Vitamin B Complexities

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This is a confession of intellectual hubris. When it came to vitamins, I thought I was pretty knowledgeable. As a kid, I had lapped up tales of the “hunger fighters” (Paul de Kruif’s term) who had discovered the causes of the terrible vitamin-deficiency diseases of beriberi, scurvy, pellagra, and pernicious anemia. In the late 1970s, I had written a long scholarly essay on the history of vitamin B1 (thiamine). It was clear to me that vitamins played essential roles in many metabolic pathways and that more of their functions remained to be discovered.

Because I felt sure that my Mediterranean-style diet was more varied than that of most Americans, I did not bother to take a multivitamin tablet. I ate foods rich in the B-vitamins: fresh fruits and vegetables, nuts, whole-grain breads, meats, even liver. Nonetheless, like so many of my generation, I figured that a vitamin B supplement couldn’t hurt. If nothing else, experience had shown that, for me, it seemed to ward off paper cuts. I knew – I thought I knew – that, unlike the fat-soluble vitamins A and D which were toxic at large doses, the water-soluble vitamins of the B-complex were benign: any excess washed out of the body every day.

A year and a half ago, however, I stopped taking vitamin B6 (pyridoxine). A brief description of symptoms of B6 overdose on The People’s Pharmacy website matched sensations that, in the midst of more urgent medical problems, I had ignored for a year or two: tingling in toes, a “stocking-glove” feeling. In short, peripheral neuropathy. A look at the label of vitamin B-complex supplement I had been taking most days for at least a decade showed that each tablet contained 100mg of B6. That was far more than the 1.5mg per day – from all sources – the Food and Drug Administration (FDA) recommends for a woman of my age, and just at the edge of the Tolerable Upper Limit. The tingling stopped within a few days. A brief re-challenge had the same result and persuaded me that I had found the cause.

Why hadn’t I been more skeptical? After all, as an acquiring editor at Rutgers University Press, I had published Rima D. Apple’s Vitamania: Vitamins in American Culture (1996), which chronicled the ways doctors, scientists, politicians, public officials, the pharmaceutical industry, and the popular press had persuaded Americans like me to “take their vitamins.” She concluded that, at the end of the twentieth century, there was still no clear-cut answer to the question, “Can extra vitamins really do you good if you eat a normal American diet?” My chagrin is all the greater because I could have found several early warnings in my own library about vitamin B6 megadoses.

In fairness to myself, I was not alone in thinking the B vitamins were harmless. Ever since the 1930s, when Paul György identified a vitamin B deficiency distinct from beriberi and pellagra and

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hypothesized the existence of “vitamin B(6),” the medical community had assumed that “the water-soluble vitamins are among the safest substances known,” and that vitamin B6 is not associated with neurotoxicity.”

By prescription or over the counter, Americans have taken vitamin B6 tablets for, among other things: body-building, carpal tunnel syndrome, premenstrual edema, vomiting in pregnancy, overdoses of isoniazide treatment for tuberculosis, and homocystinuria (an inherited metabolic disorder); very high doses (600 to 3000mg/day) had no apparent side effects on schizophrenic patients and children with autism.

Even though soon after the isolation of vitamin B6, Unna (1940) and Antopol and Tarlov (1942) had demonstrated that high doses of vitamin B6 – “far in excess of quantities employed in human therapy” – produced major neurological problems in rats and dogs, four decades passed before anyone raised the possibility that people could overdose on the vitamin. In 1983 Schaumburg et alia described the sensory neuropathy and problems with walking that had developed in seven women and men who had, either by prescription or their own choice, taken large doses of daily oral B6 supplements (from 50mg to 2-6g) for several months or more; stopping the supplements soon brought at least partial recovery. That key research was supported by a larger, controlled study of 176 women who had been taking lower doses (100-500mg daily) of vitamin B6 supplements for premenstrual syndrome.

As Schaumberg et alia observed, the very idea that pyridoxine could cause neuropathy seemed “at first improbable or paradoxical.” Peripheral neuropathy had long been seen as a primary symptom of too little vitamin B6. How could both a deficiency and an excess of the same vitamin bring about the same unhappy problem?

The paradox was not resolved until 2017, when experiments in vitro and in human neuroblastoma cell cultures by Vrolijk et alia suggested a mechanism: two different forms of vitamin B6 (the vitamers pyridoxine and pyridoxal-phosphate) compete with each other for access to key enzymes in amino acid metabolism and gene expression. When there is too little pyridoxine, cells falter or die because there is simply not enough pyridoxine available to be turned into the active vitamer, pyridoxal-phosphate; this is classic vitamin B6 deficiency. But when there is too much pyridoxine, the enzymes for the conversion to pyridoxal-phosphate are overwhelmed by the super-abundance of pyroxidine. The enzymes stop making the active pyridoxal-phosphate by negative feedback inhibition, and so the same metabolic signs of vitamin B6 deficiency appear.

+++ For vitamin B6 consumers, charting a course between “too little is not enough” and “nothing in excess” is further complicated both by recent science and by politics.

The science is not getting simpler to interpret. More and more medical conditions are being linked to insufficient vitamin B6. For people with cardiovascular disease or other inflammatory conditions, for example, the FDA’s Recommended Daily Allowance for vitamin B6 may not be enough; and high B6 intake might lower the odds of having kidney stones. For brain function, the optimal levels of the B-vitamins are not established. At the same time, the explanation of pyridoxine toxicity by Vrolijk et alia is so new that physicians are just beginning to think how it might apply to their patients.
And then there is the human biome to be reckoned with: the interplay of vitamins and bacteria in that inner realm has barely begun to be studied. Many bacterial species in our guts can synthesize plenty of vitamin B6, but it is not clear how that gets used by our bodies, nor how highly concentrated, purified supplements affect the constantly-changing responses of the microbiota.22

Meanwhile, the place of vitamins in American culture has undergone a seismic change, thanks to the 1994 Dietary Supplement Health Education Act (DSHEA).23 The DSHEA law – the result of intense lobbying by consumers, health food stores, manufacturers, marketers, and legislators themselves – redefined what the FDA could count as food.24 Under DSHEA, the FDA must regard “dietary supplements [including vitamins]” as foods, rather than as medicines. That uneasy category – in effect, creating a new food group – prevents the FDA from testing supplements for efficacy or regulating their dosage (as the agency does for medicines). Its website can point to the National Institute of Medicine’s tables of Tolerable Upper Limits. But the only “buyer beware” warning the FDA can impose is a noncommittal footnote to any health claim on a supplement label: “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”

+++ The supplement that triggered my curiosity about vitamin B6 has been banished from our house. In the kitchen, I look at favorite ingredients with a new wariness. On the People’s Pharmacy website, some readers, who report much more disastrous neurological problems from B6 overdoses than I had, say that just eating foods naturally high in the vitamin had triggered the return of their symptoms: amaranth, bananas, avocados, spinach, wheat, garbanzo beans, almonds, walnuts. Two processed foods that had been fortified with extra vitamin B6 were also mentioned: an energy drink and brewer’s yeast – the key component of Marmite and Vegex.25

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At doctors’ offices, I zealously list the components of the vitamin B-complex tablet I do take and explain the omission of vitamin B6. My primary-care physician had known that neuropathy was a
symptom of too little vitamin B6 but was puzzled that it could be also a symptom of too much. (Now I can supply the references.) In a neurologist’s waiting room, a patient information pamphlet caught my attention. "Understanding Peripheral Neuropathy" notes "poor nutrition" and "vitamin deficiency" as treatable medical causes of the symptoms. However, its only comment on vitamin B6 overdose appears in a section on “living with peripheral neuropathy”: "Avoid excess vitamin B6, which can cause neuropathy at levels more than 100mg daily."26 That advice seems to come too late in the game. At a local organic grocery, the manager of the supplements section was also surprised to learn that this water-soluble vitamin can build up in the body and pose a long-term hazard at high doses. At both the nearest drugstore and supermarket, I notice that supplements have gained much more floor space in recent remodeling: those long aisles full of vitamins must be selling well.27

By way of a control to my self-experimentation, I instead started taking a supplement that lacked vitamin B6, but did contain four other members of the B-complex, still in high dosages (thiamine, niacin, riboflavin, B12). A new complication arose shortly after stopping B6. In the course of other medical adventures, a different set of symptoms of peripheral neuropathy led to a diagnosis of vitamin B12 deficiency, apparently from malabsorption in the gut. It looks as if I will be taking B12 via a nasal spray for the rest of my life. I have no way to tell if the two problems are connected.

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This story has no tidy ending. I could file an “adverse event” report with the FDA. That would, I think, be fruitless. Without confirmatory blood tests and irreversible neurological damage to point to, my experience with vitamin B6 is just one anecdote.28 Given America’s reluctance to regulate vitamins, it would not persuade the FDA to investigate, at the very least, how common B6 overdoses are.29

I must content myself with my narrow escape and with my new appreciation that the “vitamin B-complex” is not just a term of historical and marketing convenience. It reflects physiological reality. In the foods we eat, in our bodies, and in the microbes we house, the eight B-complex vitamins take part collectively in intricate, intersecting metabolic dances.30 I know I need them, all of them. But how much and how best to get them - that remains a perplexity. It seems that in the case of vitamins, therapeutic enthusiasm trumped details of dosage.

At the very least, my experience suggests that I, along with some 150 million other vitamin-taking Americans, have been the willing and unwitting participants in an extraordinarily large, uncontrolled experiment whose results no one seems to be tracking.31 From my present vantage point, this begins to look like hubris on a very large scale.

Caution: This essay should not be taken as medical or nutritional advice.

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Freidenfelds, the many nurses and doctors who have cared for me in recent years, and my colleagues in the Princeton Research Forum.


4 “USDA National Nutrient Database for Standard Reference.” US Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory (Legacy. Version Current: April 2018). For a list of foods ranked by vitamin B6 content, search the National Nutrient Database by “vitamin B6.” See also: “Vitamin B6: Dietary Supplement Fact Sheet.” Table 1, Recommended Dietary Allowances (RDAs) for Vitamin B6; and Table 3, Tolerable Upper Intake Levels (ULs) for Vitamin B6. Office of Dietary Supplements, National Institutes of Health. See also note 3 above, Combs and McClung (2017), Table 14.1.


6 Pyridoxine is often used as a collective shorthand term for the vitamers of vitamin B6, that is, pyridoxine itself and several derivative compounds that share pyridoxine’s core structure but have assorted sidechains that allow them to act as coenzymes in a great variety of metabolic reactions, chiefly in the liver and in muscle. (The term “vitamer” was coined by analogy to “isomer.”) The vitamer pyridoxal phosphate is particularly important because it takes part as a coenzyme in amino acid reactions. See note 3 above, Combs and McClung (2017): 352, 358.

7 “Will Overdosing on Vitamin B6 Cause Irreversible Nerve Damage?” Joe Graedon posting, 15 May
2017. To the follow-up posting by Terry Graedon, 5 March 2018, “Will Excess Vitamin B6 Damage Nerves?”, I added my own response to “Thoughts Shared,” under the name Karin, 6 March 2018. For other discussions and readers’ comments on vitamin B6 deficiency/toxicity and a genetic basis for it, search these postings and The People’s Pharmacy website for vitamin B6; pyridoxine; neuropathy; MTHFR mutation. My own response appears under the name Karin (6 March 2018). Similar comments on patients’ experiences with B6 toxicity appear on the Mayo Clinic Connect website.

8 See note 4 above: “Vitamin B6: Dietary Supplement Fact Sheet”: Table 1; Table 3. For the USDA’s rankings of vitamin B6 content in foods, see above note 4. At the top of the list are highly fortified energy drinks and snack bars, powders for nutritional shakes, and enriched cereals (none part of my usual diet).

9 Rima Apple, Vitamania: Vitamins in American Culture (New Brunswick), 196, 227n13: “[In controversial 1973 House of Representatives hearings over vitamin regulation by the FDA] most participants drew a line between vitamins with little or no toxicity, such as water soluble vitamin C, and those of known toxicity, such as fat soluble vitamins A and D.” Neither Apple nor Catherine Price, in the recent book with the same main title, Vitamania: Our Obsessive Quest for Nutritional Perfection (New York: Penguin Press, 2015), allude to vitamin B6 overdoses.


vitamins, Dr. Kramer [Dr. Barnett Kramer, National Cancer Institute] said, by excreting what it doesn’t need in urine.”

12 See note 11 above, Schaumburg et al., 445n4, n5. C. Mpofu, S.M. Alani, B. Whitehouse, B. Fowler and J. E. Wraith, “No sensory neuropathy during pyridoxine treatment in homocystinuria,” Archives of Disease in Childhood 66 (1991): 1081-1082. In homocystinuria [or homocysteinuria], mutations in the genes for the enzymes that ordinarily convert the amino acid homocysteine to another amino acid, methionine, result in a build-up of homocysteine.


14 See note 11 above, Schaumburg et al.


16 See note 11 above, Schaumberg et al.

17 Somewhat surprisingly, neither Schaumburg et al. nor Dalton and Dalton (see notes 11, 15 above) alluded to the ongoing controversy over Bendectin®, a combination of pyridoxine and doxylamine (an antihistamine and antiemetic) that had been very widely prescribed to quell vomiting in pregnant women. A 1979 National Enquirer article accused Bendectin of causing birth defects. (Suspicion fell primarily on the doxylamine.) Although the FDA and Centers for Disease Control had, by 1983, declared the drug was effective and not teratogenic, Merrell Dow stopped making Bendectin that year. While lawsuits and scientific studies continued in the United States for more than a quarter-century and ultimately exonerated Bendectin, the Canadian pharmaceutical company Duchesnay, Inc., sold a formulation of pyridoxine and doxylamine, Diclectin®. In 2013, the FDA approved the use of delayed-release tablets containing doxylamine succinate and pyridoxine hydrochloride (10mg of each) to relieve vomiting in pregnancy. See the overview and timeline of Bendectin History (website mounted by Duchesnay); Joseph Sanders, “From Science to Evidence: The Testimony on Causation in the Bendectin Cases,” Stanford Law Review 46, No. 1 (November 1993): 1-86. Duchesnay, Inc., says, “Pyridoxine is a vitamin that is generally recognized as having no adverse effects” (p. 5) and does not explicitly note the possibility of pyridoxine overdoses in its "PRODUCT MONOGRAPH PrDiclectin®" (revised 15 February 2017).

18 Misha F. Vrolijk, Antoon Oppenhuizen, Eugène H. J. M. Jansen, Geja J. Hageman, Aalt Bast and Guido R M M Haenen, “The vitamin B6 paradox: Supplementation with high concentrations of
pyridoxine leads to decreased vitamin B6 function,” *Toxicology in vitro* 44 (2017): 206-212. The general idea had long been in the air. In a 1983 interview Herbert Schaumburg had surmised that “flooding the system with [vitamin B6] is probably killing nerve cells”: “Vitamin is linked to nerve damage,” *New York Times* 25 August 1983, D21. A case-study exercise drawn from Schaumburg et al. (1983) in the first edition of *The Vitamins: Fundamental Aspects in Nutrition and Health* (New York: Academic Press, 1992): 326-327, 506, Gerald F. Combs, Jr., challenged his readers to propose the enzymes potentially affected “if the toxicity of pyridoxine involves the competition, at high levels, with pyridoxal phosphate for enzyme binding sites” but warned (327n51): “while this type of mechanism may sound reasonable, it is strictly speculative at this time as the mechanism of pyridoxine toxicity is not elucidated.”


21 Elia Gebran Malek, Hassan Doumiati and Johnny S. Salameh, “Pyridoxine-induced sensory ataxic ganglionopathy: a case report and literature review,” *Acta Neurologica Belgica* (Letter to Editor, online 28 April 2018). For at least 12 years, the patient had taken 30mg vitamin B6 supplements daily and been a heavy consumer of energy drinks fortified with pyroxidine.


24 The advent of the internet in the mid-1990s enhanced the lobbying efforts and, with Google’s rapid rise in the first decade of the 21st century, amplified the marketing of vitamins under the DSHEA.

25 See note 7 above; postings to The People’s Pharmacy on 14 September 2017; 31 October 2015; 21 November 2010; 20 April 2010. Vegex had a loyal following and continued to be sold in the United States until about 2015; personal communication, Justin Goines, Center for Educational Advancement, 19 November 2018.


27 Aaron Crowe, "Biggest Drugstore Markups: Which Products You're Paying More For," WalletPop, Aol.com (9 March 2011): “A 100-count bottle of vitamin B-1 has a 395% markup, with a $5 retail
bottle costing a store $1.01 wholesale."


31 According to the Council for Responsible Nutrition’s “2018 CRN Consumer Survey on Dietary Supplements,” 83% of American adults take vitamins. Using U.S. Census population estimate for 2018, that translates to more than 150 million people. (I have only seen the online summary; the full report, for CRN members, costs $5000.) The Council for Responsible Nutrition is “a trade association representing 150+ dietary supplement and functional food manufacturers, ingredient suppliers, and companies providing services to those manufacturers and suppliers.” “Functional food” is often used as a synonym for the ingenious neologism, “nutraceutical,” coined by Stephen L. DeFelice, M.D., in 1989; neither term has legal or regulatory standing, but they encourage consumers to ascribe health benefits to any component of food that has been packaged as a supplement; see DeFelice, “The nutraceutical revolution: its impact on food industry R&D,” Trends in Food Science & Technology 6 (February 1995), as seen on his website; Ekta K. Kalra, “Nutraceutical - Definition and Introduction,” AAPS PharmSci 5, no. 3 (2003), Article 25; http://www.pharmsci.org/.