

Folic Acid Continues in the News



JULIE MILLER JONES
Food and Nutrition
Department
College of St. Catherine
St. Paul, MN

In 1931, in Bombay, Lucy Wills conducted an experiment in which she fed monkeys a diet of white rice and white bread and induced a megaloblastic anemia similar to that commonly seen in India in pregnant women. Neither administration of the then-known vitamins nor liver extract reversed the anemia. Subsequently, she showed that the anemia could be prevented by ingestion of brewer's yeast. During the next 10 years, vitamin researchers in various parts of the world, using different animal and bacterial models, identified curative factors that were each named as vitamins or other factors, including vitamin M, vitamin Bc, U factor, and *L. casei* factor.

Also during that time, the substance in brewer's yeast was identified. Researchers at the University of Texas then isolated from spinach a concentrate of *L. casei* factor that turned out to be identical to the Lucy Wills factor. Since they extracted it from spinach leaves, the vitamin was named folacin from the Latin *folium* or leaf. This early history of folate filled with aliases seems a fitting prelude to the often-confusing role of folic acid in human nutrition and health today.

For some of its functions, its role in the prevention of many conditions has been documented. For example, Canada, the United States, and Hungary have recognized folate's importance in the prevention of neural tube defects and have mandated the fortification of grain products. Other birth defects also appear to be lessened with adequate folic acid. Yet, some countries have taken a more cautious view and are worried that elevated levels in the population can put segments of the population, such as the elderly, at risk. Further, its importance in protecting against other diseases is still the subject of much study and is nearly as confusing as some of its early history.

The following segment highlights reports from recent months on the reduction of birth defects, the improvement of memory and hearing, and the reduction of cardiovascular disease and cancers. Finally, it takes a look at problems of excess.

Recent reports in the literature from France (6) and Norway (22), countries where the incidence of cleft palate is high, and from a meta-analysis (1) strongly suggest that incidence of cleft lip and cleft palate is inversely associated with folate intake in the mothers' diets. U.S. data on the incidence of cleft lip and palate show that the mandatory fortification of flour with folic acid is also associated with a small decrease in these disfiguring and problematic birth defects (25). Data show that the timing of the decline is consistent with the introduction of fortification.

These data from the various countries in aggregate strongly suggest that folate fortification reduces yet another birth defect.

Despite the truly beneficial effects of folate on pregnancy outcome, there is great concern that folate intake is decreasing. In a report issued in January 2007 (5), the U.S. Centers for Disease Control found that, among women in their childbearing years, blood folate levels in 2004 had declined by 16% from the levels recorded in 2000. At least two dietary trends may be partly responsible for this drop. First, there was the overall diet craze to eliminate carbohydrates. Second, a shift occurred from fortified, refined products to whole-grain foods. While whole-grain products have some natural folate, many of them are not and cannot by regulation (Standard of Identity) be fortified. Supplements also have not been very successful. According to the March of Dimes, the taking of supplements is limited by cost, lack of awareness, and a widespread belief among Hispanic women that a vitamin supplement could cause weight gain. Thus, the new data indicate that only 33% of women of childbearing age (down from 40%) take a vitamin supplement with folate. The March of Dimes predicts that, if folate intake continues to decrease, the gains in reduced neural-tube defects may be erased. As a result, the March of Dimes expects to join a coalition petitioning the Food and Drug Administration to double the levels of folate in enriched grains.

Data on folate intake in Canada show similar trends. According to a recent study in Toronto, the average dietary folate of 61 university-educated women was 562 µg per day during pregnancy and 498 µg per day during lactation (17). From these data, Sherwood and her colleagues estimated that one-third of the highly educated women in her sample were getting inadequate folate during pregnancy and lactation. Folate intake by other socioeconomic groups, she suggested, may be even less. While these results may suggest to some that folate fortification is ineffectual, it is nevertheless true that, without fortification, 98% of the women would have failed to meet their requirements. Health Canada is asking for comments about folate and vitamin B₁₂ in the diet (10).

In addition to its role in reducing birth defects, folate is reported to positively influence the health of other population segments. However, as in its confusing history, not all the studies agree.

Some data suggest that folate may be helpful in reducing the cognitive decline associated with aging. Previous research suggests that high serum concentrations of homocysteine are associated with poor cognitive performance and Alzheimer's disease. Since folate is involved in keeping homocysteine levels low, there is thought that this B vitamin might be involved in memory issues associated with aging. Recent articles do little to add clarity about folate's overall role, as various studies both refute and support such a relationship. For example, the overall outcome of a study on more than 1,000 multiethnic elderly people showed no relationship between Alzheimer's and any B vitamin studied,

including folic acid (14). A recent analysis of 14 randomized trials did not provide adequate evidence of an effect of supplementation with vitamins B₆, B₁₂, or folic acid, alone or in combination, on cognitive function testing in people with either normal or impaired cognitive function (2). While these data might seem conclusive, they leave some murkiness. One of the studies reviewed did show a positive effect of folate supplementation if folate levels were low at the beginning of the study. Similar findings indicate that folate level at baseline may be influential in determining the studies' outcome. In this randomized clinical trial from the Netherlands (9), subjects with a low folate status did show positive outcomes when a large amount of folate was used. The administration of 800 µg of folic acid a day for 3 years improved measures of cognitive function in some older people ($n = 818$ men and women aged 50–70 years). Those in the cohort who had high serum concentrations of homocysteine at baseline showed the positive impact of supplementation. At the end of the trial, those on supplements were better at memory tests and quicker at processing information than those taking the placebo. They also had better global cognitive function, giving them the performance equivalent of someone 1.5 years younger.

Another study, published in January of 2007, showed an inverse association between folate from both diet and supplements (as assessed by food frequency) and the risk of developing Alzheimer's disease in an elderly population (13). In this study, only the combination of dietary folate and folate supplements were significantly linked to reduced risk of Alzheimer's disease. Neither factor alone nor vitamin B₁₂ or B₆ levels were associated with Alzheimer's disease risk. Higher folate intake was modestly correlated with lower homocysteine levels. These data are consistent with *in vitro* findings that show that low folate and high homocysteine levels may enhance the effects of amyloid-beta, an Alzheimer risk factor.

One reason that the findings seem confusing may be due to researchers not considering several variables together. Folic acid was shown to have a positive effect on mental functioning if there was adequate B₁₂ status (15). In the 1999–2002 U.S. National Health and Nutrition Examination Survey, seniors with low B₁₂ status alone (defined as either B₁₂ <148 pmol/L or a serum methylmalonic acid concentration >210 nmol/L) or low vitamin B₁₂ status combined with high serum folate (>59 nmol/L) were more likely to have anemia and cognitive impairment (15). When seniors had normal vitamin B₁₂ status and high serum folate, there appeared to be protection against cognitive impairment.

Besides cognitive functioning, folic acid intake is also associated with reduced risk of other diseases, including cardiovascular disease. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC) (the Potsdam arm study involving 22,245 healthy participants aged 35–64 years) showed that an increased intake of dietary folate was associated with a decreased risk of myocardial infarction (8). The effect was especially strong among subjects with alcohol intake above the median for the group. On the other hand, a large review indicated that folate supplementation may not impact the course of cardiovascular disease or persons who already have the disease (3).

Folate's involvement in methyl transfers has long suggested that it has a role in protecting against some types of cancer. For instance, a recent review indicated that, for colorectal cancer, dietary levels of folate are associated with reduced risk (11).

However, as with some other roles for folate, this relationship may not be straightforward but may be dependent on other nutrient status or dietary intake. For example, a recent meta-analysis failed to show a relationship between breast cancer and folate intake overall (12). However, the meta-analysis did indicate that

breast cancer incidence may be reduced if folate levels are high and the subjects consume alcohol. A similar picture may exist for ovarian cancers (16).

For some of folate's roles, the actual concentration of folate may need to be optimized. This appears to be the case for at least one measure of the immune system—the cytotoxicity of the natural killer (NK) cell. Troen and colleagues (21) found, in postmenopausal women, an inverse U-shaped relation between total folate intake and NK cytotoxicity. For women in the bottom third of folate intake (<233 µg/day), NK function was decreased when they took daily supplements containing 400 µg of folic acid compared to those who took no supplementary folic acid. However, women with a dietary folate intake of 233 µg/day or more who were taking supplements providing folate at >400 µg/day showed impaired NK cytotoxicity. The authors suggest that their findings raise questions about whether excess folic acid from supplements or from too many fortified foods could suppress the NK cell's role in killing tumor and virally infected cells. The authors also suggest that research should look at the association between vitamin B₁₂ status and NK cytotoxicity, since it could be possible that poor vitamin B₁₂ status influences the metabolism of folic acid or the function of NK cells after high intakes of folic acid.

Some of the questions about the right level of folate for the diet, what form of folate should be added, and the risks of too much folate and too little B₁₂ are all wonderfully addressed in a commentary by A. David Smith (20). He asked questions that can be summarized as follows.

1. Which is more important—the balance between folate and vitamin B₁₂ or the absolute concentrations of these vitamins? Is the imbalance between folate and vitamin B₁₂ associated with adverse effects, particularly in vulnerable sectors of the population (e.g., pregnant and lactating women, infants and children, and perhaps vegetarians)? What causes anemia and cognitive impairment in persons with high folate and a low vitamin B₁₂ status? Is folate's interaction with vitamin B₁₂ also involved in the complex relationship between folate and cancer?
2. What is the role of unmetabolized folic acid in the bloodstream? Does this have an adverse effect? Would supplements of methylfolate instead of folic acid be preferable?
3. Should calls for further fortification be accompanied by data showing that this measure will not cause harm to others?
4. Should vitamin B₁₂ be added to the folate fortification standard and to folate supplements?

Answering these questions should be important for the upcoming research agenda and will be helpful in determining levels of fortification in cereal products throughout the world.

Of Dietary Fiber, Disease, and Its Functional Components

Dietary fiber intake in premenopausal women may cut breast cancer risk according to a study of 35,792 women aged 35–69 in the U.K. Women's Cohort Study (4). Those ingesting 30 or more grams per day of dietary fiber had a 52% decrease in the risk of breast cancer compared with those who ate less than 20 g per day. Cereal and fruit fiber appears to be an important contributor. Those women in the upper quintile of cereal fiber intake (13 or more grams per day) had a 41% breast cancer risk reduction, compared to the lowest quintile intake (≤ 4 g). Similarly, those with 6 or more grams per day of fruit fiber had a 29% lower risk of breast cancer risk when compared to those with 2 or less grams per day.

The authors suggested several mechanisms. First, high-fiber foods contain antioxidant nutrients that protect against free radicals. Also, some dietary fibers may control glucose availability to the body and therefore affect insulin levels. (High insulin levels are suggested by some as a cancer promoter.) Third, some components of fiber such as lignans have antioxidant and free-radical scavenging properties and the ability to alter levels of circulating estrogen. This effect would be especially relevant to the premenopausal group, who naturally have far higher levels of the hormone. (Columnist's note: The average overall intake of dietary fiber in the United Kingdom is around 12 g per day. The values are equally dismal for intake in the United States.)

Further analysis of the lignans of plant foods helps researchers to develop possible mechanisms for some of the anticancer impacts of the foods and fibers that contain lignans. In a recent study of 16 species of seeds and cereals (including sesame, linseed, wheat, barley, corn, oat bran, and four species of nuts), wheat and rye bran had the highest lignan content of all the cereals (19). However, linseeds and sesame seeds were the most lignan-rich of the studied species. This analysis, employing high-performance liquid chromatography in combination with mass spectroscopy, showed that 18 of the 24 lignans have not previously been identified in the materials tested. One newly documented cereal lignan, 7-hydroxymatairesinol, appears to be the dominant lignan in a wide range of cereals, including wheat, barley, corn, and quinoa bran and is also in amaranth. Physiologically, the lignan 7-hydroxymatairesinol is metabolized in the body to form mostly enterolactone and some 7-hydroxyenterolactone, but no enterodiol. Further studies on the health benefits of the newly identified and previously recognized lignans are currently being conducted.

Effects of Breakfast Meal Composition on Second-Meal Metabolic Responses in Adults with Type 2 Diabetes Mellitus

A low-glycemic-load breakfast containing psyllium-soluble fiber improved the breakfast postprandial glycemic, insulinemic, and free fatty acid responses in adults with type 2 diabetes over that seen with farina and no soluble fiber (the high-glycemic-load breakfast) (7). However, no second-meal effect was observed in this study with 40 adults with type 2 diabetes, as had been observed in some previous studies with other soluble fibers.

(Columnist's note: There is a small difference in the diets' carbohydrate contents. The farina diet had 78 g of carbohydrate. The low-glycemic-load breakfast meal used a fiber-loop cereal and provided 62 g of carbohydrate and 6.6 g of psyllium fiber.)

In addition to the reduced cancer risk associated with lignans and dietary fiber, soluble fibers added to a low-carbohydrate diet reduced cardiovascular and diabetes risk factors. Coronary disease risk factors were decreased in all 30 overweight subjects who ate a severely carbohydrate-restricted diet (ratio of percent carbohydrate-fat-protein = 13:60:27) for 12 weeks. In this randomized, double-blind, placebo-controlled, parallel-arm study, a carbohydrate-restricted diet reduced body weight, percentage of body fat, systolic blood pressure, waist circumference, plasma glucose, high-density lipoprotein (HDL) cholesterol, and triglyceride levels (23). The low-carbohydrate diet caused a spontaneous reduction in energy intake of 30.5% (24). The addition of the soluble fiber supplement (konjac-mannan, 3 g per day) to the carbohydrate-restricted diet further reduced low-density lipoprotein (LDL) cholesterol to less than the level in those not taking the soluble fiber supplement. These results suggest that restricting dietary intake of carbohydrates may have a beneficial effect on

cardiovascular disease risk markers, but supplementation of the diet with soluble fiber further improved LDL cholesterol levels.

In another study by the same group (18), a cookie containing soluble fiber and plant sterols also improved markers of cardiovascular risk in overweight individuals with hypercholesterolemia. This study was interesting in that there was improvement in the distribution of cholesterol particles types. The soluble fiber/sterol supplement (psyllium, 7.68 g/day, and plant sterols, 2.6 g/day, in the form of cookies) reduced the number of smaller LDL particles, the ones that have greater atherogenicity. Furthermore, a reduction was seen also in the smaller HDL particles, which have reduced capacity for reverse cholesterol transport. The authors concluded that this functional-food supplement resulted in a less atherogenic lipoprotein profile.

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Julie Miller Jones, a board-certified (CNS) and licensed nutritionist, is a professor in the Department of Family, Consumer and Nutritional Sciences at the College of St. Catherine in St. Paul, MN. She writes and speaks locally, nationally, and internationally on issues regarding nutrition and food safety, with special emphasis on whole grains and dietary fiber, carbohydrates and glycemic index, and dieting. She can be reached at juliemjones@comcast.net.

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