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Global Prevention of All Folic Acid-Preventable Spina bifida and Anencephaly by 2010

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Anencephaly · Folic acid · Food fortification · Spina bifida

Abstract
Folic acid-preventable spina bifida and anencephaly are pandemic, affecting 225,000 children a year. These birth defects are as preventable as polio. As we near the eradication of polio, it is time to make the commitment to global prevention of all folic acid-preventable spina bifida and anencephaly (FA-P SBA) by 2010. Folic acid fortification of centrally processed foods, such as wheat and corn flour, could immediately prevent all of these birth defects for much of the world's population. These fortification programs will also help adults by increasing serum folate concentration, eradicating folate deficiency anemia, providing human genome stability and reducing homocysteine serum concentration, which will probably prevent heart attacks and strokes, and may prevent colon cancer and Alzheimer's disease. Where there is no centrally processed and distributed food to fortify, intense efforts must be made to increase consumption of synthetic folic acid through vitamin supplements. Geneticists can play a major role in preventing FA-P SBA by helping to create the political will in each country to implement fortification and supplement programs to eliminate disease caused by the current pandemic of folate deficiency.

I am a co-inventor of a patent that covers adding folic acid to contraceptive and postmenopausal hormones drugs. If compensated for this invention, I would be compensated under the rules and regulations of the Centers for Diseases Control and Prevention where I worked when the invention was made. I am a paid consultant for Ortho-McNeil on this issue.

The Pandemic of Folic Acid-Preventable Spina bifida and Anencephaly

Spina bifida and anencephaly are severe birth defects [1]. CDC scientists estimate that 300,000 children are born each year with these birth defects [2]. Randomized controlled studies suggest that 75%, or 225,000, of these affected children have folic acid-preventable spina bifida and anencephaly (FA-P SBA) [3, 4]. We are in the midst of a pandemic of FA-P SBA. Furthermore, we now know that the predominate cause of spina bifida and anencephaly is folate deficiency.

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Folic Acid Is Required to Make DNA

The synthesis of DNA is dependent on sufficient folic acid/folate to make the base pairs. Folates are required for purine and thymine synthesis. Thus, timely and accurate production and repair of DNA requires sufficient folate. Without sufficient folate, cell division is slowed and uracil, rather than thymine, is incorporated into DNA [5].

Everyone Is Folate Deficient

The role of folate in the synthesis of DNA is well known. We know that folate deficiency anemia occurs when there is insufficient folate to produce enough new red cells to keep up with red cell destruction. The standard to determine whether someone is folate deficient has, until recently, been whether serum folate was below a concentration that would lead to folate deficiency anemia. Estimated requirements of folate from food were also based on providing enough folate to keep most people from having folate deficiency anemia.

In the last decade we learned that plasma or serum homocysteine is a very sensitive biomarker for folate deficiency [6]. Increased serum concentration of homocysteine is the first indication of intracellular folate deficiency. More importantly, we also learned that most of the people who participated in these studies did not have sufficient serum folate levels to keep serum homocysteine concentration down to 8 nmol/l, unless they consumed folic acid-containing vitamin supplements [7–9].

The Netherlands is a country that is economically well off, but it prohibits folic acid from being added to any food. A recent study from The Netherlands found that even the 20% of the Dutch with the best consumption of natural folate had far from sufficient blood folate levels [10]. Thus, rather than having a plasma homocysteine of 8 μmol/l, it was 11 μmol/l. The proportion of Dutch consuming sufficient folate is quite low, approaching zero. The results were similar for persons who do not consume supplements with folic acid in studies from New Zealand, Ireland, and the US. The negative impact of this folate plasma insufficiency on health has been reviewed in detail elsewhere [11].

Folate Deficiency Mutagenic

Modern society has been concerned that exposures to manmade chemicals and X-rays may be harming people through mutations. In vitro and in vivo tests in animals have been developed to generate data to be used in environmental regulations, with the basic idea of preventing cancer. Recent data suggests that folate deficiency is a mutagen, one not limited to a certain occupation or geographic region [12]. Exposure to this mutagen is nearly universal in people who do not consume synthetic folic acid supplements. Ames and colleagues [5] have shown that folate deficiency increases the incorporation of uracil into DNA by a factor of 10 because there is insufficient folate to convert uracil into thymine. Perhaps it is this mutation, promoting incorporation of uracil into DNA, that plays a role in colon cancer and is the mechanism by which long-term consumers of multivitamins reduce their colon cancer rate [12, 13].

Fenech [14] looked at classic markers of mutation-micronucleus formation and double strand breaks. He found that the concentration of folic acid in vitro is comparable to that found in the blood of people living in Western countries and that it predicts, in a dose-dependent fashion, these biomarkers of mutation. He has concluded from these data and folic acid feeding studies in people that the average human should consume 700 μg of synthetic folic acid a day (along with 6 μg of B12) to minimize mutations and to assure stability of the human genome. Since the average Western diet has only the equivalent of 100 μg a day of folic acid, Fenech's reasoning suggests that consumption of folic acid needs to be increased 7 fold. Note that this level is against a regulatory background of most Western nations lowering recommended daily allowances from 400 to 200 μg in the 1980s. In 1998, the US Institute of Medicine (IOM) revised its recommendation to about 400 dietary folate equivalents a day, which is about equal to 200 μg of synthetic folic acid, a level that leaves large segments of the population with serum folate concentrations that could be mutagenic [15]. (The IOM report, however, recommended that all women of reproductive age consume 400 μg of synthetic folic acid a day and maintain a healthy diet to prevent birth defects.)

Europe has yet to make any changes based on the massive amount of new data from the last decade. Europe is home of the 'Precautionary Principle', the idea of prohibiting exposure to manmade chemicals – even when there are no data to show that they are harmful. It is curious that no European government has taken the prudent step of fortifying foods with folic acid, even though we know it will prevent birth defects, reduce homocysteine concentrations and promote genomic stability in humans. The 'Precautionary Principle' and the lack of folic acid fortification are intellectually inconsistent.

The IOM report contained a toxicological risk assessment. Unfortunately for the health of the American peo-

ple, the risk assessment focused on the hypothetical risks of consuming too much synthetic folic acid, leading to a suggestion that the tolerable upper limit of synthetic folic acid is 1,000 μg/day. The American people would have been better served had the risk assessment considered folate deficiency the mutagen it is, and inquired into the consumption of folic acid needed to prevent mutagenic biomarkers. Based on the work of Fenech [14], a toxicological risk assessment would have found that a minimum consumption of 700 μg synthetic folic acid a day is required to minimize the mutagenic indicators. If, as is usual in toxicological risk assessment, a 10-fold safety factor against mutations had been factored in, the report would have recommended a daily consumption of 7,000 μg of synthetic folic acid, rather than suggest that 1,000 was a tolerable upper level. The recommended daily consumption of food folate or dietary folate equivalents would have been 14,000 rather than 400 μg.

The tolerable-upper-limit concept was used by the US Food and Drug Administration (FDA) and COMA to limit the folic acid concentrations required in fortification. The FDA modeled the post-fortification consumption of total folate (natural folate in foods plus synthetic folic acid) in several age-sex groups. Rather than setting the fortification concentration at a level that would have had 95% of women consume the 400 μg of synthetic folic acid recommended by the Public Health Service (PHS) and the IOM, the FDA set the fortification concentration at a level where no more than 5% of any age-sex group was projected to consume, after fortification, more than 1,000 μg of total folate. COMA also based its recommendation for fortification on a total folate consumption limit of 1,000 μg a day. The IOM report noted that it was incorrect to set a tolerable upper limit of total folate, rather, it should be set in terms of synthetic folic acid only. Had the FDA used 1,000 μg of synthetic folic acid in its modeling, it would have required fortification at a higher level. Similarly, had COMA used synthetic folic acid for its modeling, it too would have recommended a higher fortification level.

There is no tolerable upper limit for vitamin B12, and I think the current evidence suggests that there should be no tolerable upper limit for folate. If there is to be a tolerable upper limit for folic acid, it should be much higher than 1,000 μg a day. If there were no concept of a tolerable upper limit for folic acid, then folic acid fortification levels could, and I argue should, be set to maximize the prevention of FA-P SBA, which is likely to maximize the prevention of other folate deficiency-related diseases. Dickinson [16] reviewed the literature and found evidence suggesting that folic acid is safe, even for people with vitamin B12 deficiency. If one were to ensure that 95% of the population consumes 700 μg of synthetic folic acid daily in order to assure genomic stability, then a very substantial proportion –50% or more – would be consuming more than 1,000 μg of synthetic folic acid. Human beings cannot both need and be harmed by 1,000 μg of synthetic folic acid. It is time to stop letting the idea of a tolerable upper limit of 1,000 μg of synthetic folic acid restrict the concentration of folic acid fortification.

Pandemic Folic Acid-Preventable Spina bifida and Anencephaly

There is no more powerful way of demonstrating the cause of a disease process in human beings than by randomly allocating the active prevention agent and seeing the prevention of the disease process. It is unusual, maybe unique, to demonstrate in a randomized, controlled trial a causal relationship between a centuries-old and widely prevalent disease-causing agent and the disease. It has neither been done for folic acid supplementation and developmental anomalies, nor for cigarette smoking and lung cancer. Our usual modus operandi is to have animal data, case reports, controlled, but not randomized, epidemiological studies from which we deduce causality. We want a dose-response relationship, for example.

The causal relationship between folate deficiency and spina bifida and anencephaly was established by the MRC study, followed a year later by the Hungarian study [3, 4]. It was established without a dose-response curve. After causality had been established, Daly and colleagues [17] published quite a strong dose-response curve of the births to 50,000 women in Dublin. They showed a 5-fold difference in SBA rates across the range of usual (note I did not say 'normal', as many have done) serum folate concentrations. It went from 5 per 1,000 to 1 per 1,000. Wald and colleagues [18] showed that when these data are plotted on a semi-log scale, there is a linear decrease in SBA prevalence with increasing serum folate. Furthermore, the slope of the plot suggests that for every doubling of the serum folate dose, prevalence decreases by 50%. It is impossible to know from these data whether there would have been some higher serum folate concentration at which further increases would not have been accompanied by decreasing prevalence of SBA. For example, had 25% of these women been consuming 400 μg of synthetic folic acid daily, as American women do, there may have been a plateau. Thus there is a powerful

dose-response relationship between maternal serum folate and the birth prevalence of SBA in a country where women do not usually consume synthetic folic acid in supplements.

The birth prevalence data of a large Chinese intervention study showed that the untreated SBA rates ranged from 5 to 1 per 1,000 [2]. Thus in two groups of babies in populations half a world away, the prevalence range of spina bifida is the same. Actually, there were small groups in China with SBA rates at 10 per 1,000. If the lowest non-FA-P SBA rate were 1 per 1,000, the severity of the folate deficiency would determine the SBA rate in the population and the size of the FA-P SBA epidemic. The China study, however, suggests that the SBA rate can be reduced to at least 0.5 per 1,000 by a consumption of 400 μg of synthetic folic acid above the natural folate in diet. These data also suggest that, had the Irish women with the highest serum folate levels consumed 400 μg of synthetic folic acid, they could have reduced the birth prevalence of SBA in their infants from 1 per 1,000 to 0.5 per 1,000. Those with the lowest serum folate could have had their risk of having a baby with SBA reduced by a factor of 10: from 5 to 0.5 per 1,000 births.

The prevalence of FA-P SBA in a country is dependent upon how low folate consumption and serum folate levels are. Within the Dublin population, there was a 5-fold difference between the women with the highest and those with the lowest serum folate levels. The China study found a 10-fold prevalence in the north and a 2-fold prevalence in the south.

The precise amount of synthetic folic acid consumption needed to prevent all FA-P SBA is unknown. Given that 400 μg reduced the rate of SBA in a high-prevalence area of China and in a modest-prevalence area to the same level (0.5 per 1,000), one could argue that 400 μg of synthetic folic acid would be sufficient. Wald and colleagues [18] have produced a model that suggests that higher levels of consumption would result in even more reductions. It is clear that getting all women in the world to consume 400 μg of synthetic folic acid a day would be a major step towards controlling the very vast majority of the current worldwide pandemic of FA-P SBA.

Eradicating the Pandemic of Folic Acid-Preventable Spina bifida and Anencephaly

If 400 μg of synthetic folic acid above a usual diet as recommended by the US IOM is sufficient for full prevention, the challenge is to implement programs around the world that will provide 400 μg daily to all women of reproductive age. The highest-priority programs are fortification programs. Where fortification programs are not implemented or are insufficient, supplement programs can be implemented as a secondary priority and a less successful prevention strategy.

The Miracle of Folic Acid Fortification

In order to prevent FA-P SBA, the US FDA permitted in 1996, and required by January 1, 1998, that all 'enriched' cereal grains be fortified with folic acid. Note that 'cereal grains' are not breakfast cereals. Cereal grains include food staples such as wheat, corn, and rice flours. Since the early 1940s, 'enriched' grains in the US have been fortified with certain B vitamins, but not with folic acid. The FDA did not require that all grains be fortified, only those to be marked as 'enriched'. Thus, while it is now mandatory that all 'enriched' grains contain added synthetic folic acid, wholewheat and other non-enriched grains are not required to have folic acid added.

The requirement of adding folic acid to 'enriched' grains is different from voluntary addition of folic acid to breakfast cereals and other products. Before the mandatory fortification of enriched grains in 1998, Americans have had a long exposure to synthetic folic acid. The majority of pregnant women take a prenatal vitamin with 800 to 1,000 μg of synthetic folic acid. A study of postpartum women in Boston showed that 91% percent of the women in the study were consuming synthetic folic acid in supplements [19]. Mean consumption was 1,087 μg a day, and the range was from 200 to 6,759 μg per day. Seventy-three percent of the women in the study consumed 800 μg a day or more. Within this range of folic acid consumption, cord blood serum folate was 3 times higher than that of the mothers'. From this study it is clear that many pregnant American women consume much higher amounts of synthetic folic acid than would be implemented through mandatory fortification programs, and that prenatal consumption of folic acid is very common. Furthermore, the Boston study shows that supplemental folic acid is very effective in raising maternal and fetal serum folate concentrations.

Americans are also consumers of multivitamin supplements. In the US, common multivitamin preparations have contained 400 μg of synthetic folic acid since the mid-1970s. About 25% of Americans consume a daily multivitamin, with older Americans more likely to do so than younger adults. About 20% of American babies born over the last 25 years have been conceived by women consuming vitamin supplements with 400 μg of synthetic

folic acid. During the recognized pregnancy, the folic acid dose usually goes to at least 800 μg a day.

In the US, cold breakfast cereals have also been permitted to have 400 μg of synthetic folic acid per serving since the mid-1970s. Until recently, only a few brands of cereal included 400 μg per serving, but almost all had at least 100 μg per serving. Given that natural folate is only half as bioavailable as synthetic folic acid, and given that the usual Western diet contains about 200 μg of natural folate, an American eating a serving of a breakfast cereal with 100 μg of synthetic folic acid per serving doubles the folate in his/her diet. A woman eating a brand fortified with 400 μg would be increasing her consumption by a factor of 5. Those who consume a multivitamin and eat a serving of cereal with 400 μg would increase their folate consumption 9 fold.

I make the point about Americans consuming such large amounts of synthetic folic acid because the person-years exposures of adults and embryos/fetuses has been quite substantial. Human exposure to an extra 400 to 6,000 μg of synthetic folic acid a day has been prevalent and of long duration in the US. The current best evidence that we have is that supplement consumers have healthier babies, fewer heart attacks and strokes, and lower rates of colon cancer. There have been no reports of epidemics of neurological complications due to vitamin B12 deficiency. On the contrary, the Framingham study [■■■] has been the source of several papers showing that supplement takers have a lower rate of death [20, 21]. In addition to supplement consumers having lower mortality, it is reassuring that this group of elderly people who are examined every other year by excellent physicians has not been reported to have had any neurological complications of vitamin B12 deficiency associated with supplement consumption. Given this extensive exposure and no reports of harm, it is likely that exposure to folic acid in doses even greater than 1,000 μg a day is safe. If there is some undetected, serious adverse effect from such exposures, it has not been uncovered in thousands and thousands of Americans during years exposure to at least 400 μg of synthetic folic acid a day. Folic acid is not a new, potentially toxic drug that human beings have not been exposed to. While it is appropriate to be very cautious when introducing a new drug to which humans have not been widely exposed, the lack of such an exposure is not a valid reason in the case of folic acid. The exposure of human beings to synthetic folic acid has been extensive and of long duration.

Another reason to be so detailed about consumption of folic acid in the US over the last 25 years is that it differs from most of the rest of the world. Looking at mean serum folate in the US obscures the fact that the US really has two populations. One population voluntarily consumes 400 μg or more of synthetic folic acid from vitamin supplements or breakfast cereals, whereas the other does not consume supplements or cold breakfast cereals. If one wants to estimate the effect of mandatory fortification on serum folate in the US, one should compare the prefortification serum folate levels in the population that does not consume folic acid supplements or eat cold breakfast cereals with the levels after fortification – rather than look at total population changes. So far, these data have not been published from the national nutrition survey.

Since the publication of the evidence showing that folic acid prevents birth defects, the cold breakfast cereal industry in the US has been pouring folic acid into their products. Whereas only 4 products used to contain 400 μg of folic acid per serving, there are now more than 50. Other brands have increased folic acid content from 100 to 200 μg per serving. This change in the voluntary amount of folic acid added to American products has complicated the evaluation of the effect of fortification on serum folate caused by the mandatory fortification of 'enriched' cereal grain products. Mean and median serum folate levels post-fortification in the US overestimate the effect of the folic acid added through mandatory fortification, because folic acid was voluntarily added to commonly-eaten foods like breakfast cereals. To put it another way: if another country with a consumption of grains similar to that in the US would be implementing fortification at the same concentration used in the US, the postfortification mean increase in serum folate and mean reduction in homocysteine concentrations would be less than in the US. Adjusted for grain consumption and fortification levels, postfortification mean changes in Chile are likely to be a better estimate of the outcome in countries that newly implement fortification, as there is little voluntarily added folic acid in the food supply, and folic acid vitamin supplements are rarely used. Fortification in Chile is discussed further below.

The FDA required 'enriched' grains to be fortified at a concentration expected to increase consumption by 100 μg – only one fourth of the amount recommended by the PHS and the IOM. The combination of this fortification and the increased voluntary addition of folic acid to foods have resulted in quite a remarkable increase in serum folate. For women of reproductive age, the median serum folate increased from 5 to 15 ng/ml [22]. In addition, the proportion of women with serum folate levels of less than 3 ng/ml dropped from 5 to 0.5%, or less [23]. In

the whole population, prevalence of higher serum folate increased, so now more than half the population has higher serum folate than the ninetieth percentile had before fortification and the voluntary addition of folic acid to food products. In Canada, the concentration of serum B12 did not change as the folate concentration increased [24].

The health benefits of fortification are a 20% reduction in SBA rates, near eradication of folate deficiency anemia, a marked reduction in serum homocysteine concentrations and a reduction in mortality from strokes and heart attacks [25–27]. Thus, the benefits have been large. No adverse effects were expected and none have been reported [16]. Fortification did not increase the price of bread – fortification with folic acid costs about 0.1% of the total price of flour. Most of the population was unaware that their serum folate levels went up. There was no need for behaviors to change. Like providing pure water, providing improved 'enriched' grains affected the population while requiring no changes in behavior.

In countries that do have centrally processed grains, folic acid fortification can be easily and cheaply accomplished. For some poorer countries, there may be a need to prime the pump with funding to buy and install equipment, train staff, purchase vitamins for 1–2 years and perform evaluations of the program. Fortunately, the Bill and Melinda Gates Foundation and others have begun a program to promote micronutrient fortification around the world.

In my view, the epidemic of diseases caused by folate deficiency worldwide is sufficient to create a public health emergency, requiring the immediate fortification of flour and other centrally processed food staples. Folic acid fortification can be done immediately in a country like the UK, where there has been fortification with other vitamins for years. In other countries, fortification could be implemented within 24 months. Governments who could but do not assure folic acid fortification are committing public health malpractice [11, 28]. Willett and Stamfer [29] conclude that 'the failure of most countries to fortify foods with folic acid represents a major lost opportunity for improving health'.

Concentration of Folic Acid in Flour and Other Products

Universal fortification of products should be at a concentration that would assure that at least the average woman of reproductive age would consume at least 400 μg of synthetic folic acid a day. So far only Chile has taken this prudent step [30]. Chilean women eat about twice the amount of flour than women in the US. Chile stipulated a concentration of 220 μg of synthetic folic acid per 100 g of grain and started the program on January 1, 2000. Since Chile had already been fortifying flour with other B vitamins and iron, it was very simple to add folic acid. Millers add the vitamins, in the shape of a product called a vitamin 'pre-mix', at the end of the milling process. To change such a mill into a birth defect prevention factory, the miller just buys and uses a premix that contains folic acid. Once the decision to fortify has been made, fortification can be implemented within a few days. Assessment of the effects of the Chilean strategy should be available soon. The UK Department of Health Committee on the Medical Aspects of Food and Nutrition Policy recommended that there be universal fortification of flour at 240 μg of synthetic folic acid per 100 g, which was estimated to increase median consumption by about 200 μg of folic acid a day.

As the US was the first country to fortify and selected the low concentration of 140 μg per 100 g of grain, or 1.4 ppm (estimated to increase average consumption by 100 μg of synthetic folic acid), several other countries have selected 1.5 ppm. If a country does not implement a concentration to provide the average woman with 400 μg a day, I suggest that a country use the UK recommendation of 240 μg per 100 g.

Supplement Programs as Complements to Fortification Programs

Vitamin supplements frequently contain 400 μg of folic acid. In the US, about 25% of the population consume such supplements. Supplements are a very effective means to raise serum folate and reduce homocysteine [26]. The problem with a supplement program is that it costs much more than fortification and reaches at most only half of the target group [31–33]. If the supplement program is targeted at women of reproductive age, older women and men do not receive the advantage of having their folate deficiency cured, and therefore do not have the cardiovascular protection and prevention of folate deficiency anemia that comes with a reduction in homocysteine concentrations.

The Netherlands and the UK decided in the 1990s not to fortify, but to have national public and professional educational campaigns. If one regards these programs as a behavior change program, one would call them successful. Before the campaign in both countries, no more than 10% of women of reproductive age were consuming 400 μg of synthetic folic acid before pregnancy. After the programs, in both countries about 50% of women were consuming

400 μg of synthetic folic acid before and during the early weeks of pregnancy. There are not many behavior change campaigns that show a 4- to 5-fold change in behavior. The women who took their vitamins had all the benefits of such a consumption and would probably have received little, if any, additional benefit from folic acid in fortified foods.

On the other hand, the 50% that did not take any supplements received no benefit and put themselves and their fetuses at risk. These two national experiments with supplements demonstrate that such strategies are not the most effective population-wide strategy to prevent FA-P diseases. The failure of supplement programs to reach more than 50% of the population is a powerful argument that, where technically possible (as it is in The Netherlands and the UK), there should be universal fortification of grains so that the entire population benefits. The money spent on professional and health education campaigns in these countries could have paid the cost of fortification for many years.

Fortification is the first priority. Is there a place for supplement programs? I would say yes. In countries like the US, where the folic acid concentration was set too low, there should be well-financed campaigns to convince as many women as possible to consume supplemental folic acid to complement the current fortification program. Where there is adequate fortification, these programs should end.

Countries without Population-Wide Use of Centrally Processed Foods

India is such a country. About 20% of the population eat flour milled in large mills. Immediate fortification of flour produced in these mills will bring the benefits to about 200 million people and should be implemented as soon as possible. Other strategies must be found for the remainder of the population. Since much wheat is milled in small mills, an easy and effective means of fortification at small mills could help reach this segment of the population in India, and in many other countries with small mills. Research is needed to identify a process that works and can be implemented.

In the underdeveloped world, supplement programs have been implemented to try to prevent folate and iron deficiency anemias. Programs seeking to have women consuming supplements for the last 100 days of pregnancy have been of limited success. Perhaps more effective supplement programs could be tested and implemented. Effective supplement programs for women of reproductive age should perhaps be started at school. Women who have been pregnant can be encouraged to continue to take the vitamins on an ongoing basis. Contraceptive pills might have folic acid added so that the women who use these products would have a better folate status when they become pregnant. All countries should also ensure that consumers can buy vitamin supplements or cold breakfast cereals with at least 400 μg of folic acid per supplement and/or per serving of breakfast cereals.

Increasing Consumption of Foods Naturally High in Folate

Increasing consumption of foods naturally high in folate is a good idea, but it has not been shown to be as effective as synthetic folic acid in preventing birth defects or lowering homocysteine. Unfortunately, increasing consumption of foods naturally high in folate to a sufficient level would require a major and unlikely behavior change. Attempts in the US to increase consumption of fruits and vegetables have had little success. The change in consumption is far below what can be accomplished with fortification. In addition, we do not know how much folate consumption would be necessary to have the same preventive impact as 400 μg of synthetic folic acid. There have been no studies showing that increasing consumption of foods rich in folate can actually decrease the risk of birth defects.

It would be reasonable to conclude that increasing consumption of food rich in natural folate could reduce birth defects. It would also be reasonable to conclude that increased consumption would have only a small proportion of the effect in reducing birth defects a full fortification or supplement program would have. It is also likely that any increased consumption of foods with natural folates would be a very slow process, and would take decades to achieve. The potential for prevention from dietary changes is quite modest compared to the excellent prevention that can occur through universal fortification or among those who consume supplements.

There is a bias in some sectors of the nutrition community for getting vitamins and minerals only from food. This bias has led to national recommendations in some countries that are confusing and not based on best science. I think that the clearest and most data driven recommendation is the one by the US PHS and reaffirmed by the US IOM: all women of reproductive age should consume 400 μg of synthetic folic acid daily and consume a diet rich in natural folates. This simple policy should be the policy of all governments.

Recommendations for Governments, NGOs and Funding Agencies

1 Immediately stipulate universal fortification of centrally processed and widely eaten foods, such as flour, at a concentration of at least 240 μg of synthetic folic acid per 100 grams.
2 Assure consumer access to folic acid supplement pills and breakfast cereals with 400 μg of folic acid per pill or serving.
3 Fund effective supplement programs for women of reproductive age to complement fortification programs.
4 Fund effective supplement programs for women of reproductive age where there is no centrally processed food that can be fortified.
5 Conduct research to identify effective strategies for fortification in small mills.
6 Conduct research to identify effective strategies for supplement programs for countries where fortification is not possible.
7 After fortification with folic acid, conduct surveillance of adults and children for beneficial as well as potentially negative health effects.

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