Prophylactic or Poison: The Folic Acid Debate

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Deborah Blum's 2018 book, *The Poison Squad: One Chemist's Single-Minded Crusade for Food Safety at the Turn of the Twentieth Century,* was the University of Wisconsin-Madison's Go Big Read selection for the 2019-2020 academic year. In the book, Professor Blum describes the state of food adulteration in the United States at the turn of the 20th century, when milk and meat were routinely preserved with formaldehyde, beer and wine preserved with salicylic acid, canned vegetables made greener with copper sulfate, and borax added to rancid butter.[1]

Blum concomitantly tells the story of Harvey Wiley, MD, who was appointed Chief Chemist of the Bureau of Chemistry in the Department of Agriculture in 1883, which later became the Food and Drug Administration (FDA). Dr Wiley conducted the hygienic table trials – better known as the Poison Squad studies – which led to passage of the Pure Food and Drug Act in 1906. He devoted his career to raising public awareness regarding food adulteration, developing standards for food processing, and campaigning for the Pure Food and Drug Act. He vigorously fought the rampant use of potentially harmful food additives, and he promoted accurate labelling of food. While his hygienic table trials tested the effects of food additives on young healthy males, he was most concerned regarding the health effects of food additives on the most vulnerable in the population and the potentially cumulative effects of consuming low doses of food additives.

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What would Dr Wiley think about national food fortification policies – particularly folic acid – a century after the Pure Food and Drug Act? This commentary describes the difference between folate and folic acid, the level of evidence regarding the efficacy of mandatory fortification of cereal grains with folic acid, and possible repercussions of fortification – particularly in vulnerable populations related to maternal and child health.

Folate (vitamin B9) is a water-soluble vitamin found in leafy green vegetables, citrus fruits and beans. It is important for nucleotide and methionine biosynthesis, while deficiency is implicated in birth defects. The term folate refers to many related compounds, including folic acid, dihydrofolate (DHF), tetrahydrofolate (THF), 5-methyltetrahydrofolate (5-MTHF), and 5,10-methylenetetrahydrofolate (5,10-MTHF). The principal naturally occurring folates are in the THF form and polyglutamated. The synthetic folic acid used to fortify foods and found in most supplements is the fully oxidized monoglutamate form. MTHF reductase (MTHFR) is the final enzyme in a multistep pathway that converts folate and folic acid to the active metabolite 5-MTHF – the form that is transported across the intestinal mucosa – into cells and across the blood brain barrier where it functions as a coenzyme or cosubstrate in single-carbon transfers for the synthesis of nucleic acids and metabolism of amino acids. An example is the conversion of homocysteine to methionine in the synthesis of S-adenyl-methionine. When vitamin B12 is deficient, the conversion of homocysteine to methionine is inhibited, and folate is trapped as 5-MTHF, which cannot serve as a substrate for thymidine synthesis.

> While folic acid is water soluble and removed from the body through the urinary tract, high circulating levels of unmetabolized folic acid can accumulate in the blood, and vulnerable populations may be adversely affected by exceeding the tolerable upper intake limit.

Many nervous system disorders are associated with folate deficiency, including neural

tube defects during pregnancy, seizures and epilepsy, and neurodegeneration/cognitive decline. In 1996, the United States mandated national fortification of cereal grains with 140 µg folic acid per 100 g enriched product to prevent neural tube defects. Globally, countries are split on the decision to fortify cereal grains with folic acid. There are ethical issues regarding the risks to the larger portion of the population not receiving benefit.[2] In the United States, it was estimated that fortification would reduce neural tube defects by 50%. The prevalence of neural tube defects during the prefortification period of 1995-1996 averaged 7.3 per 10 000 for the White/non-Hispanic population in the Centers for Disease Control and Prevention National Center on Birth Defects and Developmental Disabilities study.[3] Another predominantly White/non-Hispanic population of 4783 subjects in the National Health and Nutrition Examination Study during 2007-2012 also exhibited a neural tube defect prevalence of 7.3 per 10 000 live births (range 5.5-9.4 per 10 000 live births).[4] While various studies report decreased postfortification prevalence of neural tube defects, the equivalent prevalence in these 2 studies spanning prefortification and postfortification periods argue against population level efficacy.

Major problems in assessing efficacy of national fortification policies include lack of prospective monitoring and absence of a nonfortification comparison group during the same time period. In 2020, neural tube defect risk at the population level was assessed in an article entitled, "Folic Acid Fortification and Neural Tube Defect Risk: Analysis of the Food Fortification Initiative Databset."[5] One would expect if national fortification was effective, then there should be decreased neural tube defects in response to fortification at the population level when comparing countries that fortify with countries that do not. This analysis demonstrates an equivalent average as well as range of high and low values for neural tube defects per 10 000 births in countries with and without fortification. Linear regression analysis indicates a very weak correlation between the prevalence of neural tube defects and the level of folic acid consumed from fortification.[6] Importantly, decreased prevalence of neural tube defects correlates strongly with better socioeconomic status,[5] which has been confirmed in another study.[7] A Cochrane systematic review found "very low certainty" regarding the efficacy of folic acid fortification in reducing neural tube defects.[8] The health benefits of vitamin B9 (folate) are well documented; however, there are numerous gaps in our understanding of the biology, physiology, and health effects of folate and folic acid.

The past century has witnessed tremendous advances with respect to food storage and safety. While there are subpopulations that experience food insecurity in the United States, the majority of the population is in a state of overconsumption versus underconsumption of food. Contrary to folic acid supplements, dosage cannot be controlled with food fortification.[9] Fortification of cereal grains with folic acid has increased the average intake double the projected level.[10] While folic acid is water soluble and removed from the body through the urinary tract, high circulating levels of unmetabolized folic acid can accumulate in the blood, and vulnerable populations may be adversely affected by exceeding the tolerable upper intake limit (UL). In regard to maternal and child health, the Maternal-Infant Research on Environmental Chemicals (MIREC) Pregnancy Cohort Study found that 25% of participants consumed more than the UL (>1000 µg/d) of folic acid.[11] Black children in the Boston Birth Cohort had a 10 times greater risk for autism spectrum disorder when they were in the highest versus the lowest quartile for unmetabolized folic acid in the umbilical cord.[12] Individuals with certain genetic polymorphisms that affect folic acid metabolism may have altered folate availability; for example, variants of the *MTHFR* gene affect about 40% of people worldwide and alter the conversion of folic acid to 5-MTHF. There are potential drug interactions between folic acid and numerous medications, such as proton pump inhibitors used to treat gastroesophageal reflux disease, anticonvulsants such as phenobarbital, the antibiotic tetracycline, and the cancer drug methotrexate.

Dr Wiley would concur with Paracelsus, 1538, who said, "All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison." Despite 26 years of fortification, a large portion of the target populations is deficient in folic acid, while a large segment is at risk for adverse health events in response to excess consumption. Could mandatory national fortification policies and overconsumption of folic acid be contributing to miscarriages, autism, Alzheimer's disease, and other health conditions? Why is neural tube defect prevalence still high in the United States if fortification policies are working? Why is folate insufficiency in women of reproductive age greater than 20%?[13] What is the best way to balance food insecurity and over consumption with public policy on fortification? Education and income are important predictors of the correct timing of supplement use in pregnancy.[14] A very low percentage of women receive nutrition information from their gynecologist prior to pregnancy.[14] The health of society would be better served if public health policy was targeted at prenatal care in women of reproductive age, for example, increased access to healthy foods and nutrition information as well as increased nutrition education in medical school curriculum. Other solutions include routine blood tests for folate levels; genetic screening for MTHFR variants; phone apps to track folic acid intake; avoidance of processed foods; and promotion of organic diets rich in leafy green vegetables, legumes, eggs, citrus fruits and beef liver.

Overall, the United States has not witnessed the projected 50% reduction in neural tube defects in response to national supplementation of cereal grains with folic acid, and current fortification levels present health concerns for large subgroups of the general population. The public health significance of fortification of cereal grains with folic acid is significant.[15] The father of the FDA in all likelihood would be opposed to national fortification with folic acid based on the lack of population-level efficacy data and the potential for harm to subpopulations. No doubt Dr Wiley's ghost haunts the halls of the FDA flabbergasted as to why at the turn of the 21st century a personalized medicine approach has not been implemented in regard to nutrient supplementation that targets women of reproductive age versus the currently employed national fortification policy with potential for harm to a large portion of the population.

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