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The Food and Drug Administration Must Require the Addition of More Folic Acid in "Enriched" Flour and Other Grains

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Pediatrics 2005;116;753-755

DOI: 10.1542/peds.2005-1536

This information is current as of September 6, 2005

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/116/3/753>

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American Academy of Pediatrics

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children with symptoms. Does this imply that asymptomatic children, therefore, do not need radiographs? In particular, would any of the 44 asymptomatic children in the Waltzman et al study who underwent endoscopy have had avoidable complications resulting from missed esophageal coins had they been managed by home observation? In considering this question, it is worth noting that it took the investigators 2¾ years to gather even this modest number of patients despite being based at one of the nation's leading pediatric referral centers. Nearly half of this group were in the study's "relatively immediate endoscopy" group; some of these patients may have passed their coins into the stomach had they been allowed a longer observation period. Additionally, study patients were kept non per os, whereas at home they would likely have eaten and drunk. Previous evidence suggests that at least some of them would have passed their coins as they swallowed their meals.^{8,14} Those whose coins remained may have developed the sorts of symptoms that parents should be advised to watch for during home observation, triggering radiography. Clearly, unanswered questions remain. A prospective study of home observation for management of asymptomatic children who have swallowed coins, including a cost-effectiveness comparison versus obtaining automatic radiographs, is an important next step in obtaining the answers.³ Until data from such a study are available, an ionizing-radiation-free scan with a metal detector (with radiographic follow-up of those suggestive of esophageal coins) remains a reasonable middle-ground alternative to automatic radiography.^{13,15}

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The Food and Drug Administration Must Require the Addition of More Folic Acid in "Enriched" Flour and Other Grains

ABBREVIATIONS. CDC, Centers for Disease Control and Prevention; FDA, US Food and Drug Administration.

In 1991 Wald and his colleagues¹ first provided unambiguous evidence that synthetic folic acid in a pill would prevent most children from getting spina bifida and anencephaly. Sufficient folic acid fortification of foods eaten by most women of reproductive age would prevent almost all folic acid-preventable spina bifida and anencephaly. In this issue, Williams and colleagues² at the Centers for Disease Control and Prevention (CDC) and in state health departments have tracked the continuing occurrence of spina bifida and anencephaly before and after folic acid fortification of "enriched" grains. 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. We brought this urgent problem to the attention of the US Food and Drug Administration (FDA) and the world medical community through a commentary in *Pediatrics* in 2000.³ However, the response for action has been inadequate. In fact, it has been ignored. The title of that commentary was "The Unnecessary Epidemic of Folic Acid-Preventable Spina

Accepted for publication Jun 23, 2005.

doi:10.1542/peds.2005-1536

Conflict of interest: 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 (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) that covers adding folic acid to contraceptive pills, and he has been a consultant to Ortho McNeil on this issue.

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Bifida and Anencephaly.” 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.⁴ There are ~200 000 children each year around the world born with these preventable birth defects.⁵ We must do better for children everywhere.

We know why folic acid–preventable birth defects continue to occur unnecessarily and tragically in the United States. Our government has failed to take the steps needed to assure that not a single child is affected with folic acid–preventable spina bifida and anencephaly. The FDA did not require a high enough concentration of folic acid in enriched grain products.⁶ Although the requirement of folic acid in enriched grain products has had important public health effects, the FDA elected to require fortification at a level that was too low for the prevention of most cases of folic acid–preventable spina bifida.⁷ The United States Public Health Service recommended in 1992 (and the Institute of Medicine reaffirmed in 1998) that women of reproductive age should consume 400 μg per day of synthetic folic acid to prevent spina bifida and anencephaly.^{8,9} Yet, the FDA required a fortification level that would provide the average woman of reproductive age only 100 μg per day of synthetic folic acid. The American Academy of Pediatrics, the March of Dimes, and the CDC all recommended the fortification level to be higher.

The FDA chose too low of a fortification level for a dubious reason. It chose to set a fortification level that would keep 90% of the population consuming <1000 μg of “total folate” (natural food folate plus synthetic folic acid) per day. This criterion was based on a faulty understanding of the biochemistry. The FDA wanted to limit upper consumption because it was concerned that people with vitamin B₁₂ deficiency may have the anemia effectively treated or prevented. Natural food folate cannot prevent or cure the anemia of B₁₂ deficiency, because the reason a person becomes anemic with severe enough B₁₂ deficiency is that the body cannot metabolize 5-methyl-tetrahydrofolate into tetrahydrofolate. Because the average person consumes ~250 μg per day of natural food folate, using total folate in the model was essentially using 750 μg of synthetic folic acid. If the FDA had used 1000 μg of synthetic folic acid in its model, it could have required a folic acid concentration of at least twice what it chose, and the hundreds of children with spina bifida and anencephaly reported by Williams and colleagues would have been born without these severe birth defects. What a tragic mistake the FDA made.

It is time for FDA to get it right. The current concentration of synthetic folic acid required should be increased by at least twofold. Given that conditions as severe as spina bifida and anencephaly have affected hundreds of children per year because there is not enough folic acid required in enriched grains, the FDA should use its emergency powers to move immediately to require at least twice the current

level. On a brisk pace it should also require that vitamin B₁₂ be added to flour so that the average person consumes at least 2.4 μg per day. The Institute of Medicine in 1998 recommended that all people >50 years old consume 2.4 μg of synthetic vitamin B₁₂ per day.⁷ Again, the FDA has not moved. It is difficult to understand how the FDA can continue to limit the prevention of spina bifida and anencephaly because of a B₁₂-deficiency issue and not require that B₁₂ be added to flour. As Williams and colleagues note, there is some evidence that vitamin B₁₂ may prevent some spina bifida and anencephaly pregnancies that folic acid does not prevent.² Thus, the next logical step toward the total prevention of folic acid–preventable spina bifida and anencephaly is for the FDA to at least double the required concentration of folic acid and require vitamin B₁₂ in enriched grains, too.

There is work for others to do if we are to prevent all folic acid–preventable birth defects. As the Williams et al article clearly shows, the rates for Hispanic Americans continue to be high and are responsive to increasing consumption of folic acid. At least 1 major manufacturer of corn flour, Gruma, does not sell an enriched product in the United States. Gruma lists on its Web page 3 mills in Texas, 1 in Indiana, 1 in Kentucky, and 1 in California in which it produces the corn flour under the brand Maseca. If Gruma were to sell only enriched Maseca (and it should do so quickly), it would prevent many children from having spina bifida and thereby make a positive contribution to the lives of the Hispanic families who use their products.

The US Congress has work to do, as well. Congress has a long history of supporting the CDC in its efforts to eradicate polio from the world. When all American children were not getting the polio vaccine, Congress established a program at the CDC to increase the number of children whose health was improved by immunizations. Surely this program must be one of the most successful government programs. The CDC worked with the American Academy of Pediatrics and pediatricians to eliminate polio from America. This highly effective collaboration between Congress and the CDC and its partners is a model of how to get research results from the laboratory to public health prevention quickly. In just 2 years in the early 1990s, this partnership virtually eliminated meningitis caused by *Haemophilus influenzae*. We are near elimination of polio from the world because Congress provided the CDC approximately \$200 million per year to enable them to provide unique and essential leadership and assistance to the polio-eradication campaign.

Congress has given the CDC a budget far too small to lead an effective campaign to prevent all folic acid–preventable spina bifida in the United States, much less a global effort. The CDC budget for the total prevention of folic acid–preventable spina bifida and anencephaly is under \$10 million per year. Many of the programs that reported the data in the Williams et al article have lost their funding and will not be able even to monitor the effectiveness of the

prevention program. It is likely that even with the increase in fortification concentration that should be required by the FDA, there will be a need for the CDC and state health departments to identify women who fail to obtain sufficient folic acid from food and build effective supplement programs for them. If Congress appropriates \$200 million per year for the CDC to lead the effort to prevent all folic acid-preventable spina bifida, it is very likely that the pace of prevention will increase remarkably and thousands of children each year, who otherwise would have been paralyzed or dead, will be running on strong legs, both in the United States and many other countries.

Until the FDA, Gruma, and Congress make their required contributions toward the total prevention or "elimination" of folic acid-preventable birth defects, pediatricians can be helpful in their practices by encouraging the mothers of all their patients to consume 400 μg of synthetic folic acid per day from either breakfast cereals or supplement pills. The women who have already had an infant are known to be fertile and are at high risk to become pregnant again. Eliminating folic acid spina bifida from this group of women will make an important contribution to prevention. Pediatricians, family physicians, and obstetricians should accept this responsibility enthusiastically.

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Pertussis Vaccines for Adolescents and Adults

ABBREVIATION. Tdap, tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis, adsorbed.

On March 15, 2005, the Vaccines and Related Biological Products Advisory Committee of the Food and Drug Administration recommended the approval of 2 tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis, adsorbed (Tdap) vaccines. These vaccines, Adacel and Boostrix, are the products of Sanofi Pasteur and GlaxoSmithKline, respectively. Food and Drug Administration licensure of these vaccines occurred in May/June 2005.

Both of these vaccines have been studied extensively for immunogenicity and reactogenicity in large studies in the United States and around the world. In addition, Adacel is licensed and used in Canada, and Boostrix is licensed and used in several countries around the world. The comparative composition of the 2 vaccines is presented in Table 1.

In general, both vaccines have similar reactogenicity profiles as adult-formulated diphtheria and tetanus toxoids. After a single dose, both vaccines elicit vigorous antibody responses to the antigens that they contain. Specifically, these responses are significantly greater than those observed in infants at 7 months of age after 3 doses of the 2 manufacturers' pediatric diphtheria-tetanus-acellular pertussis (DTaP) vaccines (ie, Daptacel and Infanrix). These bridging data indicate that both vaccines will be efficacious in adolescents and adults. In addition, efficacy in adolescents and adults has been demonstrated with an experimental vaccine that contained the pertussis antigens of Boostrix without diphtheria and tetanus toxoids.¹

The licensed indications of the 2 vaccines are different. Specifically, Adacel is approved for adolescents and adults aged 11 through 64 years, whereas Boostrix is approved for preadolescents and adolescents 10 through 18 years of age.

The increase in reported pertussis in recent years and the recognition of the contribution of adolescents and adults to this increase has resulted in numerous publications in both the lay press and the medical literature.²⁻⁴ Of major concern, for which much effort has been directed during the last 5 years, is how best to use these new vaccines. The Global Pertussis Initiative⁵ addressed the complexities of pertussis be-

Accepted for publication Apr 25, 2005.

doi:10.1542/peds.2005-0960

Conflict of interest: During the last 3 years, Dr Cherry has received honoraria from GlaxoSmithKline and Sanofi Pasteur (both manufacturers of diphtheria and tetanus toxoids and acellular pertussis vaccines) for talks and participation in meetings related to diphtheria and tetanus toxoids and acellular pertussis vaccines.

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This information is current as of September 6, 2005

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