Folate Fortification for the Prevention of Birth Defects: Case Study

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In 1996, after more than a decade of debate, the US Food and Drug Administration’s (FDA) agreed to the fortification of cereal-grain products with folic acid to reduce the occurrence of neural tube defects in newborns (1). Issues considered were 1) whether the epidemiologic evidence showed a potential benefit from increasing folic acid intake in the periconceptional period; 2) the folic acid intake in the population; 3) alternative strategies for increasing folic acid intake in the susceptible population (i.e., women at risk of becoming pregnant); and 4) the possible harmful effects, such as the possibility that folic acid fortification could interfere with the early diagnosis of anemia in persons with vitamin B12 deficiency.

This case study is a review of the decision-making process leading up to the 1996 FDA ruling and includes a discussion of particular aspects of the translation of the epidemiologic findings to public policy. Some of these aspects have recently been addressed by Elwood et al. (2), Scott et al. (3), and the Food and Nutrition Board of the Institute of Medicine (4). The debate on folate fortification has been expanded as new information accumulates about potential beneficial effects of folic acid on cardiovascular and other chronic diseases, but these issues will not be considered in this case study.

REGULATORY HISTORY OF FOLIC ACID

Folic acid is the synthesized stable oxidized form of an essential water-soluble B-complex vitamin that occurs naturally as various folates, usually in reduced, conjugated forms. Folic acid is used in supplement tablets and food fortification, while folates are found naturally in foods. Folates play an important role in single-carbon transfer reactions and in several metabolic pathways including the synthesis of purines and pyrimidines, and, hence, in the formation of DNA and RNA. These actions have complex relations with other essential vitamins, especially vitamin B12 (5). Prior to 1996, the principal food sources for folates were dark green leafy vegetables, organ meats, eggs, and citrus fruits (6). A severe deficiency of folate manifests as megaloblastosis. The addition of folic acid to foods and use of folic acid as a drug (but not as a dietary supplement) is regulated by the FDA, which uses somewhat different criteria and procedures depending upon whether the vitamin is to be used as a drug or as a food additive (7).

Folic acid as a drug

Folic acid administered orally or parenterally is effective in the treatment of megaloblastic anemias originating from tropical and non-tropical sprue or nutritional deficiency, and those that may occur during pregnancy, infancy, and childhood. Folic acid is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias involving vitamin B12 deficiency, because such treatment may delay the appearance (i.e., “mask”) and diagnosis of this type of anemia (8). Serious consequences of vitamin B12 deficiency, including severe and often irreversible neurologic damage, may progress and worsen as a result of failure to detect the anemia at an early stage and to initiate appropriate therapy with vitamin B12 (9).

The interactions between the functions of folate and vitamin B12 have been recognized for many years and are the basis for the FDA’s precautionary statement in its regulation on oral and parenteral preparations of folic acid for therapeutic use. Labeling regulations for therapeutic preparations of folic acid were published in 1971, and included the following statement (10): “Folic acid especially in doses above 1.0 mg daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive.” This statement was amended in 1980 because the agency found that a level as low as 0.25 mg of folic acid per day may obscure pernicious anemia in some individuals (8). The statement was revised to read (11): “Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission may occur while neurological manifestations remain progressive.”
Folic acid as a food additive

The addition of nutrients to food is an effective way of maintaining and improving the overall nutritional quality of the food supply. When the early fortification programs were initiated, deficiency diseases were widespread in the US population. To assist in implementing the fortification programs, the FDA often used “standards of identity” for several cereal-grain products carrying the label “enriched.” The standards require fortification at specific minimum levels with thiamin, riboflavin, niacin, and iron for foods labeled “enriched” (e.g., “enriched bread,” “enriched noodles,” “enriched flour”). The fortification program for cereal-grain products in the United States is voluntary in the sense that a manufacturer does not have to make an enriched product. If a manufacturer elects to produce an enriched product and to use the term “enriched” on the label, however, that manufacturer must include at least the minimum levels of all nutrients specified in the standard. While the majority of wheat-based cereal-grain products are currently enriched, it is possible to find unenriched versions of rice, corn meals, and certain other cereal-grain products in health food stores and specialty stores.

In 1973, the FDA published a final rule establishing safe conditions for use of folic acid in foods (12). The food additive regulation was published shortly after the drug regulation and provided that folic acid could be added to foods if the maximum daily intake did not exceed 0.4 mg/day for food labeled without reference to age or physiologic state. The regulation also included limitations based on age and the conditions of pregnancy or lactation.

When discussions turned to considerations of fortification of the general food supply, the FDA recognized that this regulation provided no guidance to manufacturers as to how to reach the stated limit of 0.4 mg/day, and, as such, was inadequate to allocate folic acid safely in the general food supply. Specifically, the regulation lacked sufficient guidance to enable vendors of foods to decide which foods were appropriate for fortification and the levels at which folic acid should be added. As the regulation stood in 1993, there was nothing to prevent the addition of folic acid to virtually any food.

In 1974, the Food and Nutrition Board of the National Research Council, National Academy of Sciences, published a proposed fortification policy for cereal-grain products and recommended expansion of the existing enrichment program for cereal-grain products to include folic acid and a number of other nutrients (13). Technical feasibility studies were carried out following the 1974 National Research Council recommendation and results were presented at a workshop in 1977 (14).

In 1980, the FDA codified a uniform set of principles to serve as a model for the rational fortification of foods (15). The FDA defined “fortification” as the addition of discrete nutrients such as vitamins, minerals, or proteins to foods, and stated that fortification should serve as a means of maintaining and improving the overall nutritional quality of the food supply. According to the codified principles, fortification is appropriate 1) to correct a dietary insufficiency recognized by the scientific community (i.e., data must demonstrate that a nutrient deficiency clearly exists); 2) to restore nutrients lost during processing; 3) to balance the vitamin, mineral, and protein content of a food based on caloric density; 4) to avoid nutritional inferiority; and 5) to comply with an existing regulation. The FDA stated in its fortification policy that the foods that are appropriate vehicles for fortification are those that are consumed by significant portions of the population in meaningful amounts. Nutrients must be provided in bioavailable form and should be stable under normal conditions of use and storage. Finally, the level of nutrients added in fortifying a food must preclude toxic effects.

HEALTH CLAIMS AND FORTIFICATION

During the 1980s, several observational epidemiologic studies reported a favorable association between folic acid supplementation and a reduced recurrence of neural tube defects. The FDA began evaluating the folate/neural tube defects relation in 1990 as part of its response to the health claims portions of the Nutrition Labeling and Education Act of 1990. In addition to its authority to regulate the use of food additives, the FDA has responsibility for the safety of substances that are the subject of health claims. For example, the FDA cannot authorize a health claim if ingestion of the substance that is the subject of the claim will increase the risk of a disease or a health-related condition in persons in the general population. In July 1991, data from the British Medical Research Council’s multicenter randomized trial in women at recurrent risk of a neural tube defect-affected pregnancy were published (16). The following month, based on the Medical Research Council’s study, the US Centers for Disease Control and Prevention issued a recommendation in the MMWR Morbidity and Mortality Weekly Report advising 4 mg/day intake for women who had had a neural tube defect-affected pregnancy and were planning to start a new pregnancy (17). A few months later in November, however, the FDA proposed to deny a health claim for the relation between folate in fortified foods and reduced risk of neural tube defects (18). This was a controversial decision. Some experts concluded it was not possible to generalize a potential beneficial effect from the therapeutic level of folic acid evaluated in the Medical Research Council’s trial (4 mg/day) to a beneficial effect from levels of folate attainable in usual diets of women in the US population, who are at much lower risk of a neural tube defect-affected pregnancy.

Careful review of the combined trial and observational data that were available was conducted (19), and in September 1992, the US Public Health Service issued a recommendation that all women of childbearing age in the United States consume 0.4 mg of folic acid per day to reduce their risk of a neural tube defect-affected pregnancy (19). Several experts concluded that the size of the risk reduction attributable to folic acid at doses of 0.4 mg calculated using the non-randomized studies (20–22) was comparable with that at doses of 0.8 mg (23) and 4 mg (16) from the randomized studies (19, 24). The US Public Health Service recommendation identified three possible approaches for delivering folate to women in the general population: 1) increased intake of dietary folate; 2) daily use
of a folic acid supplement throughout the childbearing years; and 3) fortification of the general food supply.

With regard to the first approach, it was widely recognized that it would be very difficult to get women to significantly change their diets to achieve desirable levels of daily folate (i.e., at least a twofold increase from their estimated current levels). The second approach would be effective for those women who would take folic acid supplements regularly. At present only about 25 percent of women take regular supplemental vitamins, and the percentage is lower in low income populations. Relying on women to start taking folic acid supplements at least 1 month before they become pregnant was not considered a viable universal strategy, since about 50 percent of pregnancies are unplanned in the United States and many other industrialized countries. The third approach was also fraught with many uncertainties. In order to reduce the estimated 4,000 neural tube defect pregnancies that occur annually in the United States, the entire population of 260 million people of all ages and both sexes would be exposed to additional folic acid throughout their lifetimes. It was pointed out that fortifying foods with folic acid might pose safety concerns for some not at risk for neural tube defects. These included the elderly who are at risk for vitamin B\textsubscript{12} deficiency and children who have not previously been exposed to increased levels of folate intake. Furthermore, the available information from studies of women of childbearing age did not allow for a clear description of the dose-response relation of folic acid and risk of neural tube defects so that the optimal amount of folic acid to be added to the diet was uncertain.

When the FDA’s Folic Acid Subcommittee of the Food Advisory Committee met in November 1992, the questions of health claims, fortification, and safety issues of the general population were discussed. There was concern that with the authorization of a health claim, manufacturers would add folic acid to many foods in order to be able to use the claim on food labels. As noted above, the 1973 food additive regulation provided insufficient guidance to prevent this from happening. In January 1993, the FDA denied the health claim pending resolution of safety concerns (1).

Although no new data became available regarding potential adverse effects at high intakes of folic acid, in October 1993, the FDA proposed to authorize the health claim and to provide for fortification of enriched cereal-grain products to a limited extent. The provision for fortification was carried out by issuing a rule on standards of identity for enriched foods and amending the existing food additive regulations for folic acid. Manufacturers then had to alter their ingredients in all foods subject to the rule and bearing the label “enriched.” When the Folic Acid Subcommittee had met in November 1992, there was considerable controversy over both the proposal for fortification and the proposal for allowing a health claim. While the FDA’s responsibility was to provide for safe increases in the folic acid added to foods, the agency had to consider both the needs of women of childbearing age to increase their folate consumption and potential risks to “non-benefiting” groups who might be at risk from high intakes of folate. These concerns existed despite a dearth of information about what these risks in humans might be. One way to achieve this balance was to restrict the foods to which folic acid might be added to enriched cereal-grain products and certain other foods. While the fortification program could not guarantee that a large proportion of women of childbearing age would receive 0.4 mg of folate/day, it did provide for significant increases in intake for most women (by approximately 0.1 mg/day) while not exposing non-target groups to levels considered too high (figure 1). On the other hand, several scientists concerned with helping women of childbearing age meet the US Public Health Service recommendations advocated fortification of enriched cereal-grain products with higher doses of folic acid (24–28).

A health claim for dietary supplements on the relation between folate and neural tube defects was authorized in January 1994. The Federal Register documents authorizing a health claim for folate and neural tube defects on food labels and authorizing the addition of folic acid to enriched cereal-grain products and to certain non-standardized foods were published in March 1996, with the effective date for the fortification set for January 1, 1998 (29–31). The standards of identity for enriched flour and other enriched cereal-grain products were amended to include folic acid at levels of 0.095–0.308 mg/100 g.

**EPIDEMIOLOGIC EVIDENCE LINKING FOLIC ACID AND NEURAL TUBE DEFECTS**

Neural tube defects affect approximately 2,500 births in the United States each year. Since the neural tube is closed by the 28th day after conception, the factors leading to neural tube defects have already had their impact on neural tube development before the woman may realize she is pregnant. In areas of high prevalence of neural tube defects, it is often found that women of lower socioeconomic status are at higher risk for bearing children with this condition (2). There have been marked variations in rates of neural tube defect-affected pregnancies over time, including reductions in recent years, even prior to fortification policies. These variations and differences between geographic areas suggested the effect of environmental factors. That neural tube defects have a strong familial or genetic component was widely recognized, since the recurrence rate of neural tube defect births among women who had previously had a neural tube defect pregnancy was many times greater than the risk for women without a prior neural tube defect birth (1–2 per 100 versus 1 per 1,000, or a relative risk of 10– to 20-fold) (2, 32). The recent decline in the prevalence of neural tube defects at birth is partly explained by prenatal diagnosis and termination of pregnancies, but it is also believed that there has been a reduced incidence of neural tube defects in early pregnancy in many Western countries due to generally improved nutrition.

Folic acid was suggested as a protective factor by Hibbard (33) following reported associations of inadequate doses of a folate antagonist used as an abortion agent with malformed fetuses (34) and a report that rat embryos in folate-deficient dams were almost all malformed (35). Hibbard and Smithells (36) reported that mothers who had
just delivered a baby with a central nervous system malformation had a reduced formiminoglutamic acid excretion test, which is suggestive of folate deficiency. The hypothesis inspired several intervention studies to be planned in women with a previous pregnancy affected by a neural tube defect in south Wales, and a multicenter study in England and Northern Ireland. One of three ethics committees reviewing Smithells' multicenter study insisted that all mothers receive treatment with the multivitamin preparation (containing 0.360 mg of folic acid), preventing a randomized controlled trial. Thus, it appears, at least one group felt there was already enough evidence for beneficial effects of folic acid to make withholding it from some mothers unethical; yet there was insufficient evidence to warrant the general obstetric practice of advising that women planning to become pregnant consume supplemental folic acid. This could be considered a major missed opportunity to rigorously evaluate the benefits of folic acid supplementation. Smithells proceeded with a non-randomized study in which all subjects who had affected children and enrolled in the study before conception were treated with 0.360 mg of folic acid, while those subjects who came for care after conception, or refused to take the treatments, were used as a comparison group (37–39).

At about the same time, Laurence et al., in south Wales, conducted several studies to prevent recurrence of neural tube defects involving both dietary education (40) and a double-blind randomized controlled trial of periconceptional high dose folic acid supplementation at a daily dose of 4.0 mg (41).

The two studies using folic acid supplementation had provocative results suggesting significant benefits of folic acid supplementation in reducing the rate of neural tube defects (the recurrence rate), but both had methodological problems. In the Smithells trial (38), criticism was leveled at the lack of a comparable concurrent control group. Laurence et al. (41) found a significant reduction in recurrence of neural tube defects in the group treated with folic acid, but their results were not widely accepted because of post-hoc analyses with treatment group reassignments after the event. A re-analysis as an intention to treat analysis (19) found the treatment differences not statistically significant. The trials failed to show significant benefits using the original groupings but did so after reclassification of some of the participants after the outcomes of the pregnancies were known.

Following these trials, a number of observational case-control studies were conducted (21, 22, 42–44). With one exception, all showed significantly lower odds ratios in women who used multivitamins in the periconceptional period. Even the one exception showed a non-significant reduction in risk of neural tube defects in the folic acid users (43). Nonetheless, these studies were not considered definitive because vitamin users were a self-selected, probably health conscious group. Furthermore, in many of these studies, the “multivitamins” were defined differently and their actual compositions were not known.
One prospective cohort study avoided some of the limitations of these case-control studies. That was the study of women identified at prenatal screening whose periconceptional vitamin usage was assessed (in 93 percent of the participants) before the outcome of the pregnancy was known (20). Women took various supplements prior to conception and attempts were made to relate folate content of the supplements with pregnancy outcome (i.e., reduction in risk of a neural tube defect pregnancy and folate content of the supplements used). The use of multivitamins containing folic acid during the first 6 weeks of pregnancy was associated with a significant reduction in risk of neural tube defects, while use of supplements that began after the first 6 weeks was not.

The issue was finally resolved by two randomized clinical trials, one in women who had had an affected child and one in a general obstetric population. The first, conducted by Nicholas Wald for the Medical Research Council (16), used a factorial design. Woman were given folic acid (4.0 mg.) alone, multivitamins alone, both, or neither. Recurrence rates were significantly lower in the groups that received folic acid compared with the groups that did not. In fact, the authors estimated that folic acid prevented 72 percent of neural tube defects (95 percent confidence interval 29, 88 percent).

Czeizel and Dudas (23) conducted a randomized trial of multivitamins (with 0.8 mg of folic acid) versus copper, manganese, zinc, and low dose vitamin C in women without a history of prior neural tube defects coming to a preconceptional care clinic. Slightly over 2,000 women in the multivitamin group experienced no neural tube defects, while the same number of women in the other group had six neural tube defects. The difference was statistically significant.

On the basis of these studies, the decision was made by the FDA that folic acid can prevent neural tube defects when taken in the periconceptional period. Shortly after this decision was made, the case-control study by Werler et al. (22) of women in Boston, Philadelphia, and Toronto provided confirmatory information about the likely effectiveness of a dose of folic acid of 0.4 mg in the periconceptional period in reducing the risk of neural tube defects. In comparison with several of the previous observational studies, the relative risk estimate, namely 0.3, was remarkably similar to that found in the Medical Research Council trial that used 10 times that dose (4.0 mg) for women with a prior affected pregnancy. The study also presented data for women not taking supplements, suggesting a trend of reduced risk of neural tube defects with increasing levels of daily dietary folate. A similar trend for total folate intake (supplements and dietary sources) had previously been found by Bower and Stanley (42) in Australia. The protective effect suggested with dietary folate alone was far less than that estimated with folic acid supplements, but the estimated protection would likely be attenuated because of measurement variability associated with estimating dietary intake. Therefore, the true protection of dietary folate intake of about 0.3 mg might be greater than the estimated 60 percent. These two studies suggest some benefit (although not maximal benefit) for doses of folic acid or food folate below 0.4 mg daily.

**INTAKE OF FOLIC ACID AND FOLATES IN THE UNITED STATES PRIOR TO FORTIFICATION**

The consumption of folic acid and food folates by the population has been estimated by ongoing national surveys. The National Health and Nutrition Examination Survey conducted by the National Center for Health Statistics (45), and the Nationwide Food Consumption Survey and the Continuing Survey of Food Intakes by Individuals conducted by the US Department of Agriculture (46) are the principle sources of information. These surveys include the ability to estimate the consumption of folates naturally occurring in foods and the ingestion of folic acid in dietary supplements. Prior to fortification, data from the 1988–1994 National Health and Nutrition Examination Surveys showed that the combined intake of both forms was distinctly bimodal and skewed, with a primary peak at about 0.2 mg/day and a secondary smaller peak at about 0.6 mg/day. The latter reflected the intake, by about 25 percent of the population, of vitamin supplements containing the standard dose of 0.4 mg of folic acid. Approximately 5 percent of the population consumed more than 1.0 mg of folic acid per day, while about 25 percent ingested less than 0.2 mg/day. The distribution patterns differed somewhat by age and sex. Among women aged 19–50 years, about 65 percent consumed less than 0.4 mg of total folates per day, but of females aged 14–18 years, about 85 percent consume less than 0.4 mg/day, as shown in figure 2 (4). Among pregnant women, most of whom are taking prenatal vitamin supplements, approximately 70 percent are consuming more than 0.4 mg of total folates per day and about half are consuming more than 1.0 mg/day.

Several levels of fortification were considered. The estimated cumulative proportion of the Framingham study population at selected folate intake levels at three levels of fortification are indicated in figure 1 (47). It has been estimated that the current levels of fortification with folic acid at 0.095–0.308 mg/100 g of grain products would raise the average intake levels of women at risk of pregnancy by about 0.1 mg/day, and that the proportion of women consuming more than the recommended 0.4 mg/day will increase from 35 percent to about 55 percent.

**CURRENT SITUATION**

We are in the early years of the folic acid fortification program. Since the symposium during which this case study was examined, two studies have been published indicating increased serum folate concentrations among women of childbearing age (48) and a 19 percent reduction in neural tube defects following implementation of the fortification program (49). The results of another surveillance study suggested a decrease in neural tube defects between 1996 and 1998 (50) when folic acid fortification was being phased in by manufacturers after the 1996 ruling (30). There is still considerable need to determine what the long-term impact of the fortification program will be. Several aspects are being addressed, while others are lagging behind.

Improving methods for quantifying folate intake

It has been recognized for many years that the methods for estimating folate in foods are inadequate and likely underestimate the amount of naturally-occurring folate in the food supply. Improved methodologies and protocols are being developed and the American Association of Cereal Chemists and the Association of Official Analytical Chemists are working to develop a protocol for a major collaborative study of an improved method. Use of better methods will give a much more accurate idea of the amounts of folate in specific foods, as well as the amounts now added in the fortification program. In time, better food composition data will be available, and this should greatly enhance our ability to estimate intakes from all sources from food consumption data.

Dietary recommendations

The Institute of Medicine (4) recently published its revised recommendations for adequate intakes of a number of water-soluble vitamins, including folic acid. For the first time, the Institute of Medicine defined an “Estimated Average Requirement” expressed as “Dietary Folate Equivalents.” This term attributed considerably greater bioavailability to free folic acid (1.7 times) than to naturally-occurring folates. The Institute of Medicine, also for the first time, set a “Tolerable Upper Intake Level” for several vitamins, including folic acid. In the case of folate, the upper limit was 1 mg/day of “folate from fortified foods and supplements.”

It should be noted that the emphasis on bioavailability is not without controversy. There is current interest in greatly increasing fortification with free folic acid because of its greater bioavailability and because it has been estimated that a large proportion of women of childbearing age are still not consuming folic acid at US Public Health Service-recommended levels. On the other hand, there remains a concern that the potential for adverse effects is also greater with the more bioavailable form of the vitamin. Some have estimated that any increased levels of fortification would result in significant numbers of the population ingesting more free folic acid than the current Institute of Medicine-recommended upper limit.

Safety

Several concerns remain about the safety of increasing the folate intake for persons not at risk of neural tube defect pregnancies. A key one is the potential for masking of vitamin B₁₂ deficiency, thereby delaying the diagnosis of macrocytic anemia while allowing irreversible neurologic damage to progress. This is particularly important for elderly persons.

Several concerns arise from the absence of data on, for example, the effects of long-term consumption of high folic acid levels on children, or the effects of free folic acid, as opposed to metabolized folates, in the blood stream which...
may occur after ingestion of high doses of folic acid. It is known that folic acid supplements interfere with other medications, particularly antiepileptic and cancer chemotherapeutic drugs. It may be necessary for further adjustment of dosage levels of these drugs depending upon the patient’s consumption of enriched grain products.

Avoidance of high intakes

It is not clear from the published literature as to what constitutes inadvisably high levels. The FDA has had warnings for the use of folic acid as a drug at levels as low as 0.1 mg. There seems to be a general consensus that intakes above 1.0 mg/day of folate from fortified foods and supplements should be avoided.

Adequate dosage for women at risk of pregnancy

One of the most contentious issues in establishing the current fortification policy has concerned the appropriate level of fortification. The epidemiologic data have not established an adequate dose-response relation. The recommended level of 0.4 mg/day of folic acid is based on the lower range of dosages found to have a protective effect in observational epidemiologic studies. Some have argued that intakes lower than this are adequate for most women, millions of whom have had normal babies with far lower intakes. On the other hand, several proponents for an aggressive fortification policy argue that the current level of fortification will have relatively slight beneficial effect in decreasing the occurrence of neural tube defects and advocate doubling (or even greater increases in) the fortification levels (26). The main basis for advocating for increasing the fortification levels further is that the proportion of the target population likely to reach the daily target level of 0.4 mg was estimated to be less than 50 percent, and perhaps as low as 33 percent. Biologic data on the impact of fortification and careful surveillance of neural tube defect births over the next few years will be needed to assess the adequacy of the current policy.

Mechanism of folic acid’s role in neural tube defects is not known precisely

Despite tremendous progress in understanding the role of folic acid in metabolism during the last few decades, the precise mechanism of its role in neural tube defects is not clear. Current thinking includes considering a role for the enzyme methionine synthase and several genetic defects (3). Since 1993, a potential role for methylene tetrahydrofolate reductase has been recognized. If a genetic susceptibility can be established, the possibility of developing screening tests to identify high-risk women could become a tenable option for public health policy.

Surveillance systems evaluate beneficial and harmful effects

The present folic acid fortification policy has been established on the basis of a preponderance of epidemiologic evidence gathered from many countries and two large randomized trials. However, many uncertainties about both the effectiveness and hazards of this policy remain. The evaluation of these outcomes will be based on continued monitoring of the rate of neural tube defect births and the rates of occurrence of untoward events (such as delays in diagnosis of pernicious anemia). Future National Health and Nutrition Examination Surveys will provide critical data to evaluate the impact of folic acid fortification on the nutritional status of the US population. The National Birth Defects Prevention Network, in cooperation with 18 state-based surveillance programs and the US Centers for Disease Control and Prevention, is currently conducting surveillance and research (51).

LESSONS LEARNED

The Working Group felt that several lessons had been learned by its examination of the role of the epidemiologist in the development of the science base underlying the formulation of the current folic acid fortification policy.

Evaluating the available evidence

Although evidence-based practice has become a dominant theme in recent years, no rules have been established as to what constitutes sufficient evidence to promulgate new policies. Various stakeholders will have different concerns and interpret the available evidence in diverse ways. Even more important, in the absence of adequate evidence about safety, the fears and concerns of participants in the policy-making process, and their personal interpretations of risks and vulnerabilities of subgroups of the population, can lead to a decision not to act.

Evidence for a protective effect of maternal diet in reducing the risk of neural tube defects had been accumulating for many years, but quantitative data were lacking. Observational studies had suggested a possible role for several nutrients, among them folic acid, vitamin B12, and vitamin C. Uncertainty about the role of diet diminished with publication of the randomized placebo-controlled Medical Research Council trial, which demonstrated that intake of 4 mg of folic acid alone by women at recurrent risk of a neural tube defect pregnancy significantly reduced the risk of recurrence. The findings of the Medical Research Council trial were somewhat bolstered by the Hungarian trial, which used a lower level of folic acid in a multivitamin (0.8 mg) in women without a history of neural tube defects and showed that this intervention reduced the risk of neural tube defects in women at recurrent risk. The comparison group in the Hungarian trial, however, were women given a trace element mixture rather than the multivitamin without folinic acid.

Following identification of folic acid as a protective nutrient, questions arose as to the best way to provide women of childbearing age with an appropriate dose. Enhanced intake of folic acid and folates should be routine since many pregnancies are unintended and the benefits of folic acid in preventing neural tube defects must occur in the first 3 weeks after conception, before the neural tube closes. The pros and
Based largely on how to get adequate levels of folates to eliminate neural tube defects is still not clear. The policy options considered were based largely on an implicit assumption that most women are vulnerable. Programs to identify specific high-risk subgroups (other than women who had already had an affected child) were not deemed feasible because of lack of information about risk factors with high sensitivity and specificity. One of the major areas of interest was the risk of neural tube defects is concentrated in a relatively small group of women and infants due to factors affecting folate absorption or metabolism, such as genetic factors or anti-folate drugs. If this were the case, an alternate policy to screen for these risk factors and target folate supplementation to these vulnerable groups may be more appropriate than the current policy which impacts on the entire population.

CONCLUSIONS AND RECOMMENDATIONS

This case study of folate fortification for the prevention of birth defects exemplifies the difficulty of formulating sound policies when the required information is incomplete and evolving only gradually over time. The tension between public health officials who wish to “do good” and those whose primary orientation is to “avoid harm” can lead to vigorous and even acrimonious debate that cannot always be resolved on the basis of available evidence. Virtually all of the evidence available in this case study comes from epidemiologic studies—case-control, cohort, and randomized clinical trials. Evidence from laboratory and clinical studies have dealt primarily with some of the factors that have made the policy formulation difficult—potential genetic heterogeneity of the target population, potential for adverse impacts on subgroups that will not benefit from the program, and incomplete knowledge of the biologic mechanisms involved. Yet after several years of debate, a policy has been implemented that is a compromise among several competing views. There is much skepticism, and also much optimism, about the efficacy of the policy. A major concern of many of those responsible for the policy is that surveillance systems currently in place may not be able to fully answer the questions regarding the efficacy and safety of the program. It would indeed be unfortunate if these issues could not be fully resolved within a few years after initiating the program.

Some have argued that more research was needed to define the dose-response relation of folates and birth defects more precisely before the policy was implemented. Others argue that large observational studies should have been done to study potential effects of folates on children and elderly persons. One of the prominent views now is that the implementation of the current folate fortification program is itself an intervention study using the entire US population as the study group. The importance of having sufficient data systems in place to evaluate the outcomes of this intervention study is therefore emphasized.

Obviously epidemiologists have played a lead role in providing the scientific evidence and formulating the folate fortification policy. They were prominent as advocates for this policy and argued vigorously to persuade the policy-makers at the US Department of Health and Human Services that...
the potential benefits of the policy outweighed the potential adverse effects. This required them to interpret the available data and use their professional judgements to foster a compromise position that could be implemented by the regulatory agency (in this instance, the FDA) to promote a preventive public health program. Continued involvement by epidemiologists in providing outcome data to evaluate the policy will be crucial in closing the loop from a scientific finding to sound public policy.

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DISCLOSURE

Dr. Manning Feinleib was Senior Scientist, Centers for Disease Control and Prevention, and Research Professor, Georgetown University Medical Center, at the time the panel convened. He is currently Professor, Department of Epidemiology, and Director, Doctor of Public Health Program, Bloomberg School of Public Health, Johns Hopkins University. Previously, as Director of the National Center for Health Statistics, he directed the National Health and Nutrition Examination Surveys which provided the data on population intakes of folates and folic acid.

Dr. Shirley Beresford is Professor of Epidemiology and member of the core faculty of the Nutritional Sciences Program in the School of Public Health at the University of Washington, and Member of the Cancer Prevention Research Program at the Fred Hutchinson Cancer Research Center. Her research focuses on the role of folic acid intake on health and disease and in dietary intervention studies to improve the healthy eating habits of individuals, particularly those with low socioeconomic status. Dr. Beresford was a member of the Professional Advisory Council of the Spina Bifida Association of America from 1985 to 1991, and acted as a consultant to the Centers for Disease Control and Prevention on potential health effects of folic acid from 1990 to 2000, including being an observer to the Cooperative Oversight Committee for a Randomized Controlled Trial of Neural Tube Defect Prevention in northern China.

Dr. Barbara Bowman was Chief of the Chronic Disease Nutrition Branch at the Centers for Disease Control and Prevention (CDC) and co-authored several epidemiologic studies of folate status in the US population. She has served as a member of the CDC’s Folic Acid Working Group since its inception in 1993. She is currently Associate Director for Policy Studies in the CDC’s diabetes unit and co-editor of the 8th edition of Present Knowledge in Nutrition.

Dr. James Mills is in the Senior Biomedical Research Service at the National Institute of Child Health and Human Development. A pediatrician-epidemiologist, he has done research on the biochemical and genetic causes of birth defects for over 20 years. He is particularly interested in folate related birth defects. Dr. Mills has addressed the Congressional Biomedical Research Caucus and has been awarded the National Institutes of Health Director’s Award twice.

Dr. Jeanne Rader is the Director of the Division of Science and Applied Technology, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, US Food and Drug Administration (FDA), Washington, DC. She participated in the writing of the FDA’s proposed and final rules regarding health claims for folate and reduced risk of neural tube defects and in the writing of the FDA’s proposed and final rules for fortification of enriched cereal-grain products with folic acid. She has also been active in developing and validating analytical methods for the measurement of total folate in foods.

Dr. Jacob Selhub is a nutritional biochemist with expertise in folic acid and other B vitamins. He serves as a senior scientist and director of the Vitamin Metabolism Laboratory at the Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging and as a Professor in the School of Nutrition at Tufts University. Dr. Selhub’s interest is on the metabolism, intestinal absorption, and nutritional requirement of folic acid and other B vitamins in health and disease with emphasis on the relation to aging. Currently Dr. Selhub is studying the association between homocysteine and B vitamin metabolism with emphasis on effects on vascular disease. Most recently Dr. Selhub has been studying the impact of folic acid fortification of grain and cereal products on folate and homocysteine status in the Framingham Study population. He is a consultant to the Israeli Health Ministry on the subject of fortification of flour with iron and vitamins.

Dr. Elizabeth Yetley is the Lead Scientist for Nutrition at the Center for Food Safety and Applied Nutrition of the US Food and Drug Administration (FDA). She is the lead FDA regulatory scientist dealing with issues of food label health claims (i.e., claims relating to diet and health relations) and fortification of the US food supply. In this regard, she was intimately involved with expert advisory groups and the scientific and regulatory decisions related to the folic acid fortification and health claims regulations that were published between 1993 and 1996. For her leadership in this area, she has received several awards and honors from both the FDA and outside groups.

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