The Weston A. Price Foundation

Folic Acid and Glyphosate

MAY 4, 2016 BY STEPHANIE SENEFF, PHD
(HTTPS://WWW.WESTONAPRICE.ORG/AUTHOR/SSENEFF/)

Synergistic Toxicity

Neural tube defects (NTDs), such as spina bifida, anencephaly and exencephaly, are severe birth defects that result from failure of neural folds closure during embryonic development.[1] While many factors may be involved in disrupting development in this way, it has been known since the 1970s that folate deficiency during the first trimester is a significant risk factor.[2]

As a consequence, the United States and many other countries have introduced laws to require fortification of certain staple foods with folic acid. In the U.S., in particular, a regulatory requirement was introduced in 1998 for wheat-based products to be fortified with folic acid and iron. Pregnant women are also encouraged to take folic acid supplements during the first trimester, which often continue throughout the pregnancy.

At first glance, this seems like a good idea, but the European Union (aside from the United Kingdom) has steadfastly refused to adopt this requirement, despite pressures from the U.S. Is there a down side to folic acid supplementation? Do the Europeans know something that the U.S. government does not?

If you were paying attention, you noticed that I said “folate” deficiency and “folic acid” supplementation. Folate and folic acid are the same thing, right? Interchangeable. Wrong! I have seen research papers use these words interchangeably, but they are definitely not the same thing. The folic acid supplement that’s added to flour is a synthetic version of the B vitamin, which is oxidized and missing the methyl group.

The active form of the vitamin is technically called methyltetrahydrofolate. Folic acid is much more stable, whereas folate easily breaks down with aging or with heat (as in baking the bread). Folic acid is a (cheaper) synthetic molecule whereas folate is natural.

According to the U.S. government's Code of Federal Regulations, Title 21, Volume 2, fortified wheat products must contain 0.7 milligrams of folic acid and 20 milligrams of iron. This regulation became law in 1998, at a time when genetically modified (GM) RoundUp-Ready corn and soy crops had been on the market for a few years and were rapidly expanding market share. Correspondingly, glyphosate usage as an herbicide on these crops was also growing at an alarming rate. Glyphosate is the active ingredient in RoundUp, and the crops were engineered to be resistant to glyphosate's toxicity through the insertion of a bacterial gene. The incidence of spina bifida was also increasing at that time, which is what alerted the government to a potential problem with folate deficiency.

One has to wonder whether somebody involved in the introduction of this law knew something about the potential of glyphosate to cause spina bifida. It would not take a rocket scientist to think that disruption of the gut microbes that naturally produce folate for the host would lead to folate deficiency. In fact, it is a direct hit: folate is produced from products of the shikimate pathway, and this is the pathway that even Monsanto admits is disrupted in plants and microbes by glyphosate. Furthermore, the microbes that synthesize folate for the host, lactobacillus and bifidobacteria,[3] are the ones that glyphosate preferentially kills.[4] A continued rise in spina bifida would raise public awareness of a hidden environmental toxicant that might be causing this rise. Making sure that pregnant women were well supplied with external folic acid might mask the problem.

A definitive study from 1991 involving thirty-three centers in seven countries seemed to support the decision, suggesting a clear benefit from folic acid supplementation with little down side.[6] A bold assumption in supplementing with folic acid rather than folate was that the gut microbes would take care of reducing folic acid to folate

(adding two hydrogen atoms and reducing double bonds) and then adding the all-important methyl group, prior to its absorption into the blood stream. If this doesn't happen, the folic acid is useless, and may even have toxic effects. Figure 1 shows the molecule for methyltetrahydrofolate with the methyl group and the four hydrogens circled.

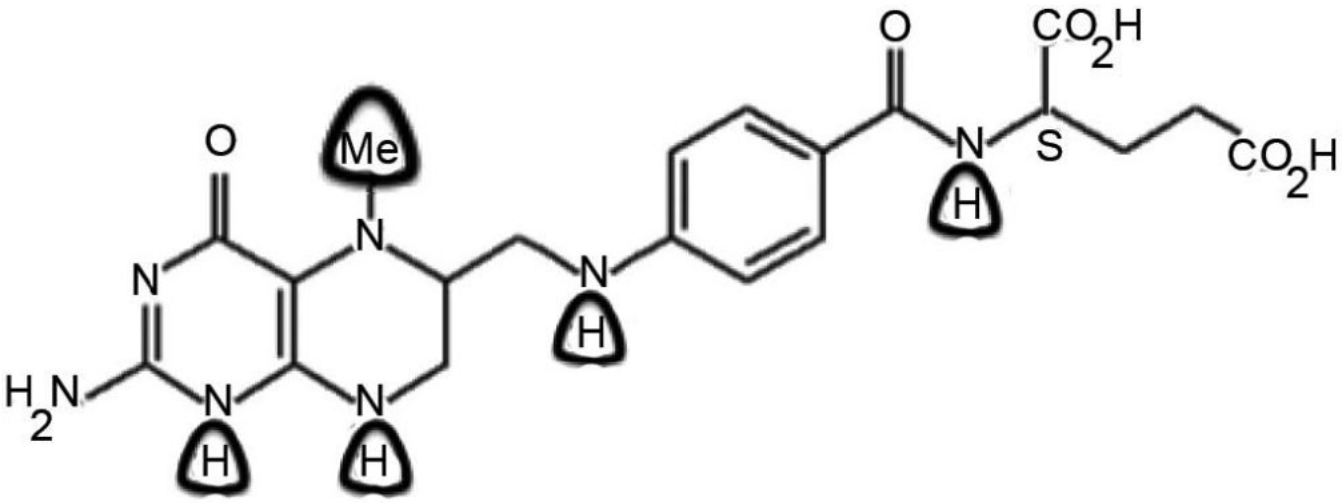

Figure 1: The methyltetrahydrofolate molecule, with the four hydrogens and the methyl group circled for clarity.

A much more recent study, from 2014, suggests that this assumption was wrong.[7] Through direct measurements of folic acid metabolites in the hepatic portal vein, they discovered that the human gut can methylate folate but it can't efficiently reduce folic acid, a step that is necessary prior to methylation. This means that the unreduced and unmethylated folic acid makes its way to the liver, which then is tasked with both reducing it and methylating it. This costs the liver dearly, both in antioxidant capacity and in methylation capacity. In fact, it can be expected to drive the liver toward a hyperoxidized state, with a high ratio of oxidized-to-reduced glutathione and a depletion of an important compound called nicotinamide adenine dinucleotide phosphate (NADPH) and methionine, all of which lead to liver stress. Unfortunately, glyphosate does all of these things in the liver as well.[8]

In a study comparing three hundred sixty autistic children to two hundred five controls, it was found that children with autism had a high ratio of oxidized-to-reduced glutathione in the blood, indicating impaired antioxidant capacity, along with low serum methionine, and a low ratio of methionine to homocysteine, a direct indicator of low methylation capacity.[5] In other words, these children exhibited features you would expect from toxic exposure of the liver to excess amounts of both folic acid and glyphosate.

FOLIC ACID, FOLATE AND CANCER

Folate is intimately involved in the complex biological pathways that maintain S-adenosylmethionine, the universal methyl donor, and it also feeds into the synthesis of purine and thymidine units in DNA and RNA. The one-carbon metabolic pathway (one-carbon = the methyl group), mediated by folate, plays a vital role in hemoglobin synthesis and DNA synthesis, repair and methylation.[9] For these reasons, it is generally believed that a diet high in folate should be protective against cancer, which

arises from DNA mutations. In particular, there is a fairly compelling case for folate being protective against colorectal cancer (CRC).[10] Folate may also be protective against breast cancer and uterine cancer.[11]

Given the above, one would expect that folic acid supplementation would decrease the incidence of colorectal cancer. Ironically, epidemiological data in both the U.S. and Canada showed an increase in the incidence of colorectal cancer beginning when folic acid fortification in wheat-based products became mandatory.[12] These authors wrote in the abstract: “We therefore hypothesize that the institution of folic acid fortification may have been wholly or partly responsible for the observed increase in CRC rates in the mid-1990s.”

A study by Troen and others confirmed that unmodified and therefore inactive folic acid was present in the blood among 78 percent of one hundred five post-menopausal women.[13] Over half of them were taking a folic acid supplement daily. The study found that the ability of natural killer cells to destroy neoplastic (potentially cancerous) cells was reduced when folic acid levels were elevated. What is probably happening is that the inactive folic acid is binding to the folate receptors and preventing access by the methyltetrahydrofolate. This gives a hint as to how excess folic acid might increase risk to cancer: by getting in the way!

(Methyltetrahydro) folate protects from cancer by preventing DNA mutations, which can turn off cancer-protective genes and cause cells to start proliferating uncontrollably. However, folate also *fuels* proliferation, because it is necessary for the synthesis of certain DNA nucleotides. Once you have a cancer growing, folate will encourage the cancer to grow bigger. Part of the chemotherapy program used to treat cancer involves anti-folate drugs: drugs that interfere with folate signaling.[14-17] While these drugs prevent growth of the existing tumor, they also encourage further DNA mutations, which could lead to metastasis from the tumor, and it will also cause an increased risk of new cancers.

A randomized placebo-controlled trial intended to test the potential benefit of folic acid supplements in colon cancer showed instead that people with a history of colorectal adenomas had an increased risk of a more severe recurrence if they took 1 mg folic acid per day.[18] Another paper showed that oral folic acid supplements increase the risk of prostate cancer. Meanwhile, anti-folate chemotherapy treatments are being widely administered to actively reduce the bioavailability of folate, which has been shown to fuel cancer growth, for both breast cancer and non-Hodgkin's lymphoma.[14-17]

HOW MUCH IS TOO MUCH?

On top of the folic acid that is present as fortification of flour, bread and pasta, about 30-40 percent of North Americans also take folic acid supplements. And supplements are usually recommended during pregnancy, with a disregard for potential toxicity. There is an increasing concern that the widespread practice of folic acid fortification is leading to an over-consumption of folic acid. A study of four healthy adult volunteers involved administering folic-acid-enriched bread and then analyzing for the presence of synthetic unmodified folic acid in the blood. Serum folic acid was found in all subjects at all doses tested.[19]

In an experiment to test the effects of folic acid on mammary tumors in female Sprague-Dawley rats, rats with tumors were randomized to receive a diet containing varying amounts of folic acid supplements, for up to twelve weeks, and the growth of their tumors was monitored.[20] Folic acid supplementation at all levels significantly promoted the progression of mammary tumors, with increases in both weight and volume compared to the control diet without any supplement. These authors wrote: "This is a critically important issue because breast cancer patients and survivors in North America are likely exposed to high levels of folic acid owing to folic acid fortification and widespread supplemental use after cancer diagnosis."

GLYPHOSATE AND NEURAL TUBE DEFECTS

I have claimed that glyphosate causes neural tube defects. Is there any evidence that this is true? Fifty-two cases of malformations in the offspring of pregnant women

exposed to agrochemicals included anencephaly, microcephaly, facial defects, myelomeningocele, cleft palate, ear malformations, polydactily and syndactily.[21] Of course, they were exposed to many different chemicals, so it is not possible to place the blame on glyphosate without more direct evidence of glyphosate's ability to induce these problems.

The U.S. Centers for Disease Control have reported on an excessive number of anencephaly births in Tacoma, Washington, at four times the national average rate.[22] This increase coincided with a large increase in the use of glyphosate to control waterway weeds. Alarming trends of increases in birth defects such as microcephaly, anencephaly, cleft palates and other facial defects have occurred in regions of South America and Paraguay where glyphosate is used extensively on core crops.[21, 23] Recently, an epidemic in microcephaly was reported in northern Brazil, where GM RoundUp-Ready corn and soy crops are a major export commodity. While this increase is being attributed to the Zika virus, glyphosate may well be a contributing factor. An investigation of forty-nine deaths linked only five of the cases directly to Zika virus, leaving much room for alternative explanations.[24]

A study on tadpoles, specifically focusing on glyphosate formulations, conducted by Carrasco and others,[25] showed similar defects, including a reduction in head size, cyclopia (only one eye), reduction of the neural crest territory at neurula stages and craniofacial malformations. These defects occurred upon exposure to minute amounts of glyphosate: dilutions of 1/500,000 produced developmental abnormalities in 17 percent of the embryos. They suggested that the mechanism might involve over-production of retinoic acid, which is a known teratogen. This makes sense, because retinoic acid is broken down in the liver by cytochrome P450 enzymes, which glyphosate disrupts.[8]

However, I believe that there may be more to the story than retinoic acid, and more than glyphosate's disruption of folate synthesis by gut microbes. This has to do with glyphosate's potential disruption of the folate one-carbon cycle, due directly to suppression of glycine metabolism. Glyphosate is a synthetic amino acid, an analogue

of glycine. Hiding inside the glyphosate molecule is a glycine molecule, and there is potential for protein-making machinery to get confused and place glyphosate instead of glycine when constructing a brand new protein according to a DNA code for glycine. As we will see in the next section, there are multiple ways that glyphosate could mess up the machinery that produces the one-carbon (methyl group) that feeds into the one-carbon cycle.

GLYPHOSATE AND GLDC

Glycine decarboxylase (GLDC) is likely an enzyme you have never heard of. However, its importance for one-carbon metabolism is nonpareil. This is how you link impaired glycine metabolism directly to folate deficiency and neural tube defects, as well as to autism.

The chemistry involved is not completely straightforward, but it is not too hard to grasp. Figure 2 schematizes the most important parts. First of all, glycine, as one of the twenty-two amino acids that are building blocks of proteins, is nonetheless toxic to microbes and to human cells if it is present in too high concentrations as a free amino acid in the environment. The gut microbes normally metabolize glycine, using GLDC, among other enzymes, to carbon dioxide, ammonia and a methyl group. The methyl group is very important, because it feeds into folate one-carbon metabolism; that is, it methylates tetrahydrofolate.

An elegant and compelling study by researchers in London, published in 2015, goes a long way toward explaining how glyphosate could lead to both spina bifida and autism, without, however, ever mentioning glyphosate.[26] If GLDC isn't working, two problems quickly arise: glycine toxicity and a deficiency in the supply of methyl groups. A mutation in GLDC, if inherited from both parents, causes a rare disease called non-ketotic hyperglycinemia (hyperglycinemia standing for high glycine). This enzyme has also shown up as a mutation linked to neural tube defects, in both mice and humans.[27] The focus of the London study was to explain how these very different outcomes could arise from the same defect. What they found was that mice engineered to have defective GLDC genes inherited from both parents fell into two

Figure 2: Simple schematic of biological pathways by which glycine is stripped of a methyl group to methylate tetrahydrofolate, which then provides methyl groups to other biologically important molecules. GLDC, GCSH, AMT, and DLD are all enzymes involved in the metabolism of glycine.

distinct groups: those whose neural tubes failed to close (and this group didn't survive long after birth) and those who were relatively spared but suffered from hyperglycinemia during their entire lifespan.

Mice that were homozygous for the defective gene (meaning that the copies of this gene inherited from both parents were defective) did not fare well. Half of them developed hydrocephalus (water on the brain) with evident brain swelling and dramatic enlargement of the ventricles in the brain (which house the cerebrospinal fluid). These mice all died within the first twelve weeks of life. Some of the embryos displayed exencephaly, a brain defect whereby neural tissue bulges from the brain. Others had strikingly enlarged ventricles, even prenatally. Autism, attention-deficit hyperactivity disorder (ADHD), and schizophrenia have all been linked to enlargement of the ventricles in the brain,[28] although fortunately these individuals don't suffer from the more severe defects observed with the double gene mutation.

Glyphosate could disrupt glycine decarboxylase in at least two ways. One is through displacing glycine as substrate. Glyphosate has been shown to disrupt other enzymes that have glycine as substrate, such as the rate-limiting enzyme in the synthesis of the pyrrole ring, a building block of cobalamin and hemoglobin. But another possibility is more insidious: insertion into the amino acid chain in place of glycine at a location where glycine is essential for proper function of the protein. A glycine-rich region is very near the active site of glycine decarboxylase, and it maintains the shape and flexibility of the active site.[29] Glycine is a very special amino acid because, unlike all the others, it has no side chains. This makes it tiny and flexible, and proteins have taken advantage by putting glycine residues where flexibility is needed. Substitution of glyphosate for any of the glycines in this region is likely to impair enzyme function. This would be true regardless of the gene variant, and therefore has little to do with genetics. Glyphosate could thus suppress the activity of glycine decarboxylase by inserting itself into the protein in place of glycine, and this could cause effects that mimic, but to a lesser degree, the pathology of the homozygous mice.

An interesting observation from the London study was that the female mice were more susceptible to neural tube closure problems than the male mice. This might be part of the explanation for the skew of autism toward males. Affected females are more likely to be "weeded out" early on due to life-threatening defects, probably often manifested as a spontaneous abortion early in the pregnancy.

The London authors found that GLDC is intensely expressed in the neural tube during its development, and that this enzyme is required for neural tube closure, and beyond, during brain development.[26] By examining the timing of events in embryos with the genetic defect compared to normal mice, the authors noted that neural tube closure was delayed in the defective mice, along with delayed development in general. In some cases it never closed, but, if it did succeed in closing, then the pressure built up due to accumulating fluids, resulting in hydrocephaly and exencephaly. They also confirmed, as expected, that the defective mice had a reduced supply of methylene tetrahydrofolate, the immediate precursor to methyltetrahydrofolate, as can be anticipated by examining Figure 3.

Previous research from a subset of these authors had shown that maternal folate deficiency alone can induce neural tube defects in the offspring.[30,31] It is interesting to note that it was not enough to simply remove dietary folate from the mouse dams. They also had to expose them to antibiotics in order to remove folate-synthesizing gut microbes, beginning even before the dams were mated. This makes it very clear that our gut microbes supply important amounts of folate under normal circumstances, and this supply is at risk if they are chronically exposed to glyphosate, a patented anti-microbial agent.

CEREBRAL FOLATE DEFICIENCY

Cerebral folate deficiency (CFD) is defined as a condition where the serum levels of folate appear to be fine, but the levels in the cerebrospinal fluid are low, leading to deficiencies in the brain and central nervous system. Idiopathic CFD is a neurometabolic syndrome that develops from the age of four months, starting with irritability and sleep disturbances, and progressing to limb stiffness, impaired balance and gait, and involuntary muscle movements.[32] Many of these children also develop epilepsy, as well as slowed head growth, reminiscent of the microcephaly in the Brazilian infants. As the children grow to ages three to six years old, they develop visual disturbances and hearing loss. The condition is due to a malfunctioning of the folate receptors in the brain, which blocks the transfer of folate from the blood to the cerebrospinal fluid. One possible reason for this is that excess folic acid in the serum

Figure 3: Simplified schematic of the methylation pathways. AdoHcy: adenosylhomocysteine; AdoMet: adenosylmethionine; DHF: dihydrofolate; DMG: dimethylglycine; MS: methionine synthase; MTHFR: methylenetetrahydrofolate reductase; THF: tetrahydrofolate. Adapted from Figure 1 in Refsum, 2001.[35]

has bound to the receptors and blocked their access to methyltetrahydrofolate. Clearly, over-exposure to folic acid through diet and supplements can promote the development of CFD.

A study on twenty-five low-functioning autistic children revealed a clear link between autism and low cerebral folate levels.[33] Despite normal serum folate, CSF 5-methyltetrahydrofolate was low in twenty-three of twenty-five autistic patients examined. Folate receptor antibodies were identified in nineteen of the patients. Although this was investigated, no link was found with any genetic mutations in the gene coding for the folate receptors. It seems likely to me that irreversible binding of folic acid to the folate receptors could induce an autoimmune response to the receptor-folic acid complex that leads to the development of antibodies to the folate receptors.

Antibodies to the folate receptors in the mother are also linked to neural tube defects in the fetus. A study from 2004 showed that women in the United States who have had a pregnancy with a neural tube defect were more likely to have autoantibodies to the human placental folate receptor,[34] which will then block the supply of folate to the fetus.

MTHFR, B_{12} and METHYLATION-TRANSSULFURATION PATHWAYS

An article on folate would not be complete without a diagram of the methylation cycle; these biological pathways may seem daunting to the novice but are actually fairly straightforward once you follow the logic. A simplified diagram of the methylation cycle is given in Figure 3. Most notable are two very important enzymes, methylene tetrahydrofolate reductase (MTHFR) and methionine synthase (MS). Defects in MTHFR have been linked to chronic fatigue syndrome[36] and to autism,[37] as well as other conditions. These defects are a major source of the so-called “folate trap,” because the all-important methyl group piles up in useless accumulations of methylene-tetrahydrofolate, while methionine synthesis can’t happen, so homocysteine piles up as well.

Methionine synthase is also a vulnerability point in the pathway. This is the crucial reaction that converts homocysteine to methionine, after which methionine can deliver its cargo of a methyl group to all kinds of recipients. The methyl group is transferred from methyltetrahydrofolate to methionine, but, crucially, vitamin B_{12}

(cobalamin) is an essential cofactor to catalyze the reaction. Cobalamin, in turn, depends crucially on the mineral cobalt to function, and cobalt is one of the minerals that is chelated by glyphosate, making it unavailable. Furthermore, glyphosate disrupts the synthesis of the corrin ring in cobalamin, with glycine being one of the important substrates for pyrrole synthesis, and pyrrole forming a core building block of corrin.[38] Once again, glyphosate getting in the way of glycine can cause trouble, in this case leading to vitamin B_{12} deficiency.

Postmortem studies on brains of people with autism and schizophrenia, as well as elderly people, revealed low levels of cobalamin in the brain in all three groups.[39] In the autistic subjects, this was associated with decreased activity of methionine synthase and elevated levels of homocysteine.

Folic acid supplementation masks the symptoms that doctors have been trained to look for in vitamin B_{12} deficiency, also known as pernicious anemia. As a result, doctors are missing cases of severe B_{12} deficiency, which can lead to significant loss of myelin, brain fog, and extreme physical weakness and fatigue, along with back pain due to degeneration of the spinal cord if the deficiency lasts too long. All of these symptoms seem to be more and more prevalent in our society. Pain killer prescriptions are at an all-time high and people are overdosing in record numbers.

Folic acid supplementation insidiously corrects for macrocytosis associated with B_{12} deficiency, as has been explained very well by Sally Pacholok in her excellent book, *Could it be B_{12}?*.[40] This idea is also supported by at least one published study.[41] This results in a delayed testing for B_{12} deficiency for elderly presenting with symptoms of dementia and fatigue linked to B_{12} deficiency. It is tragic when a B_{12} supplement could restore mental health but there is no awareness among the medical practitioners that this is the problem. This effect applies not only to the elderly. Among those younger than sixty-five years old, the percentage with low serum vitamin B_{12} without macrocytosis significantly increased from 45 percent in the pre-fortification period to 85 percent in the post-fortification period.[41]

Vitamin B_{12} is only found in animal products, so vegans have a difficult time getting adequate amounts. Many medicines, including metformin, statin drugs and acid reflux drugs, interfere with B_{12} absorption from the gut. It is estimated that as many as 30 percent of people in the U.S. suffer from B_{12} deficiency. Fortunately, there is another pathway from homocysteine to methionine where betaine serves as the source of methyl groups, and this depends on neither folate nor B_{12}. It is likely that a diet high in betaine can reduce the need for folate and B_{12}.

Celiac disease has become an epidemic in recent years, and untreated celiac patients often suffer from deficiencies in both folate and B_{12} due to absorption problems.[42] In previous work together with Anthony Samsel, I proposed that the epidemic in celiac disease may be due to glyphosate contamination in the wheat, because glyphosate is increasingly being used as a desiccant on wheat right before the harvest.[43]

Nitrous oxide can cause irreversible oxidation of B_{12} to an inactive form, such that levels can test as adequate even when usable levels are much too low. Nitrous oxide can arise through oxidation of ammonia, which will build up if glutamine synthase is defective. Glutamine synthase combines ammonia with glutamate to make glutamine. This process depends on manganese, a metal that glyphosate chelates, making it unavailable.[38]

Finally, homocysteine itself, the precursor to methionine, can be deficient. In fact, the bottom of the graph in Figure 3 that shows other ways homocysteine can be used should not be neglected. Sulfate, cysteine and taurine are biologically important molecules that play many roles in the body. These molecules all contain sulfur, a mineral that is neglected by the nutrition experts and widely deficient in the population.[44] Sulfur deficiency can be induced by glyphosate as it has been shown to interfere with sulfur uptake in plants. Methylation capacity can be reduced simply because homocysteine is more urgently needed as a precursor to these other biologically active molecules.

CONCLUSION

Folate deficiency, together with vitamin B_{12} deficiency, are widespread in the U.S. population today, despite the fact that most people are not lacking resources for adequate nutritional intake. The problem, I believe, mainly stems from disruption of the gut microbes due to chronic low-dose exposures to glyphosate, a patented anti-microbial agent. Various popular drugs and antibiotic treatments compound the problem. In 1998, the U.S. implemented a plan to fortify wheat-based products with folic acid, in the hopes of decreasing the incidence of spina bifida and other neural tube defects. Unfortunately, folic acid is a synthetic form of folate, and converting it to the active form is costly to the liver. Unconverted folic acid accumulating in the blood can cause unanticipated problems related to cerebral folate deficiency.

Folic acid supplementation during early pregnancy protects from spina bifida and avoids either a spontaneous miscarriage or a severe developmental defect causing early postnatal death, associated with spina bifida, microcephaly or anencephaly. However, continued folic acid supplementation throughout pregnancy can result in an accumulation of unmodified folic acid in the fetal blood, causing fetal cerebral folate deficiency during the second half of gestation. This will disrupt methylation pathways in the brain, and may result in hydrocephaly and enlarged ventricles, and, in the extreme case, exencephaly. Impaired methylation pathways, enlarged ventricles, and disrupted folate homeostasis are all features of autism.

The best way to maintain adequate supplies of folate and cobalamin is to eat a strictly organic diet that is rich in fresh vegetables, seafood, eggs, and grass-fed beef and liver. Particularly good sources of folate include beef liver, spinach, black-eyed peas, asparagus, Brussels sprouts, avocado, broccoli, mustard greens, green peas and kidney beans.

SIDEBARS

THE METHYLATION PATHWAY OR THE ONE-CARBON CYCLE

Carbon is one of the basic elements in the periodic table and the core building block of living systems (carbon-based life forms). Methane gas is one of the simplest carbon-based molecules, containing a single carbon atom bound to four hydrogen atoms. A methyl group is essentially a methane molecule that's missing one hydrogen: it is a constituent of a larger molecule where the displaced hydrogen atom has been substituted by a biological molecule that has thus become "methylated." The "methylation pathway" is the biological pathway by which a methyl group is passed around from one molecule to another—usually from glycine or betaine to tetrahydrofolate to homocysteine—to finally produce methionine. Methionine then becomes a "methyl source," as it can donate its methyl group to multiple types of biologically important molecules, such as to various proteins (protein methylation) or to DNA molecules (DNA methylation). DNA methylation is an epigenetic process that can turn on or off the expression of various genes. DNA methylation is an important component of embryonic development. The entire biological pathway from glycine/betaine to methyl folate to methionine and finally to protein and DNA methylation is referred to as the "methylation pathway" or the "one-carbon cycle/pathway."

REFERENCES

1. Greene ND, Copp AJ. Development of the vertebrate central nervous system: formation of the neural tube. *Prenatal Diag* 2009; 29: 303-311.
2. Smithells RW, Sheppard S, Schorah CJ. Vitamin deficiencies and neural tube defects. *Arch Dis Child*. 1976;51(12):944-50.
3. Rossi M, Amaretti A, Raimondi S. *Nutrients* 2011;3:118-134.
4. Krüger M, Shehata AA, Schrdl W, Rodloff A. Glyphosate suppresses the antagonistic effect of Enterococcus spp. on Clostridium botulinum. *Anaerobe* 2013;20:74078.
5. James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, Gaylor DW, Neubrander JA. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *Am J Clin Nutr* 2004;80(6):1611-7.
6. MRC Vitamin Research Group. Prevention of neural tube defects: Results of the Medical Research Council Study. *Lancet* 1991;338:131-137.

7. Patanwala I, King MJ, Barrett DA, Rose J, Jackson R, Hudson M, Philo M, Dainty JR, Wright AJA, Finglas PM, Jones DE. Folic acid handling by the human gut: implications for food fortification and supplementation. *Am J Clin Nutr* 2014;100(2):593-599.
8. Samsel A, Seneff S. Glyphosate's suppression of cytochrome P450 enzymes and amino acid biosynthesis by the gut microbiome: Pathways to modern diseases. *Entropy* 2013; 15:1416-1463.
9. Choi SW, Mason JB. Folate and carcinogenesis: An integrated scheme. *The Journal of Nutrition* 2000;130:129-132.
10. Kim YI. Folate and carcinogenesis: Evidence, mechanisms, and implications. *J Nutr Biochem* 1999;10: 66-88.
11. McCullough ML, Giovannucci EL. Diet and cancer prevention. *Oncogene* 2004;23:6349-64.
12. Mason JB, Dickstein A, Jacques PF, Haggarty P, Selhub J, Dallal G, Rosenberg IH. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. *Cancer Epidemiol Biomarkers Prev* 2007;16(7):1325-9.
13. Troen AM, Mitchell B, Sorensen B, et al. Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. *J Nutr* 2006;136:189-94.
14. Dixon KH, Trepel JB, Eng SC, Cowan KH. Folate transport and the modulation of antifolate sensitivity in a methotrexate-resistant human breast cancer cell line. *Cancer Commun* 1991;3(12):357-65.
15. Fleming GF, Schilsky RL. Antifolates: the next generation. *Semin Oncol* 1992;19:707-719.
16. Takimoto CH. New Antifolates: Pharmacology and Clinical Applications. *The Oncologist* 1996; 1(1 & 2):68-81.
17. Wang ES, O'Connor O, She Y, Zelenetz AD, Sirotnak FM, Moore MA. Activity of a novel anti-folate (PDX, 10-propargyl 10-deazaaminopterin) against human lymphoma is superior to methotrexate and correlates with tumor RFC-1 gene expression. *Leuk Lymphoma* 2003;44(6):1027-35.
18. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, McKeown-Eyssen G, Summers RW et al. Folic acid for the prevention of colorectal adenomas: A

randomized clinical trial. *JAMA* 2007;297(21):2351-2359.
19. Sweeney MR, McPartlin J, Weir DG, Leslie D, Scott JM: Post-prandial serum folic acid response to multiple doses of folic acid in fortified bread. *British Journal of Nutrition* 2006; 94:1-8.
20. Manshadi SD, Ishiguro L, Sohn K-J, Medline A, Renlund R, Croxford R, Kim Y-I. Folic Acid supplementation promotes mammary tumor progression in a rat model. *PLoS ONE* 2014; 9(1): e84635.
21. Benítez-Leite S, Macchi ML, Acosta M. Malformaciones congénitas asociadas a agrotóxicos [Congenital malformations associated with toxic agricultural chemicals] *Archivos de Pediatría del Uruguay* 2009;80:237-247.
22. Person A, Spitters C, Patrick G, Wasserman C, Kelen PV, VanEenwyk J, Gilboa S, Kucik J, Sorenson R, Ailes E, Stahre M. Notes from the Field: Investigation of a Cluster of Neural Tube Defects Central Washington, 2010-2013. *Morbidity and Mortality Weekly Report* (MMWR) 2013;62(35):728-728.
23. Campana H, Pawluk MS, Lopez Camelo JS. [Births prevalence of 27 selected congenital anomalies in 7 geographic regions of Argentina]. *Arch Argent Pediatr* 108(5) 2010: 409-17. 24. BBC News. Zika virus triggers pregnancy delay calls. Jan. 23, 2016. http://www.bbc.com/news/world-latin-america-35388842 (http://www.bbc.com/news/world-latin-america-35388842). [Last accessed January 23, 2016].
25. Paganelli A, Gnazzo V, Acosta H, López S, Carrasco AE. Glyphosate-based herbicides produce teratogenic effects on vertebrates by impairing retinoic acid signaling. *Chem Res Toxicol* 2010;23(10):1586-1595.
26. Pai YJ, Leung KY, Savery D, Hutchin T, Prunty H, Heales S, Brosnan ME, Brosnan JT, Copp AJ, Greene ND. Glycine decarboxylase deficiency causes neural tube defects and features of non-ketotic hyperglycinemia in mice. *Nat Commun* 2015;6:6388.
27. Narisawa A, Komatsuzaki S, Kikuchi A, Niihori T, Aoki Y, Fujiwara K, Tanemura M, Hata A, Suzuki Y, Relton CL, Grinham J, Leung K-Y, Partridge D, Robinson A, Stone V. Gustavsson P, Stanier P, Copp AJ, Greene NDE, Tominaga T, Matsubara Y, Kure S. Mutations in genes encoding the glycine cleavage system predispose to neural tube defects in mice and humans. *Human Molecular Genetics* 2012;21(7):1496-1503.
28. Gilmore JH, Smith LC, Wolfe HM, Hertzberg BS, Smith JK, Chescheir NC, Evans DD,

Kang C, Hamer RM, Lin W, Gerig G. Prenatal mild ventriculomegaly predicts abnormal development of the neonatal brain. *Biol Psychiatry* 2008;64(12):1069-76.
29. Kume A, Koyata H, Sakakibara T, Ishiguro Y, Kure S, Hiraga K. The Glycine Cleavage System: Molecular cloning of the chicken and the deduced protein structures. *JBC* 1991; 266(5):3323-3329. 30. Burren KA, Savery D, Massa V, Kok RM, Scott JM, Blom HJ, Copp AJ, Greene ND. Gene-environment interactions in the causation of neural tube defects: folate deficiency increases susceptibility conferred by loss of Pax3 function. *Hum Mol Genet* 2008;17:3675- 3685.
31. Burren KA, Scott JM, Copp A J, Greene ND. The genetic background of the curly tail strain confers susceptibility to folate-deficiency-induced exencephaly. Birth Defects *Res. A Clin Mol Teratol* 2010; 88:76-83.
32. Ramaekers VT, Blau N. Cerebral folate deficiency. *Dev Med Child Neurol* 2004;46(12):843-51.
33. Ramaekers, V, Blau N, Sequeira JM, Massogne M-C, Quadros EV. Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits. *Neuropediatrics* 2007: 38(6): 276-281.
34. Rothenberg SP, da Costa MP, Sequeira JM, Cracco J, Roberts JL, Weedon J, Quadros EV. Autoantibodies against folate receptors in women with a pregnancy complicated by a neural-tube defect. *N Engl J Med* 2004;350(2):134-42.
35. Refsum H. Folate, vitamin B12 and homocysteine in relation to birth defects and pregnancy outcome. *British Journal of Nutrition* 2001; 85(Suppl. 2): S109-S113.
36. Craig C, The Folic Acid Controversy, MTHFR and Chronic Fatigue Syndrome. Aug 12, 2014. http://www.cortjohnson.org/blog/2014/08/12/folic-acid-controversy-mthfr-chronic-fatigue-syndrome/ (http://www.cortjohnson.org/blog/2014/08/12/folic-acid-controversy-mthfr-chronic-fatigue-syndrome/) [last accessed January 28, 2016].
37. Boris M, Goldblatt A, Galanko J, James SJ. Association of MTHFR gene variants with autism. *Journal of American Physicians and Surgeons* 2004;9(4):106-108.
38. Samsel A, Seneff S. Glyphosate, pathways to modern diseases III: Manganese neurological diseases, and associated pathologies. *Surgical Neurology International* 2015; 6:45.
39. Zhang Y, Hodgson NW, Trivedi MS, Abdolmaleky HM, Fournier M, Cuenod M, Do KQ, Deth RC. Decreased brain levels of vitamin B12 in aging, autism and

schizophrenia. *PLoS One*. 2016;11(1):e0146797.
40. Pacholak SM, Stuart JJ. *Could It Be B12?: An Epidemic of Misdiagnoses*. Paperback. January 26, 2011. Quill Driver Books, Fresno CA, USA.
41. Wyckoff KF, Ganji V. Proportion of individuals with low serum vitamin B12 concentrations without macrocytosis is higher in the post-folic acid fortification period than in the pre-folic acid fortification period. *Am J Clin Nutr* 2007;86:118792.
42. Dahele A, Ghosh S. Vitamin B12 deficiency in untreated celiac disease. *Am J Gastroenterol* 2001;96(3):745-50.
43. Samsel A, Seneff S. Glyphosate, pathways to modern diseases II: Celiac Sprue and gluten intolerance. *Interdiscip Toxicol* 2013; 6(4): 159-184.
44. Seneff S. Sulfur deficiency: A possible contributing factor in obesity, heart disease, Alzheimer's and chronic fatigue. July 2, 2011. http://www.westonaprice.org/health-topics/abcs-of-nutrition/sulfur-deficiency/#sthash.vfZTfcHC.dpuf (http://www.westonaprice.org/health-topics/abcs-of-nutrition/sulfur-deficiency/#sthash.vfZTfcHC.dpuf) [last accessed Jan 29, 2016].

This article appeared in Wise Traditions in Food, Farming and the Healing Arts, the quarterly journal of the Weston A. Price Foundation, Spring 2016 (http://www.westonaprice.org/journal/journal-spring-2016-folic-acid-glyphosate/)

About Stephanie Seneff, PhD

Stephanie Seneff, PhD received her Bachelor's degree in Biology with a minor in Food and Nutrition in 1968 from MIT. She received her Master's and PhD degrees in Electrical Engineering and Computer Science in 1979 and 1985, respectively, also from MIT. Since then, she has been a researcher at MIT, where she is currently a Senior Research Scientist in the Department of Electrical Engineering and

Computer Science, and a Principal Investigator in the MIT Computer Science and Artificial Intelligence Laboratory. Throughout her career, Dr. Seneff has conducted research in diverse areas including human auditory modeling, spoken dialogue systems, natural language processing, human language acquisition, information retrieval and summarization, computational biology, and marine mammal socialization. She has published over one hundred fifty refereed articles on these subjects, and has been invited to give keynote speeches at several international conferences. She has also supervised numerous Master's and PhD theses at MIT. She has recently become interested in the effect of drugs and diet on health and nutrition, and she has written several essays on the web articulating her view on these topics. She is the first author of two recently published nutrition-related journal papers, one on the metabolic syndrome and one on Alzheimer's disease. Two papers on theories related to cholesterol sulfate are currently under review. Stephanie will give an all-day workshop on metabolism at Wise Traditions 2011.