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Commentary on de Walle and de Jong-van den Berg

Inertia on Folic Acid Fortification: Public Health Malpractice

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"Never before have we had so little time in which to do so much." —Franklin Delano Roosevelt, Fireside Chat, February 23, 1942

Globally, 500,000 children are born each year with spina bifida and anencephaly, two of the most common and severe birth defects (Berry et al., '99). One causes permanent paralysis and the other fetal or infant death (Botto et al., '99). For more than a decade, we have had randomized controlled trial proof that increased consumption of supplemental, synthetic folic acid will prevent approximately 375,000 of these birth defects each year (MRC Vitamin Study Research Group, '91; Czeizel and Dudas, '92). This prevention is urgent! To paraphrase Roosevelt, we can "in little time" implement fortification programs that will "do so much."

The advent of the polio vaccine brought a war-like urgency. In the US, within a few months of the conclusion of the trial establishing that the vaccine prevented polio, a massive amount of vaccine was produced, movie theaters across the country were rented to educate the medical community, and, within a year of the completion of the study, American children received 4.0 million doses of vaccine.

Folic acid-preventable birth defects are as preventable as polio! Preventing these birth defects is equally urgent. The technology to fortify is simple and can be inexpensively and almost immediately implemented for large population groups.

MIRACLE OF FOLIC ACID FORTIFICATION

Folic fortification in the United States

Folic acid fortification of enriched products like flour and bread has remarkably improved the health of Americans. Plasma and serum folate concentrations have increased, and plasma and serum total homocysteine (tHcy) concentrations have decreased, folate deficiency anemia has virtually disappeared, the rate of neural tube defects has decreased as has the mortality from stroke and heart attacks.

The US Public Health Service (USPHS) recommended on September 11, 1992, that all women of reproductive age consume daily 400 μg of folic acid to prevent birth defects (Centers for Disease Control and Prevention, '92). Although the Food and Drug Administration (FDA) soon thereafter called the first public meeting to consider fortifying enriched cereal grains, a slow and arduous process finally led to publication of regulations in 1996 permitting all enriched cereal grains such as flour and corn meal to be fortified with synthetic folic acid and requiring fortification by January 1, 1998 (Food and Drug Administration, '96). The FDA chose to require a concentration of synthetic folic acid in enriched cereal grains estimated to increase the average woman's consumption of synthetic folic acid by only 100 μg a day, only one-fourth that recommended by the USPHS. The required concentration was 140 μg of folic acid/100 g of grain or 1.4 parts/1,000,000. Synthetic folic acid is the folate that is added to enriched and fortified foods and to vitamin supplement pills. Synthetic folic acid is about twice as effective in raising serum folate as is an equal amount of folate from natural sources.

The requirement that all enriched grains be fortified with folic acid resulted in nearly universal fortification of wheat flour and corn meal, because most flours and meals produced and eaten in the US are enriched. A miller is required to fortify product only if he wishes to label it enriched and ship it to other states. Some millers, especially small local corn mills, do not ship to another state or do not wish to claim that the product is enriched.

Although the FDA required a concentration projected to be too low for maximum prevention of folic acid-preventable birth defects, even that level of fortification has had immediate and important effects. As

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shown on the cover, the median serum folate measured in representative samples of women of reproductive age increased from 4.8 ng/ml before fortification to 14.8 ng/ml after fortification (Centers for Disease Control and Prevention, '00). As the cover also shows, the post-fortification median serum folate concentration (14.8 ng/ml) was higher than the pre-fortification 90th centile (11.7 ng/ml). Manufacturers of breakfast cereals have also increased the folic acid in many of their products in recent years. The contribution to the change in median serum folate from folic acid voluntarily and newly added to breakfast cereals has yet to be determined. Folate deficiency anemia virtually disappeared (Lawrence et al., '99). Spina bifida and anencephaly rates were reduced by about 20%, much less than one would have predicted based on the randomized controlled trials. These data suggest that fortification did prevent ~800 of the 2,000–3,000 annual cases of spina bifida and anencephaly that the PHS predicted that folic acid could prevent (Honein et al., '01). It remains likely that had 95% of all women consumed the 400 μg of synthetic folic acid a day as recommended by the US Public Health Service and the Institute of Medicine, the level of reduction would have been much greater.

About 25% of adult Americans consume daily multivitamins with 400 μg of synthetic folic acid and 6 μg of synthetic vitamin B12 (Jacques et al., '01) These multivitamin consumers have the normal low homocysteine concentrations compared to those who do not take supplements (8.1 μmol/L vs. 10.1 μmol/L) Homocysteine is a recognized risk factor for occlusive cardiovascular disease (Boushey et al., '95). Homocysteine concentration is elevated usually because a person does not consume enough folic acid. After folic acid fortification, the serum homocysteine concentration of those consuming multivitamins did not change, as they were already consuming sufficient folic acid and vitamin B12 (Jacques et al., '99). Those who were not consuming multivitamin supplements showed a marked reduction in homocysteine after fortification. Thus, fortification caused a substantial reduction in a major cardiovascular risk factor among those not taking supplements.

Boushey et al. ('95) projected that folic acid fortification of enriched grains at the concentration required by FDA would prevent 40,000 heart attack deaths each year. Tice et al. ('01) projected that the range for reduction in deaths from heart attacks after fortification would be between 1 and 13%. In 1998, the year that fortification was completed, there were 22,000 fewer heart attack deaths and 5,000 fewer stroke deaths than in 1997, a 3.4% reduction in mortality for each condition (Martin et al., '99). These findings suggest that folic acid fortification may have prevented many more deaths from heart attacks and strokes than it prevented pregnancies affected with birth defects.

Chile is leader in preventing folic acid-preventable birth defects

So far, only one country, Chile, has implemented a sustainable folic acid fortification program designed to increase the average woman's consumption of synthetic folic acid by 400 μg (Freire et al., '00). How did Chile become the current international leader in preventing folic acid-preventable diseases?

Dr. Wilma Freire, Coordinator of Food and Nutrition Programs for the Pan American Health Organization, was working in Central and South America to promote fortification of flour with iron. When she learned of the role of folic acid in preventing birth defects, she immediately knew that adding folic acid to the ongoing enrichment process for flour would be an inexpensive, sustainable, and effective way to rid a country of folic acid-preventable birth defects. She called on scientists at the Center for Disease Control and Prevention, Emory University, and the March of Dimes to assist her and her colleagues in producing a policy for folic acid fortification of wheat flour. With the policy in hand, she discussed folic acid fortification of flour in Chile, where wheat flour had been successfully fortified with iron and several B vitamins for 20 years. Technically, it is very easy to add folic acid to an ongoing fortification program; millers have a vitamin "pre-mix" that they add in low concentration at the end of the milling process. Once the millers buy a pre-mix with folic acid in it, flour mills immediately become birth defect prevention factories!

Dr. Freire ('00) and colleagues at the Institute of Nutrition and Food Technology in Chile suggested to the government that wheat flour be fortified at a level so the average women would consume 400 μg of synthetic folic acid a day. Because Chilean women eat each day about 300 g of bread that is about 80% flour, they chose a concentration of 2.2 mg/kg (2.2 parts/1,000,000 or 220 μg/100 g of flour) and implemented it on January 1, 2000. This fortification program should markedly increase serum folate and decrease serum homocysteine concentration. The health of the people of Chile is likely to be improved by the prevention of birth defects, heart attacks, and strokes.

Recent policy reviews in the United States and the United Kingdom support folic acid fortification

In 1998, The Food and Nutrition Board of the US Institute of Medicine reaffirmed the PHS recommendation that all women should consume 400 μg daily of synthetic folic acid from enriched and fortified food products or vitamin supplements (Food and Nutrition Board IoM, '98). The UK Committee on Medical Aspects of Food and Nutrition (COMA) performed a systematic review of all the evidence and in early 2000 recommended universal fortification of flour.

> On scientific, medical, and public health grounds, the Committee concluded that universal folic acid

fortification of flour at 240 μg/100 g in food products as consumed would have a significant effect in preventing NTD-affected conceptions and births without resulting in unacceptably high intakes in any group of the populations (Committee on Medical Aspects of Food and Nutrition Policy [COMA], '00).

FOLIC ACID FORTIFICATION SHOULD BE IMPLEMENTED IMMEDIATELY

Folic acid fortification works. It is safe, cheap, and remarkably improves the health of children and adults. Universal (or near universal) folic acid fortification should be implemented immediately where there is centralized processing of such commonly eaten foods as wheat flour. Although new information could suggest a different level, for the foreseeable future flour should be fortified at 240 μg/100 g of grain. Fortified flour can also be the vehicle for other B vitamins, including vitamin B12, and for the minerals iron and zinc. Fortification of flour with folic acid, however, should not be delayed by protracted discussions of what other nutrients to add. If there can rapidly be an agreement about including other vitamins and minerals, they should be added. If the discussions are to be drawn out, folic acid fortification should proceed immediately.

In many developing countries, policy makers accept the evidence that fortification with vitamins and minerals can improve the health of the people, and various international agencies are moving rapidly to implement fortification. For some developing countries, lack of resources has been retarding the rate of fortification. The Melinda and Bill Gates Foundation and other private and public donors are considering providing resources to promote fortification in developing countries.

INERTIA ON FOLIC ACID FORTIFICATION

No country in Europe has required universal or near universal fortification with folic acid. This inertia daily causes hundreds of children and adults to die, to be disabled, and to have illnesses that can be prevented by folic acid fortification. The impediments are not from lack of resources, nor from ignorance. The impediments are driven by cultural, philosophical, and policy fads. Because of these fads, European governments have failed to implement folic acid fortification in a timely manner. There is insufficient recognition that there is near universal folate deficiency and that adults in the population will also benefit from fortification. Those who advocate delay raise issues of risk that are hypothetical and probably do not exist. I will consider these impediments to fortification.

Nutrition culture

The predominant cause of spina bifida and anencephaly is exposure to folate deficient diets. In 1991, The Lancet published the results of the MRC trial that proved that supplemental, synthetic folic acid would prevent the majority of spina bifida and anencephaly affected pregnancies (MRC Vitamin Study Research Group, '91). This landmark paper, building on the earlier work of Laurence et al. ('81) and Smithells et al. ('83) is worthy of the Nobel Prize in Medicine. Not only did this study prove that folic acid-preventable birth defects are as preventable as polio, but it also added folate deficiency to rubella infection, alcohol consumption, and maternal diabetes as a major known cause of birth defects rooted in nature.

In some ways, it is unfortunate that a man-made chemical was not found to be the predominant cause of spina bifida and anencephaly. The current culture of environmental concern leads to major public policy actions and expenditures seeking to protect human beings on much less evidence than the evidence that folic acid prevents spina bifida and anencephaly. For example, regulations in the US seek to keep exposure to potential cancer causing, man-made chemicals below a level that is hypothesized to keep the rate of cancer below 1 in 1,000,000 exposed population. If the MRC study had proved in human beings that a man-made chemical was the cause of 75% of two of the most common and severe birth defects, and that the birth defects occurred at the rate of 5,000/1,000,000 exposed population, the chemical would have been swiftly removed and global prevention of these preventable birth defects would have been accomplished by now.

We are, however, far from global, total prevention of folic acid-preventable birth defects. United Kingdom and other European nutritional policy makers have unnecessarily contributed to the delay in prevention by failing to assure folic acid fortification. All governments should immediately take the inexpensive and simple step of requiring that flour be fortified with folic acid at a minimum of 240 μg/100 g of flour, a public health action recommended in 2000 by a UK expert nutrition committee (COMA) and one that is certain to prevent each year thousands of cases of birth defects and folate deficiency anemia, and likely an order of magnitude more heart attacks and strokes.

We are all folate deficient

Many in the nutrition community adhere to the concept that any nutritional factor needed for human health can and should be obtained only by consuming a healthy and balanced diet. This belief in the US and many other countries leads to the conclusion that fortification and supplement programs simply are not needed. This position is not supported by current folic acid evidence and by the well known benefits of fortification with iodine, iron and other minerals and vitamins.

Estimates of the amount of folate needed for human beings have been, for decades, based on how much is needed to prevent folate deficiency anemia. Several decades ago, the amount recommended for this purpose was 400 μg of folate/folic acid/day (unfortunately the terms folate and folic acid are often used interchangeably even though synthetic folic acid is twice as effective as natural folates in foods). In the 1980s, many

food advisory bodies arbitrarily decreased the recommendation to 200 μg/day, based on studies of estimates of natural folate consumption from food suggesting that the average consumption was 200 μg of natural folate a day in most Western countries. Because folate deficiency anemia was of low incidence, the recommended daily allowance was lowered to 200 μg folate/folic acid. The advisory bodies and their consultants have been slow to accept the fact that almost all who do not consume an additional 200–400 μg of synthetic folic acid a day, above the 200 μg of natural folate in their diet, are folate deficient. Now the science has advanced. The old folate deficiency anemia standard underestimates the amount of folate needed for health and ignores the fact that almost all who do not take synthetic folic acid supplements or fortified foods are folate deficient.

Homocysteine is a good biomarker of folate status. At sufficiently high serum/plasma folate concentrations (adequate), homocysteine concentrations are reduced to a plateau of approximately 7–8 nmol/L (Lewis et al., '92). Below a certain serum folate, there is a linear increase in homocysteine concentration as folate declines. Data from New Zealand, Ireland, the Framingham study and the NHANES III study show that the vast majority of people are not consuming enough natural folate to reduce their homocysteine to the plateau (Selhub et al., '93, '99; Riddell et al., '00; Jacques et al., '01).

A recent Dutch study agrees (deBree et al., '01). Among non-supplement takers, there is a graded reduction in homocysteine over increasing quintiles of estimated consumption of natural folates. Thus, natural folates in food can reduce homocysteine. In the highest quintile of natural folate consumption, however, the concentration of homocysteine remains high at 12.2 nmol/L for women and 13.0 nmol/L for men, rather than the 7–8 nmol/L one would expect with sufficient folic acid consumption. In the Netherlands, even the highest quintile of consumers of natural folates in food do not reach the low, normal homocysteine plateau. In an Irish study, Quiniivan et al. ('02) showed that individuals fed 400 μg of folic acid a day achieved homocysteine levels of about 7 μl/L. In a study from Aberdeen, Rydlewicz et al. ('02) noted: "We deliberately studied the elderly (65–75 years) …because they have a higher dietary requirement than younger people …". Based on their feeding of different amount of folic acid, they suggest that it would be necessary for people 65–75 years of age to consume 400–600 μg of synthetic folic acid a day to reduce homocysteine to 10 μl/L. The non-supplementing Dutch are all folate deficient. Because the Dutch are an economically advantaged population, it is reasonable to suggest that almost everyone in the world who is not supplementing is also folate deficient.

Using homocysteine concentrations to estimate folate need may also underestimate human need for folic acid. The studies estimating need for folic acid based on a homocysteine standard all are based on data observed in adults. Cell division in an embryo or fetus is much faster than in an adult; hence there is an increased need for folic acid to supply building blocks for DNA base pairs. Consumption of folic acid should be sufficient to protect the developing nervous system from spina bifida and anencephaly.

Fenech ('01) has reviewed the role of low folate in causing chromosomal breaks, hypomethylation of DNA, uracil misincoorporation in DNA and micronucleus formation. These are all indicators of mutation and instability of the human genome. He notes that, based on the micronucleus index in lymphocytes, the consumption of 700 μg of synthetic folic acid and 7 μg of vitamin B12 a day would be appropriate for stabilizing human genomic DNA. This level of consumption results in homocysteine concentrations of 7.5 μmol/l. Thus Fenech ('01) suggests that keeping DNA healthy requires a much higher consumption of folic acid (and B12) than the current recommendations and usual consumption.

Public health policies and programs designed only to increase the consumption of natural folates in food are inadequate because they will prevent too little of what is preventable

The randomized controlled trials proving that folic acid would prevent spina bifida and anencephaly were conducted with women eating their usual diets and consuming a supplement of at least 800 μg of synthetic folic acid in a pill. There have been no randomized controlled trials to show that a change in diet alone will lower the risk of spina bifida and anencephaly.

There are, however, data that suggest that increasing consumption of natural folates would have some limited protective effect. A study of largely un-supplementing Irish women shows that the risk of having a child with spina bifida or anencephaly decreases with increasing plasma and red cell folates (Daly et al., '95). The Irish women with the lowest quintile of plasma folate had a spina bifida and anencephaly rate of ~40/10,000 births. The Irish women in the upper quintile of plasma folate had a rate of spina bifida and anencephaly pregnancies of 10/10,000. In a large study in China where supplementation is also rare, the rate of these birth defects in the North of China was 48/10,000 and the rate in the South was 10/10,000 births (Berry et al., '99). There is a remarkable consistency of the range of spina bifida and anencephaly in two otherwise quite different non-supplementing populations. It is reasonable to conclude that, across the range of consumption of natural folates in the diet, there is a dose response between natural folate consumption and risk of these birth defects. Thus, increasing consumption of natural folate is likely to provide some protection against having a baby with SBA.

The China study was a large community trial conducted in two different areas, one in the North and one in the South. In Chinese women who received 400 μg of synthetic folic acid a day above the natural folate in their diet the rate of spina bifida and anencephaly

decreased to 7 or 6/10,000. In the North where the background rate of SBA was 48/10,000 pregnancies, the rate was reduced by 85% to 7/10,000. In the South, where the background rate was 10/10,000, the rate was reduced 40% to 6/10,000. It is reasonable to assume that, had the Irish women been consuming an extra 400 μg of synthetic folic acid, the spina bifida and anencephaly rate would have been lowered by 85% in the women in the lowest quintile of plasma folate and by 40% in the women in the highest quintile of plasma folate. To prevent all folic acid-preventable birth defects requires consumption of synthetic folic acid even for women who are currently at the upper end of the distribution of natural folates.

The best public health policy would lead to an immediate prevention of all folic acid-preventable birth defects. A public health policy that relies solely on recommendations and programs to increase consumption of natural folates is insufficient. Randomized controlled trials to increase consumption of fruits and vegetables have shown that current intervention strategies, even if they could be applied effectively to the population, make scant improvements in dietary consumption. These studies usually show an increased consumption of no more than one serving of fruit a day or about the equivalent of 25 μg of synthetic folic acid. Thus, although it is clear that improving diets would likely reduce the risk of birth defects, that reduction would be modest and slow. A rapid and full reduction in these preventable birth defects requires an increased consumption of synthetic folic acid.

Supplement programs are helpful but leave at least 50% of women unprotected from increased risk of having children with folic acid-preventable birth defects

Many in the nutritional community have argued against fortification by claiming that a well-funded professional and public health education campaign to promote consumption of vitamin supplements with synthetic folic acid by women of reproductive age would be as effective as a fortification program to prevent birth defects. United Kingdom and the Netherlands conducted well-financed and well-run programs of professional and public health education to promote consumption of folic acid vitamin supplement pills. We now know that such programs are ineffective for at least half of women of reproductive age.

De Walle and de Jong-van den Berg report in this issue an evaluation of the national and multi-year campaign in the Netherlands to promote the daily consumption of 500 μg of synthetic folic acid in supplements from 4 weeks before pregnancy through the first 8 weeks of pregnancy. When the campaign began in 1995, the use of folic acid containing supplements in the recommended time period was less than 10%. The percentage of proper use peaked around 40% in 1998 and was unchanged at 36% in 2000. Although the campaign changed behavior remarkably and rapidly, it was far from sufficient from a population viewpoint. There was an ~400% increase in the percentage of pregnant women consuming folic acid at the recommended times for prevention of birth defects, a rate rare for a behavioral intervention program. Results of the supplement campaign in the UK were similar to the Dutch experience (Raats et al., '98). Any woman who was consuming folic acid supplements as advised markedly increased her serum folate and eliminated or almost eliminated her risk of having a child with a folic acid-preventable birth defect. For these women the results of the campaign were good.

Despite the success of the Dutch and UK supplement programs, no more than 50% of targeted women consumed sufficient supplemental folic acid to prevent birth defects. The Dutch and UK supplement programs provide conclusive evidence that, if we are to prevent more than 50% of the preventable birth defects, we need near universal fortification of a commonly eaten food staple like flour with sufficient folic acid.

Wald et al. ('01) suggest that, for maximum prevention, there should be universal folic acid fortification of flour at 240 μg/100 g of grain (as recommended by COMA) and a program to promote 5.0 mg supplements for all those women planning a pregnancy. Given that no more than 50% are likely to take the supplement, I would prefer to have a fortification level that assured that 95% of women of reproductive age are consuming 400 μg of synthetic folic acid. A higher level of fortification would leave a smaller part of folic acid-preventable spina bifida and anencephaly to be prevented by supplements.

LACK OF UNIVERSAL FOLIC ACID FORTIFICATION HARMS ADULTS

The decision by the Dutch Health Council not to recommend fortification is an error in public health judgment. It fails to acknowledge that all non-supplementing Dutch are folate deficient and that the health of the Dutch population would be improved by consumption of folic acid fortified products. As shown from the US experience, fortification at 140 μg/100 g of flour leads to the near elimination of folate deficiency anemia and a remarkable reduction in plasma homocysteine.

Failure to recognize the importance of data suggesting that folic acid will prevent heart attacks and strokes

The Dutch Health Council noted, "It is not impossible that this recommendation will need to be reviewed once further insights have been obtained into the possible positive effects of extra folic acid on homocysteine metabolism and accordingly the prevention of cardiovascular diseases" (this is code for we will not recommend folic acid fortification until more randomized controlled trials show that reduction in homocysteine by folic acid will prevent cardiovascular disease). The sentence from the Dutch report does not reflect the extensive literature on the subject, literature which has con-

clusively shown that folate deficiency is the primary cause of increased homocysteine, that 400 μg of supplemental folic acid will remarkably reduce homocysteine levels, and that homocysteine level is a risk factor for occlusive cardiovascular disease (Boushey et al., '95; Graham et al., '97). As the primary reason homocysteine is increased is insufficient serum folate, it is conceivable that folate deficiency, rather than elevated homocysteine concentrations is the modifiable risk factor for occlusive cardiovascular disease. A large, multicenter European study published in 1997, including Dutch investigators, Dutch subjects and Dutch financial support, stated:

> We conclude that an elevated plasma tHcy level is now established as a strong and independent factor associated with all categories of atherosclerotic disease in both men and women. An elevated plasma tHcy level interacts strongly with smoking and hypertension. It is known that folate supplementation reduces homocysteine levels both in the fasting state and after methionine loading and that pyridoxal 5′-phosphate can lower post methionine homocysteine levels. Users of these vitamins have lower homocysteine levels than nonusers do, and there is a suggestion of reduced risk in vitamin users in the present study (Graham et al., '97).

This large, well conducted, controlled study concludes that homocysteine is a strong predictor of atherosclerotic vascular disease and that consumption of a simple multivitamin is associated with a strong protective effect—a statistically significant 62 percent reduction in atherosclerotic vascular disease. The Dutch Health Council report should have considered how likely is it that the Dutch older than 50 would have been helped by consuming extra folic acid rather than looking only at the possibility for harm, for which there is little supporting data. The comparison of risk with benefit for those over 50, would have shown that the possibility of benefit far exceeded the possibility of risk.

Causal inference does not require randomized controlled trials

There are times when good public health policy can and should be made without evidence from randomized controlled trials. For example, there are no randomized controlled trials showing that cigarette smoking causes lung cancer, but we have built public health programs to try to prevent smoking.

The usual position of review bodies, discussions in scientific papers, and editorials is to dismiss all data suggesting the possible protective effect of folic acid on cardiovascular disease until there are randomized controlled trials. Such trials are currently underway (Clarke and Armitage, '00). Bostom has noted the likelihood of demonstrating benefit in the US is greatly diminished because the fortification substantially reduced plasma homocysteine (Bostom et al., '01). Meanwhile, pertinent randomized controlled trials have been published.

There is a randomized controlled trial from China showing that a multivitamin supplement containing 800 μg of folic acid, 18 μg of vitamin B12 and 6 mg of vitamin B6 reduces stroke mortality by 37% (RR = 0.63; 95% CI: 0.37–1.07) (Mark et al., '96). Although not measured, plasma homocysteine concentrations were likely substantially reduced by the vitamin consumption. For men there was a 58% reduction in stroke mortality (RR = 0.42; 95% CI: 0.19–0.65) whereas for women there was little effect (RR = 0.93; 95% CI: 0.44–1.98). In the Framingham study, stroke mortality is 80% higher in those in the upper quartile of plasma homocysteine as compared to those in the lowest quartile (B vitamin supplement consumers) (Bostom et al., '99). Schnyder et al. ('01) conducted a randomized controlled trial that showed that a folic acid, vitamin B12 and pyridoxine supplement decreased the rate of "restenosis and the need for revascularization of the target lesion after coronary angioplasty." There are many well controlled studies in which folic acid administration reduced homocysteine levels. As noted above, Boushey et al. ('95) projected the likelihood of a profound benefit for those 50 and older.

The authors of the European study quoted above offer:

> We believe it is time to consider whether existing recommended daily allowances of the vitamins that modulate homocysteine metabolism are adequate and to undertake randomized controlled trials of the effects of folic acid and perhaps pyridoxine in the secondary prevention of cardiovascular disease (Graham et al., '97).

The recommendation for more randomized controlled trials rather than folic acid fortification is now several years old and has been acted upon. Continued waiting for new trials and complete results is short-sighted and causes harm to the public health. To deny those 50 and older access to foods fortified with folic acid likely puts older adults at an unnecessary risk of an occlusive vascular death.

Sir Bradford Hill was a powerful promoter of randomized controlled trials for drugs and other medical interventions. He realized, however, that randomized controlled trial evidence was not always necessary for public policies.

> The Case for Action. Finally, in passing from association to causation I believe in "real life" we shall have to consider what flows from that decision. On scientific grounds we should do no such thing. The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it-or who hangs because of it. But in another and more practical sense we may surely ask what is involved in our decision. In occupational medicine our object is usually to take action. If this be the operative cause and that be deleterious effect, then we shall wish to intervene to abolish or reduce death or disease.

> While that is a commendable ambition it almost inevitably leads us to introduce different standards before we convict. Thus on relatively slight evidence we might decide to restrict the use of a drug for early-morning sickness in pregnant women. If we are wrong in deducing causation from association no great harm will be done. The good lady and the pharmaceutical industry will doubtless survive.
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> Sir Austin Bradford Hill. The Environment and Disease: Association or Causation? (Hill, '65)

For the US, Boushey et al. ('95) estimated that adding an additional 300 μg of synthetic folic acid in the diet through fortification would decrease deaths from coronary artery disease alone by 50,000 deaths a year. For public health comparisons, there are about 30,000 deaths from motor vehicle crashes each year.

If there were no randomized controlled data proving that folic acid prevents birth defects and if one had to justify the decision for folic acid fortification on the cardiovascular data alone, should we not "ask what is involved" in making a causal inference and a fortification decision? The data are strong enough to assume "operative" causality and move to fortification. If we conclude operative causality and move to folic acid fortification, we stand to risk that society will have spent some extra money unnecessarily if it is later conclusively shown that there is no protective effect. The cost of fortification is trivial compared to the cost of already funded educational campaign in UK and the Netherlands to promote supplement taking. On the other hand, if we reject operative causality and do not fortify and causality is later established, our lack of action would have caused hundreds of thousands to have morbidity, disability and death from cardiovascular disease that we could have prevented. It is better "…to intervene to abolish or reduce death or disease." Because we know that folic acid will prevent hundreds of cases of severe birth defects a year, it is just as unethical to prevent folic acid fortification of grains in Europe to conduct randomized controlled trials of cardiovascular endpoints as withholding penicillin from Tuskegee men to study the natural history of syphilis.

Folate deficiency mutagenesis and colon cancer

The potential of folic acid fortification to prevent colon cancer has not been adequately considered in policy discussions of fortification. Ames ('01) and Giovannucci et al. ('98) have shown that folate deficiency increases the incorporation of uridine in DNA. Ames ('01) argues that mutations through this mechanism can play a role in colon cancer and may explain why nurses who consumed multivitamins with folic acid and vitamin B12 for 15 years have been found to have a 75% reduction in colon cancer. We must make our inferences about causality between folic acid consumption and prevention of colon cancer from observational studies. It is highly unlikely that there will ever be a 15-year randomized controlled trial to see if supplemental folic acid will prevent colon cancer. If a man-made chemical had been shown to be mutagenic in a test tube and had been shown in a Harvard School of Public Health longitudinal study to cause a four-fold increase in colon cancer, there would likely have been swift action to remove the exposure. It is inappropriate that a current scientific fashion has precluded consideration of the prevention of colon cancer in the policy discussion of folic acid fortification.

Folic acid is safe—nothing to fear but fear itself

Policy reviews of folic acid fortification raise three issues related to vitamin B 12 deficiency as possible reasons not to institute folic acid fortification of flour. These issues are "masking," a rapid course of neurodegeneration from vitamin B12 deficiency, and the mild B12 deficiency common among those over 50 years of age.

The data suggesting risk at any consumption level of synthetic folic acid are weak, especially when considering the 100–400 μg median increases of folic acid consumption that might occur from a fortification program. There is, unfortunately, a tendency to dwell on these mostly theoretical concerns and overlook the data showing profound benefits of increased folic acid consumption for those 50 and older. The risk issues are repeatedly raised in ways that confuse the folic acid fortification discussion.

The myth of "masking"

There are clinical studies showing that persons with megaloblastic anemia or neuropathy from severe vitamin B12 deficiency who are treated with large doses of folic acid, usually at least 5,000 μg/day or more, can have a remission of the anemia and a progression of or onset of neuropathy (Vilter et al., '47). This observation led to speculation that, if persons consumed high doses of folic acid and were B12 deficient, they would not become anemic (anemia would be "masked") and doctors would not make a timely diagnosis of the B12 deficiency; neuropathy would unnecessarily develop or progress because the anemia and therefore the B12 deficiency was not diagnosed. Dickinson ('95) found, in the medical literature, that pernicious anemia in the first half of the 20th Century presented with neurological symptoms alone about 25% of the time. The view that pernicious anemia progresses from anemia to neuropathy is incorrect. "Pernicious anemia" is in fact a disease that can present with anemia, neuropathy, or both. Clinicians must be on the alert to perform a proper diagnostic work up of any of the presentations.

Fortunately, excellent blood tests are now available for measuring vitamin B12 levels. Consistent with a timely diagnosis and treatment, the severe forms of vitamin B12 deficiency, such as combined systems disease, have been very rarely reported in the last 40 years in developed countries (Lindenbaum et al., '88).

An adverse effect of a drug is found usually after there is wide exposure to the drug. Since the early 1970s, about 25% of Americans have consumed at least

an extra 400 μg of synthetic folic acid and 6 μg of vitamin B12 by consuming multivitamin supplements with folic acid in them or breakfast cereals with 400 μg of synthetic folic acid per serving. There have been more than 1 billion person-years of exposure. If consumption of 400–800 μg of synthetic folic acid can make the course of vitamin B12 deficiency worse, one would have expected the natural history of B12 deficiency in the US to become more severe; instead, the disease has become less severe (Lindenbaum et al., '88). To be fair, I do not know of a study that has specifically focused on the question. On the other hand, the participants from the Framingham cohorts are examined frequently. As far as I am aware, there are no reports from Framingham of adverse effects on the course of pernicious anemia among vitamin supplement consumers. In fact, it is the supplement takers with lower homocysteine levels that have been shown to have lower mortality. With such a large exposure to synthetic folic acid and with the well known hypothesis of "masking," reports with milder and milder presentations of vitamin B12 deficiency likely mean that supplemental folic acid does not delay the diagnosis and does not affect the course of vitamin B12 deficiency. The US Institute of Medicine report dismissed the idea of "masking" as a reason not to fortify (Food and Nutrition Board, '98). Evidence for harm from folic acid to anyone with vitamin B12 deficiency is non-existent. "Masking" of B12 deficiency is not a concept based on contemporary medicine and should finally be discarded.

Lack of treatment with vitamin B12 responsible for rapid course of pernicious anemia, not folic acid

The Dutch report mentions that "rapid" neurological progression (6 months from first mild symptoms to full blown combined systems disease) of pernicious anemia has been occasionally reported in persons untreated with vitamin B12 but treated in error with large doses of folic acid. Dickinson ('95) found similar case reports of "rapid" progression before synthesized folic acid was available. There are no controlled studies suggesting that folic acid treatment affects the course of untreated vitamin B12 deficiency. There are no data to indicate that rapid progression is anything other than one of the clinical courses to be expected in untreated B12 deficiency, whether or not folic acid is consumed.

The US Institute of Medicine review quotes a paper purporting to show a more rapid progression of B12 induced neuropathy in monkeys treated with folic acid than those not treated (Agamanolis et al., '76). The IOM report, however, did not discuss a very serious design flaw in the paper. At the beginning of this experiment, eight monkeys were made B12 deficient by a diet poor in vitamin B12 and three of them were treated with vitamin B12. Two of the five untreated vitamin B12 deficient monkeys died, one at 39 months with few symptoms and one at 53 months. Four additional monkeys were added to the experiment at the beginning of the second year. These four were made B12 deficient and three were given large doses of folic acid. None of the monkeys treated with folic acid died after 48 months of vitamin B12 deficiency. Thus, only monkeys not treated with folic acid died.

An autopsy on the untreated monkey that died at 39 months of vitamin B12 deficiency found optic nerve pathology. Forty-three months after the first monkeys were begun in the study, funduscopic exams were started on the remaining seven monkeys in the first cohort and the three folic acid treated vitamin B12 deficient monkeys that had entered the study 12 months later. None of the first eight monkeys were examined before they had experienced at least 43 months of vitamin B 12 deficiency. After folic acid-treated monkeys had been in the study for 33 months, all three of the B12 deficient, folic acid treated monkeys were observed to have slight optic atrophy, earlier than observed in the monkey who died after 39 months in the study. Funduscopic exams, however, were never performed on the dead monkey. Given the design flaw, the failure to examine the first set of monkeys earlier, these data do not constitute reasonable evidence that the B12 deficient monkeys had earlier onset of disease or were harmed by folic acid. Notwithstanding the IOM conclusion, this experiment is consistent with the idea that the folic acid prevents mortality in vitamin B12 deficient monkeys.

Mild B12 deficiency is common and easily corrected with 2.4 μg of synthetic vitamin B12

The Dutch report notes that 25% of the elderly may have mild biochemical indicators of intracellular vitamin B12 deficiency. This deficiency is not pernicious anemia but is caused by decreased absorption of protein-bound B12 associated with the decrease in gastric acid production that occurs increasingly above age 50. The US Institute of Medicine noted this phenomenon and recommended that all aged 50 and older consume 2.4 μg of synthetic vitamin B12 a day (Food and Nutrition Board, '98). Because there are no data suggesting that consuming folic acid harms anyone with mild B12 deficiency, this situation should not be used as an excuse to prevent folic acid fortification. The obvious solution to this B12 deficiency in Holland, the US and elsewhere is to add synthetic B12 to the flour, not to delay adding folic acid to the flour. It is puzzling that the Food and Drug Administration in the US has yet to follow the recommendation of the IOM report and fortify grains with vitamin B12.

Randomized controlled trials will not determine the risk to persons with vitamin B12 deficiency

Clarke and Armitage ('00) review randomized controlled trials testing the effectiveness of homocysteine-lowering vitamins to prevent cardiovascular disease. There is almost no chance that the eight clinical trials they describe will provide any meaningful new evidence between folic acid consumption and untreated

vitamin B12 deficiency. Six of the eight trials use sufficiently large doses of oral vitamin B12 to cure even the B12 deficiency caused by pernicious anemia. There will be no subjects with B12 deficiency to observe for the effects of increased consumption of folic acid. The other two studies contain only 14,000 subjects, a small cohort to examine for a possible rare adverse effect. There is no reason to delay fortification waiting for data that will be non-informative.

Those who see the world only through the eyes of randomized controlled trials apparently forget that the primary purpose of such trials is to show efficacy. Most adverse effects of drugs are discovered when there is wide exposure after marketing of the drugs. These post-marketing discoveries of adverse effect are almost always based on observational studies, which result in the removal of drugs from the market, not the randomized, premarket studies of a limited number of patients.

Exposure to at least 400 μg of synthetic folic acid has been common in the US since the early 1970s. There have been one billion person-years' exposure. Case-control studies in the US population are much more likely to find adverse effects, if there are any, than any randomized studies in progress (Rodrigues and Smith, '99). Case-control and longitudinal studies have shown that folic acid supplement takers have less disease than those who do not consume. Collectively there is no evidence of, or suggestion of, any adverse effects. The lack of adverse effects does not derive from insufficient exposure. It is a mistake for anyone to suggest that folic acid fortification should be delayed until we have "safety" evidence from cardiovascular randomized controlled trials. Such suggestions fail to recognize the current evidence and fail to acknowledge that the current trials will be uninformative.

Controlled field trial is unethical

Wharton and Booth ('01) argue that a "controlled field trial" should be conducted before there is folic acid fortification in the UK. Their arguments are not persuasive. They suggest there might be a hazard from folic acid fortification that might be found in a field trial. The probability that such a problem exists is negligible. Given the more than 1 billion person-years' exposure to at least 400 μg of folic acid a day over the last 25 years in the US and no discernible problem, it is unlikely any problem would be discovered in a controlled field trial with a few thousand person-years. The statistical power will simply not be there.

In a controlled field trial, how could one ethically justify the spina bifida cases that would occur in the non-fortified areas? Eight front-seat airbag deaths a year in the US led to changes in design and policy. Wharton and Booth ('01) propose controlled field trials that, if possible to perform, would take 10 years and would provide little useful information that is not now available. During these 10 years of no fortification, 4,000 pregnancies from the UK alone will develop folic acid-preventable birth defects; thousands of children and adults will have unnecessary folate deficiency anemia. In addition, nearly the entire population of adults will be exposed to homocysteine concentrations that will put them at risk for heart attacks and strokes. Boushey et al. ('95) estimate that folic acid would prevent at least 10 times the number of heart attacks as neural tube defects. Thus a 10-year delay is likely to cause about 40,000 men and women in the UK to die prematurely from heart attacks, to say nothing of the number who would die from strokes.

In June, 1991, my CDC colleagues were about to start a large randomized controlled trial of synthetic folic acid in a large group of Chinese women to determine its efficacy in preventing neural tube defects. When we learned of the results of the MRC study, we concluded that efficacy of folic acid had been conclusively shown. We also concluded that it would no longer be ethical to conduct a placebo, randomized controlled trial in China. Based on the US Public Health Service folic acid recommendation, the Chinese Ministry of Health decided to conduct a public health campaign to prevent NTDs by asking women who were planning to get married to take a daily pill containing 400 mcg of folic acid until the end of the first trimester (Berry et al., '99). A randomized controlled trial in India to examine the possible role of multivitamins in preventing the recurrence of open neural tube defects was also terminated when the MRC results were published (Indian Council of Medical Research Collaborating Centres and Central Technical Coordinating Unit I New Delhi, '00).

The UK has the capacity to fortify flour with folic acid immediately. A major policy review body has recommended fortification at 240 μg/100 g of flour. This fortification will increase plasma folates, will lower folate deficiency anemia, will lower homocysteine levels and will probably prevent substantial numbers of deaths from heart attacks and strokes with little risk, if any. It is wrong to delay fortification for any reason. No placebo controlled field trial would be ethical for women of reproductive age.

CONCLUSION

There is proof that folic acid fortification will prevent a large proportion of spina bifida and anencephaly, and folate deficiency anemia. There is also strong evidence indicating that folic acid fortification may prevent cardiovascular disease including strokes. There is less, but interesting evidence that folic acid may also prevent colon cancer. The UK Committee of the Medical Aspects of Food and Nutrition Policy (COMA) reviewed the evidence and recommended that flour in the UK be required to be fortified at 240 μg of folic acid/100 g of flour (2.4 parts/1,000,000). Fortification of wheat flour with 240 μg of folic acid/100 g of flour (2.4 ppm) should be implemented as quickly as possible in the UK and across Europe and the rest of the world to prevent birth defects and folate deficiency anemia. Such actions are also likely to have at least an order of magnitude larger protective effect against cardiovascular disease.

The opportunity to implement a sustainable, inexpensive, passive population intervention to prevent major human diseases comes rarely. Folic acid fortification of centrally processed grains is one of those rare opportunities. Governments that have not moved to assure that centrally processed grains are almost all fortified with sufficient folic acid are acting irresponsibly. They are committing public health malpractice.

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