial positive effects on folate status and reduction in NTDs, the possibility remains that certain segments of the population may benefit less and may even experience some adverse effects from increased folic acid intakes, which have turned out to be even greater than originally modeled.<sup>18</sup> The absence of systematic studies of safety means that we do not know which outcomes are the most sensitive predictors of risk, although all

nutrients, including water-soluble ones, are assumed to present risks at higher intakes. Critical evaluations of new data are needed before consideration can be given to increasing the level of fortification. In addition, it is necessary to document that current levels of fortification are inadequate and that raising levels of fortification would have an impact on the women who are at risk for folate-sensitive NTDs.

Many issues and potential outcomes must be considered when evaluating the effects of a nationwide food fortification program. In the case of the folate fortification program, the rapidity with which folate status changes were recognized and the results published emphasize the importance of well-designed and executed surveillance systems such as NHANES. The safety and the effectiveness of the fortification program must continue to be monitored over time to determine that the program is functioning as expected and does not have unintended consequences.

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## THE LOST CHILDREN

“A generation from now non-Hispanic whites will make up less than 60 percent of the US population, and by 2050 they will be just half. Nine out of 10 American students currently attend public schools. It is likely that within a decade fewer than half of the public school students will be white. The dramatic changes in public school enrollment will not be a result of white flight, according to a new study by the Civil Rights Project at Harvard University: ‘It is because of a changing population structure created by differential birth rates and age structures and a largely nonwhite international flow of millions of immigrants. Since whites are older, marry at later ages, have smaller families and account for a small fraction of immigrants, these changes are almost certain to continue.’ . . . One of the weirder things occurring in American education is the disappearance of kids—especially black and Hispanic kids—from high school. The *San Antonio Express-News*, reporting last March on a study by a local research association, said that ‘more than a third of Texas high school freshman students are disappearing from the system or otherwise failing to obtain a high school diploma in four years.’”

Herbert B. *New York Times*. January 30, 2006

Noted by JFL, MD

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