Triumph and/or Tragedy: The Present Food and Drug Administration Program of Enriching Grains With Folic Acid

Robert L. Brent and Godfrey P. Oakley, Jr

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COMMENTARY

Triumph and/or Tragedy: The Present Food and Drug Administration Program of Enriching Grains With Folic Acid

Robert L. Brent, MD, PhD[a], Godfrey P. Oakley, Jr, MD, MSPM[b]

[a]Department of Pediatrics, Radiology, and Pathology, Thomas Jefferson University, Alfred I. duPont Hospital for Children, Wilmington, Delaware; [b]Department of Epidemiology, Rollins School of Public Health of Emory University, Atlanta, Georgia

Financial Disclosure: Dr Brent owns no stock in companies that make or distribute folic acid or sell or distribute grains. Some of his research that is supported by the National Institutes of Health has dealt with the use of folic acid to prevent neural tube defects as well as the metabolism of folic acid and methionine. Dr Oakley is a co-inventor of a patent that covers adding folic acid to contraceptive pills (while at the Centers for Disease Control and Prevention, compensation, if any, will be under the regulations of the Centers for Disease Control and Prevention) and has been a consultant to Ortho McNeil on this issue.

In this issue of *Pediatrics*, Bol et al[1] report on the survival and severity of neural tube defects (NTDs) during the period that the Food and Drug Administration (FDA) mandated folic acid fortification of grains. They conducted a retrospective cohort study of 2841 infants with spina bifida and 638 infants with an encephalocele born between 1995 and 2001. The investigators reported that the 5-year survival of 92.1% of infants born with spina bifida was improved significantly when compared with the 90.3% survival in infants born before folic acid fortification. The clinical impact of these data is that the 5-year mortality from spina bifida decreased from 93 to 79 per 1000 spina bifida births. These data indicate that a child born with spina bifida in the United States is 10 times as likely to die in the first 5 years as the average newborn child. The survival of infants born with encephaloceles was higher also during the fortification period, but the difference was not statistically significant. The authors concluded that folic acid fortification "may play a role in reducing the severity of NTDs" in addition to the prior publications that indicate that folic acid prevents the occurrence of NTDs.

This is a well-planned and well-performed study. The investigators' conclusions are biologically plausible. They indicate that there may be confounding factors that affect the data, that is, the variable frequency and decisions for interrupting pregnancy because of the presence of an NTD, the use of historical controls, improvement in medical and surgical care, and the possible effect of differences of delivery on the mortality of the infants with NTDs. The authors do not believe that in utero surgical intervention had a significant impact on their data. After considering all these possible confounding factors, the authors determined that their conclusions are valid, namely, that the mortality of infants with NTDs had decreased and the severity of NTDs was reduced during the postfortification period. These are reasonable conclusions based on the data.

The investigators also concluded: "As survival rates of NTD-affected infants improve, health care, education and family support must expand to meet their needs." It is the last sentence of their conclusions that prompted the title of this commentary, "Triumph and/or Tragedy." Although reduction in mortality is good, it is a shortfall when compared with full prevention. Is it not a tragedy that we are not preventing all spina bifida that our current knowledge permits? We have failed to create the political will, force, and enthusiasm to prevent the occurrence of folic acid–preventable spina bifida and anencephaly in a single state, much less the whole country.

In 2000, Brent et al[2] published a commentary in *Pediatrics* concerning the FDA's program[3] of enriching

Abbreviations: NTD—neural tube defect; FDA—Food and Drug Administration; CDC—Centers for Disease Control and Prevention

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Address correspondence to Robert L. Brent, MD, PhD, Department of Pediatrics, Radiology, and Pathology, Thomas Jefferson University, Alfred I. duPont Hospital for Children, Box 269, Wilmington, DE 19899. E-mail: rbrent@nemours.org

grains to prevent folic acid–preventable NTDs. The commentary suggested that the amount of folic acid mandated by the FDA was too low. This commentary was in response to the Stevenson et al[4] article published in the same issue of *Pediatrics*,[5] which clearly supported the concept that folic acid can prevent NTDs. However, the Stevenson et al study demonstrated that if the program were not all-inclusive, many newborns would be born with NTDs that could have been prevented.

Evidence of the protective effect of folic acid was old news. Wald et al[5] first provided unambiguous evidence that synthetic folic acid in a pill would prevent children from developing spina bifida and anencephaly in 1991. Since 1991, pediatricians have built the political will and implemented immunization programs that have eliminated *Haemophilus influenza* B meningitis and croup and have prevented most cases of pediatric AIDS in this country. However, we have failed to communicate this tragic story of children continuing to be born with a preventable disease. Sufficient folic acid fortification of foods eaten by women of reproductive age would prevent almost all folic acid–preventable spina bifida and anencephaly. Berry et al[6] demonstrated that adequate amounts of folic acid dramatically reduced the incidence of NTDs in China in 1999.

As described in the September 2005 issue of *Pediatrics*, Williams et al[7] at the Centers for Disease Control and Prevention (CDC) and in state health departments tracked the continuing occurrence of spina bifida and anencephaly before and after folic acid fortification of "enriched" grains. Although their study definitely demonstrated that the incidence of NTDs was decreased after fortification, it also indicated that preventable NTDs were filling hospital rooms and wheel chairs. It is a tragic failure of public policy, both in the United States and around the world, that a single case of folic acid–preventable spina bifida and anencephaly occurs. In 2005, we published a second commentary[8] in the same issue containing the Williams et al article. As mentioned previously, we brought this urgent problem to the attention of the FDA and the world medical community in a commentary in *Pediatrics* in 2000[2] that has been ignored. The title of that commentary was "The Unnecessary Epidemic of Folic Acid–Preventable Spina Bifida and Anencephaly."[2] Unfortunately, it is not a few cases here and there. The CDC estimates that 2000 cases of folic acid–preventable spina bifida and anencephaly pregnancies continue to occur yearly in the United States.[9] There are ~200 000 children each year around the world born with these preventable birth defects. We must do better for children everywhere.

The Bol et al[1] article is a stern reminder that, although the severity of spina bifida may have decreased with fortification, too many children continue to develop spina bifida because our enriched grains do not have enough folic acid. If we double our concentration from 140 to 280 μg of folic acid per 100 g of grain, we would be fortifying at the level recommended in the United Kingdom by an expert committee and at the level permitted in Australia and New Zealand. It would be slightly less than the concentration used in Chile, but women in Chile eat more wheat. Doubling the concentration would be safe and would prevent a higher proportion of preventable spina bifida cases. This accomplishment would improve the lives of children and families and reduce the number of women who would face the difficult decision that results from the prenatal diagnosis of spina bifida and anencephaly. In the future we may need to do more than double the concentration of folic acid in grains to attain the ultimate goal. Increasing the concentration of synthetic folic acid in flour is attainable now and is an urgent, essential initial step for improving child health in the United States.

It is of interest that the 2 NTD epidemiology publications in 2005[1,7] for which we have prepared the 2 *Pediatrics* commentaries did not demand that the concentration of folic acid be increased. In fact, neither of these publications raised the issue of the underenrichment of folic acid in enriched grains. It is important to remember that when we see a child with spina bifida, the most likely etiology is that the mother was not consuming flour that had been sufficiently enriched with folic acid. We should be as shocked and surprised by the sight of a child with an NTD in our hospital as we would be by seeing a child with poliomyelitis.

When research provides the knowledge that enables society to prevent serious diseases, we should fully implement effective prevention programs. If we do not, why do we do research? Not only do discoveries that prevent disease save children's lives, but the research can save medical care dollars. Our task should be to get the prevention to the "bedside" as rapidly as possible. We have done better than Europe in preventing folic acid–preventable spina bifida, but we need to implement programs that prevent all the spina bifida and anencephaly that can be prevented by folic acid. We urge our pediatric and obstetric colleagues, who know the impact of spina bifida and anencephaly on the child and his or her family, and organizations such as the American Academy of Pediatrics (AAP), American Medical Association, American Pediatric Society, the March of Dimes, and the Spina Bifida Association of America to petition the FDA to increase the concentration of folic acid required in all enriched grains. Given that the Institute of Medicine's Food and Nutrition Board has recommended that all who are 50 years and older should consume 2.4 μg of synthetic vitamin B_{12}, we encourage the American Medical Association and AAP to petition the FDA to require enough vitamin B_{12} in flour as well.

In the mean time, we should persuade all women of reproductive age to consume 400 μg of folic acid, which is widely available in multivitamin supplements and in

many breakfast cereals. Data released, as we write this commentary, demonstrate that we have made little, if any, progress in increasing consumption of multivitamins in the United States. Only ~30% of women of reproductive age consume folic acid voluntarily. These data from the March of Dimes survey, published by the CDC in the *Morbidity and Mortality Weekly Report*, are yet another current reminder that full prevention of folic acid–preventable birth defects is attainable.[10] We must immediately increase the folic acid concentration in enriched grains, because these products are consumed by almost all women of reproductive age.

The prevention of spina bifida and anencephaly that has occurred as a result of folic acid fortification has saved the country approximately $250 million dollars per year in medical care costs. Thus far, this saved money has not been reinvested in the CDC's birth-defects budget. We urge the US Congress to increase the CDC's birth-defects budget by $200 million so that it can have the resources it needs to lead the campaign for the sustainable elimination of folic acid–preventable spina bifida and anencephaly, not only in the United States but also throughout the world. The effective leadership that the CDC has shown in the global polio-eradication program suggests that, with resources similar to those available for polio eradication, that CDC can be effective in the total prevention of folic acid–preventable birth defects. The successful prevention of all of these birth defects will improve the lives of children and, at the same time, save even more money and resources.

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