

## Points of View: On Folic Acid, Folate Fortification, and Neural Tube Defects

The two Viewpoint articles here represent a new venture for the *Journal of Nutrition Education*: the presentation of distinctly different views on the same topic. Dr. Marion Nestle's article, "Folate fortification and neural tube defects: policy implications," was submitted to the Viewpoints section of *JNE* earlier this year, with a note suggesting that we invite someone with a contrasting view to comment. We were pleased that Dr. Adrienne Bendich agreed to contribute her perspective on the fo-

lic acid and neural tube defect debate. Though neither of the articles is presented with direct reference to the other, Dr. Bendich had the opportunity to read Dr. Nestle's manuscript before preparing her assessment.

Now, it is your turn to comment. I encourage you to read both positions carefully and to consider how your own views, understanding of the science, and philosophy affect your own point of view. Please send your responses directly to me in the

form of a Letter to the Editor (up to two pages, double spaced). We will publish as many as we can in a future issue of *JNE*.

The issues here are relevant not only to the question of folic acid and birth defects but to broader nutrition policy and nutrition education themes as well. I look forward to hearing from many of you.

Karen Glanz, Editor  
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## Folate Fortification and Neural Tube Defects: Policy Implications

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### INTRODUCTION

In October 1993,<sup>1</sup> the U.S. Food and Drug Administration (FDA) proposed to amend existing food labeling regulations in order to permit food and supplement package labels to contain health claims about the relationship of folate to neural tube defects (NTDs) — spina bifida, anencephaly, and other seriously debilitating brain and spinal cord defects that result from incomplete closure of the neural tube during days 17 to 30 of fetal development.<sup>2</sup> In anticipation of the consequences of such action for the marketing of folate-containing food products, the FDA also proposed to require the addition of folate to any cereal grain product or breakfast cereal labeled as "enriched." This action marks a departure from previous uses of fortification to correct widespread nutrient deficiencies among the general population.<sup>3</sup> Instead, the FDA proposes to fortify the entire food supply with folate as a means to reduce the incidence of a

congenital condition that affects a limited segment of the population, estimated as comprising about half of the approximately 4000 infants with NTDs conceived each year.

The impetus for these unusual actions was an Act of Congress. The 1990 Nutrition Labeling and Education Act (NLEA) required the FDA to examine the validity of 10 specific nutrient-disease associations, among them folate and NTDs, as a basis for allowing health claims on foods and dietary supplements. In response to this directive, the FDA reviewed available research on folate and NTDs and found that all but one of more than a dozen studies conducted since 1980 had reported similar findings: women who consumed adequate amounts of folate during the first month of pregnancy were about half as likely to give birth to infants with NTDs as those who did not.<sup>1,4,5-7</sup>

The doses of folate used in these studies varied by more than tenfold, and few clearly distinguished the benefits of folate from those of other supplementary vitamins. Despite these and other concerns about methods,<sup>4,8</sup> the studies have been widely interpreted as providing definitive evidence of a need for more vigorous public policies to raise overall consumption levels of folate among women of childbearing age.<sup>5,9-11</sup>

At issue is the best means to achieve this goal without inducing health risks that might result from excessive folate intake. In 1992, the Public Health Service (PHS) recommended that all women of childbearing age consume 0.4

Based on remarks presented during a panel discussion of folate and neural tube defects, American Public Health Association annual meeting, San Francisco, October 27, 1993. Dr. Nestle was appointed to the FDA Food Advisory Committee in 1992 as a consumer representative.

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mg — but no more than 1.0 mg — folate daily as a safe approach to reduction of NTD risk. Without indicating a preference, the PHS outlined three potential methods that the FDA might choose to promote folate intakes within this range: use of dietary supplements, improved dietary habits, and fortification of the food supply.<sup>5</sup>

Some experts favor dietary supplements as the preferred means to achieve recommended levels of intake.<sup>12</sup> For the FDA and certain other experts,<sup>10,11,13</sup> however, fortification is the method of choice, and they cite many reasons to support their concern that providing supplements to a specified target group is unlikely to be effective. They note that risk factors for NTDs are poorly defined; only 5% of NTD births are recurrences (to mothers who have already given birth to an NTD infant); high-risk women cannot be identified in advance; many pregnancies are unplanned; and neither supplements nor diets are likely to reach all women of childbearing age. Although 0.4 mg is precisely the amount of folate recommended for daily consumption during pregnancy,<sup>14</sup> and is a level easily met through consumption of diets consistent with current recommendations,<sup>15,16</sup> these experts view diets as too difficult to change to consider public education as a reasonable alternative.

Although such judgments appear to be well supported by research, many aspects of the relationship of folate to NTDs remain uncertain. Such uncertainties suggest a need to reconsider fortification as the preferred option and to examine whether the health of infants as well as the public might be better served by more forceful public policies to promote overall improvements in dietary intake.

## FORTIFICATION POLICIES

Fortification began in the U.S. in 1920 when iodine was added to salt as a means to prevent goiter. Today, vitamin D is added to milk and infant formulas, vitamin A to margarine and low-fat milks, fluoride to drinking water, and thiamin, riboflavin, niacin, and iron to cereal grains. These additions have been credited with the virtual disappearance of goiter, rickets, pellagra, beriberi, and other classic syndromes caused by deficiencies of single nutrients.<sup>17</sup> In at least some cases, however, factors other than fortification may also have contributed to the decline in deficiency diseases, prompting the FDA to assign only partial responsibility for the decline to fortification itself.<sup>1</sup>

The case of niacin and pellagra best illustrates this point. Death rates from pellagra were declining well *before* the initiation of mandatory niacin fortification, and the rates consistently fell by half every 4 years from 1938 (when there were 3200 deaths) to 1954 (when there were less than 200). Congress mandated niacin fortification in 1943 but repealed it in 1946, and only 22 states required fortification by 1948.<sup>17</sup> Under these circumstances, the proportion of pellagra deaths prevented by niacin fortification is difficult to determine.

Folate fortification of cereal-grain products was first proposed by the Food and Nutrition Board (FNB) of the National Academy of Sciences in 1974, at a level of 0.07 mg per 100 g, then believed to be equivalent to the amount lost during the milling of whole wheat to white flour. Although later technical studies reported that the folate content of whole-wheat flour was only 0.044 mg per 100 g, and that of white flour 0.026 mg per 100 g,<sup>18</sup> the level of 0.07 mg per 100 g continues to be referred to as "restoration." Thus, the FDA's new requirement to add folate to flour, rice, corn meal, pasta, and other cereal grain products at a level of 0.14 mg per 100 g, defined as twice restoration,<sup>1</sup> will actually bring the total amount of folate in fortified white flour to nearly four times the amount present in whole-grain flour.

## FOLATE FORTIFICATION: POLICY DEVELOPMENT

Table 1 summarizes key events that have led to current FDA policies. Because folate fortification policies are inextricably linked to policies for health claims, labeling, and dietary supplements,<sup>19</sup> this history is complex and difficult to follow. In addition to their scientific and health rationale, FDA policies also must be understood in their larger socioeconomic context; they derive, in part, from increasing pressure on Congress from the dietary supplement and health food industries to pass legislation that these industries "can live with."<sup>20</sup> This pressure, in turn, must be understood as industry response to increasing competition for consumer food purchases.<sup>21,22</sup>

In the past, health claims were prohibited on food package labels in order to avoid having to regulate them as drugs. In 1984, The Kellogg Company, with the support of the National Cancer Institute, placed a statement on its Bran Flakes packages suggesting that eating such cereals would help reduce cancer risk ("The National Cancer Institute believes eating the right foods may reduce your risk of some kinds of cancer...that's why a healthy diet includes high fiber foods like bran cereals."). This marketing strategy was reported to have increased sales of high-fiber cereals by as much as 47% in just 6 months.<sup>23</sup>

In an attempt to regulate such claims, the FDA proposed to allow package labels to state only messages that are based on valid, publicly available scientific evidence. Reportedly, this standard was viewed by the White House Office of Management and Budget (OMB) as too restrictive to the food industry and it delayed the release of the FDA-proposed health claims rules until 1987.<sup>24</sup> In 1988, when the FDA again attempted to draft rules, the OMB again blocked approval.<sup>25</sup> Only in 1990, after the Department of Health and Human Services (DHHS) announced its Food Labeling Initiative, was the FDA finally able to propose revised rules for the development of health claims.

**Table 1.** Key events in the history of current FDA proposals related to folate and NTDs.\*

|               |  |
|---------------|--|
| 1971 (Apr 9)  | FDA evaluates use of folate as drug; cautions that therapeutic doses above 1.0 mg/day may obscure pernicious anemia (36 FR 6843)   |
| 1974          | National Academy of Sciences' Food and Nutrition Board (FNB) proposes expansion of cereal-grain enrichment to include folate at 0.07 mg/100 g ("restoration" level)  |
| 1980 (Oct 17) | FDA amends 1971 caution statement to say that therapeutic folate doses above 0.1 mg/day may obscure pernicious anemia (45 FR 69043)  |
| 1984 (Oct)    | Kellogg's advertisements suggest that eating its high-fiber cereals may help reduce cancer risk  |
| 1985 (May 22) | Kellogg petitions FDA to permit food package labels to contain health claims considered valid by qualified experts   |
| 1987 (Aug 4)  | FDA proposes policy change to permit health messages on food labels (52 FR 28843)  |
| 1990 (Feb 13) | FDA withdraws 1987 proposals and replaces them with new proposed rules for health claims (55 FR 5176)  |
| 1990 (June)   | FNB issues report on nutrition during pregnancy; judges evidence on vitamin supplementation and NTDs inconclusive; makes no recommendation <sup>6</sup>  |
| 1990 (Nov 8)  | Nutrition Labeling and Education Act (NLEA, PL 101-535) amends 1938 Food, Drug, and Cosmetic Act; requires FDA to evaluate 10 nutrient-disease relationships, including folate and NTDs, as basis for permitting health claims |
| 1990 (Nov 14) | House Government Operations Committee charges that OMB interference with health claims proposals has delayed FDA action for at least 3 years <sup>25</sup>   |
| 1991 (Mar 28) | FDA asks for information about 10 nutrient-disease topics including folate and NTDs (56 FR 12932)  |
| 1991 (July)   | Medical Research Council multicenter trial reports large reductions in NTD recurrences among women taking high-dose (4.0 mg/day) folate supplements <sup>26</sup>  |
| 1991 (Aug)    | CDC advises women with history of NTD pregnancy to take 4.0 mg folate/day prior to and 3 months after the onset of pregnancy <sup>9</sup>  |

**Table 1.** (continued)

|                   |   |
|-------------------|---|
| 1991 (Nov 27)     | FDA proposes general requirements for health claims to conform to the NLEA (56 FR 60537); denies health claim for folate and NTDs on basis of insufficient evidence that usual dietary levels can reduce risk (56 FR 60610)                                       |
| 1992              | FNB updates 1990 pregnancy report; recommends that women with history of NTD pregnancies take high-dose folate supplements; notes that several key questions require further research <sup>7</sup>  |
| 1992 (Jul 23)     | FDA reopens comment period in response to reports of new studies on folate and NTDs (57 FR 32751)   |
| 1992 (Sept 11)    | PHS recommends that all women of childbearing age in the U.S. consume 0.4 mg folate/day in order to reduce NTD risk by 50%; identifies improved diet, use of supplements, or fortification as options <sup>5</sup>  |
| 1992 (Oct 6)      | Congress passes Dietary Supplement Act (PL 102-571); imposes moratorium on FDA implementation of 1990 NLEA rules on dietary supplements; directs FDA to issue proposed rules by 15 June 1993 and final rules by 31 Dec 1993                                       |
| 1992 (Nov 23, 24) | FDA Folic Acid Subcommittee supports PHS recommendations in principle but recommends against health claims and is divided on fortification  |
| 1993 (Jan 6)      | FDA issues final rule on NLEA; requires health claims to be based on well-designed studies and on significant scientific agreement among qualified experts (58 FR 2478); denies health claim for folate and NTDs because of unresolved safety issues (58 FR 2606) |
| 1993 (Mar 10)     | House introduces Birth Defects Prevention Act of 1993 (HR 1296) to establish CDC as coordinating agency for birth defects prevention, research, and monitoring programs   |
| 1993 (Apr 7)      | Dietary Supplement Act of 1993 introduced (S 784 by Hatch; HR 1709 by Richardson) to permit health claims on dietary supplements and to create new office at NIH to coordinate research and advise on supplement issues   |
| 1993 (Apr 15)     | Folic Acid Subcommittee meets, expresses diverse opinions, supports health claim and fortification proposals in close vote  |

Table 1. (continued)

|                   |  |
|-------------------|--|
| 1993 (June 18)    | FDA proposes rules for health claims on dietary supplements in response to Dietary Supplement Act; initiates review by Folic Acid Subcommittee of folate and NTDs to ensure that health claims regulations are consistent with science (58 FR 33700) |
| 1993 (Aug 12)     | CDC convenes meeting to discuss surveillance and monitoring of risks and benefits of folate fortification; discussion reveals inadequacy of current methods for such surveillance <sup>41</sup>  |
| 1993 (Oct 14)     | FDA proposes to allow folate health claims (58 FR 53254) and to fortify cereal-grain products (58 FR 53305; 58 FR 53312); requests comments until 13 Dec 1993  |
| 1993 (Oct 14, 15) | Food Advisory Committee and Folic Acid Subcommittee discussion reveals substantial disagreement on both health claims and fortification <sup>28</sup>  |
| 1993 (Nov)        | Dietary Supplement Moratorium Acts introduced (HR 3650 by Waxman; S 1762 by Hatch) to extend the moratorium on dietary supplement regulations  |
| 1993 (Dec 31)     | FDA fails to meet deadline set by the 1992 Dietary Supplement Act, thereby permitting health claims for folate supplements   |
| 1994 (Jan 4)      | FDA issues final rules confirming the Oct 14, 1993 proposals for folate health claims for dietary supplements (59 FR 433)  |

\*Adapted, unless otherwise indicated, from information in reference 1 and other Federal Register (FR) notices cited by volume and first page number.

At that point, the evidence relating folate to NTDs was considered too weak to merit public health recommendations.<sup>6</sup> Nevertheless, in passing the NLEA, Congress specifically required the FDA to examine this relationship as a basis for permitting a health claim. When the results of the long-awaited Medical Research Council intervention trial identified large reductions in NTD recurrences among women taking high-dose folate supplements,<sup>26</sup> the Centers for Disease Control (CDC) issued an advisory that women with a history of an NTD pregnancy should take supplements before and during pregnancy.<sup>9</sup> Despite this action, the FDA ruled that scientific agreement was insufficient to

authorize a health claim for folate and NTDs. Thus, the policies of at least two PHS agencies — the CDC and the FDA — were revealed to be in conflict.

When new studies provided further evidence for the benefits of folate in preventing NTDs, the FDA reopened the comment period. Soon after, PHS agencies issued their joint recommendation that all women of childbearing age consume 0.4 mg per day of folate to reduce NTD risk.<sup>5</sup> Despite this announcement, interagency conflicts over methods for achieving this goal remained unresolved.<sup>27</sup>

Perhaps for that reason, the FDA's actions were viewed as insufficient by Congress, which amended the Food, Drug, and Cosmetic Act by passing the Dietary Supplement Act of 1992. This act prevented the FDA from immediately applying restrictions on health claims for conventional foods to dietary supplements, required extensive investigation of the agency's methods for developing regulations, and required the FDA to publish final rules by December 31, 1993.

In response to such pressures, the FDA appointed a Folic Acid Subcommittee of its Food Advisory Committee to advise the agency on issues related to folate and NTDs. The subcommittee's initial meeting revealed substantial disagreement about multiple issues related to the FDA's health claims and fortification proposals. When the FDA issued final rules for conventional foods in January 1993, it again denied authorization of a health claim for folate and NTDs on the basis of unresolved safety issues. In April, Congress proposed additional legislation to permit health claims on dietary supplements and to weaken the FDA's ability to regulate such claims. These bills were strongly supported by the dietary supplement industry.<sup>20</sup>

In response, the FDA proposed new rules on health claims and dietary supplements and announced initiation of a subcommittee review to ensure that health claims on folate and NTDs would be consistent with the available research evidence. On October 14, 1993, the FDA published its proposed rules on folate fortification and health claims<sup>1</sup> and convened a joint meeting of the Food Advisory Committee and its Folic Acid Subcommittee to review them. The discussions at this meeting were characterized by mild to substantial disagreement on virtually every issue related to the quality of the studies, the basis for a health claim, the value of fortification, and the level of fortification. One point of consensus was that uncertainties in the data on these issues made them exceedingly difficult to resolve.<sup>28</sup>

By the end of 1993, the FDA had failed to meet the deadline for final rules established by the 1992 Dietary Supplement Act, thereby permitting the package labels of dietary supplements to carry health claims for folate and NTDs. In January 1994, the agency issued final rules for folate health claims on dietary supplements but delayed issuing rules for claims on foods. Pending completion of such rules, the FDA advised producers that it would not

take action against health claims for folate-containing conventional foods but that it was discouraging their use for foods fortified with folate. As of September, 1994, the FDA still had not issued final rules for folate health claims or fortification of conventional foods.

## UNRESOLVED ISSUES

Although an increasing number of studies support the benefits of folate in preventing new and recurrent NTDs, critical aspects of these studies remain unresolved.

**Decline in prevalence.** Overall rates of NTDs have declined steadily since their peak in the 1930s, for reasons that remain uncertain. Current rates are less than 1 in 1000 live births and may represent a baseline genetic level.<sup>29</sup> Rates of NTD recurrences also have declined, although to a lesser extent.<sup>30</sup> These secular trends raise questions about the level of benefit that might be expected from fortification.<sup>31</sup>

**Cause.** The etiology of NTDs remains uncertain. Folate is likely to be only one among a number of environmental factors that affect NTD risk.<sup>2</sup> Deficiencies of several nutrients have been associated with NTDs in animal studies.<sup>32</sup> One recent human study concluded that both vitamin B<sub>12</sub> and folate are independent risk factors for NTDs, and that both should be included in supplement programs.<sup>33</sup>

**Risk factors.** Prevalence varies by geographic location, ethnicity, and class, as well as by nutrient intake, but not always systematically,<sup>2</sup> and insufficient information exists to identify groups at especially high risk.

**Responsive populations.** One recent intervention trial of periconceptional folic acid-containing multivitamins demonstrated that they reduced NTD risks among Caucasian women but not among those of Mexican descent, raising the possibility that more targeted strategies may be needed to prevent NTDs in this group.<sup>34</sup>

**Optimal intake.** Because clinical studies have used single doses of folate that were often much higher than amounts commonly consumed, the minimal amount needed to reduce NTD risk is undefined. The recommended level of 0.4 mg per day can be achieved through normal dietary intake. At least one study has demonstrated an association between dietary intake levels below 0.2 mg per day and increased NTD risk.<sup>35</sup>

**Food folate.** Although surveys suggest that average folate intakes are well below recommended levels,<sup>36</sup> most were based on food composition data derived from older assay methods that were prone to error. The best of these

methods, for example, required enzymatic release of bound folate, followed by measurement of the ability of the released folate to promote bacterial growth; food composition data based on this method were first published only in 1977.<sup>37</sup> Surveys based on these or any other data obtained prior to the late 1980s, when methods improved, are most likely to have underestimated food folate content.<sup>38</sup>

**Fortification safety.** Existing data cannot yet resolve safety concerns about the impact of folate fortification on individuals with undiagnosed pernicious anemia (especially the elderly), conditions requiring anticonvulsant medications, hypersensitivity reactions, or problems with zinc absorption,<sup>39</sup> on those taking antifolate medications,<sup>40</sup> or on children.<sup>32</sup> The prevalence rates of conditions that might be induced by excess folate are not well known, however, and it will be difficult to determine whether folate fortification affects them.<sup>31</sup> In any case, no upper limit of safe intake of folate has been defined.

**Optimum fortification level.** Representatives of the March of Dimes and the CDC have expressed concerns that fortification at twice restoration will fail to raise average intakes to 0.4 mg per day, and that much higher levels — 5 to 10 times restoration (0.35–0.7 mg/100 g) — should be used.<sup>25,41</sup> Although some epidemiologists support this view,<sup>42</sup> others do not.<sup>31</sup> Existing data do not permit estimation of the proportion of the at-risk population that will be reached by fortification or of the effects of various levels of folate fortification on NTD or other risks.

## LACK OF CONSENSUS

FDA regulations allow proposals for health claims only when qualified experts are in significant agreement that the scientific evidence supports the claim.<sup>1</sup> In the case of folate and NTDs, the governments of several countries, agencies of the PHS, and members of FDA advisory committees disagree markedly about the implications of existing research for public policy.

Uncertainties in the data and concerns about safety have led the governments of Canada<sup>43</sup> and the Netherlands<sup>44</sup> to recommend only that all women of childbearing potential eat a healthy diet but that women at special risk take supplements. On the other hand, the government of the United Kingdom advises all women planning a pregnancy to take a daily supplement of 0.4 mg.<sup>45</sup>

Policy disagreements among staff of PHS agencies are especially pronounced,<sup>24</sup> with some individuals strongly promoting much higher levels of fortification and others arguing against any fortification at all.<sup>25</sup> Such public displays of opposing views among staff members of one federal agency are highly unusual and reflect divergent interpretations of an uncertain data base.

## POLICY IMPLICATIONS

Despite the debates and data limitations, the FDA chose to propose the new folate rules. Whether these proposals would be effective in raising folate intake and reducing NTD rates remains to be determined. Given the uncertainties, federal promotion of its own dietary recommendations deserves much more serious consideration as a policy option.

The current FDA policy proposals are a "techno-fix"<sup>46</sup>; they are designed to promote technologic "improvement" of foods in response to specific guidelines on nutrition and health.<sup>47</sup> Techno-fixes do not truly address the underlying social and economic determinants of NTDs or other conditions related to poor dietary intake. Like all such approaches, this one is likely to promote the proliferation and consumption of processed foods, cost more, and, as we have already observed, require long and complex federal regulations<sup>17</sup> — all unnecessary actions.

To meet folate recommendations, individuals need only follow current dietary advice to emphasize intake of fruits, vegetables, and minimally processed grains.<sup>15,16,48</sup> Such diets are well worth promoting for their additional benefits in vitamin, mineral, antioxidant, and fiber consumption, and for their well-documented association with prevention of a wide range of chronic diseases.<sup>49</sup> If the history reviewed here teaches us any lesson, it is the multiple health benefits of diets that meet current recommendations. The casual rejection of dietary approaches to NTD prevention misses a "teachable moment" in which to address NTD risks while improving the overall nutritional health of the population.

I am unconvinced by arguments that nutrition education will not work and that people will not consume healthy diets;<sup>10</sup> substantial evidence supports the value of education in reducing dietary risks for conditions of undernutrition<sup>50</sup> as well as overnutrition.<sup>51</sup> Instead, as some critics have noted, nutrition education for the general public in this country has "scarcely been tried."<sup>47</sup> The U.S. government has never promoted fruit and vegetable consumption with anywhere near the resources or policy initiatives used routinely to promote processed, meat, and dairy foods.<sup>21,46,47</sup> Before concluding that dietary approaches are ineffective, such policies should be implemented and evaluated. The National Cancer Institute's 5-A-Day campaign to encourage daily consumption of at least five fruits and vegetables is a small step in the right direction,<sup>52</sup> but its promotional resources are hardly comparable to those routinely deployed by the dietary supplement industry.

In the meantime, the PHS must be urged to fund investigations designed to answer at least some of the remaining scientific questions about the role of folate in NTDs and to address the additional questions about the value and efficacy of the FDA's new folate policies that are sure to arise when such policies are implemented.

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