Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Editor-in-Chief's Note

Vitamins C and D

I'd like some vitamins for my grandson.
Which ones—A, B, C, or D?
It doesn't matter; he's too young to know the alphabet!
(*adapted from* http://www.jokebuddha.com/Vitamins)


Richard I. Shader, MD

I grew up in Central Florida where our father was heavily involved in the citrus industry. Not surprisingly, we routinely drank freshly squeezed orange or grapefruit juice and had plenty of sun exposure. At the onset of a cold or other upper respiratory infection (URI), our household remedy was hot grapefruit juice with orange blossom honey mixed in. We were true believers. Actually I still am—I use hot grapefruit juice with honey at the sign of any cold and urge others to do so. In my uncontrolled experience, it really works—for me. I can claim effectiveness but not efficacy. People who know me well would likely agree that I rarely have troublesome colds, even while those around me are sneezing and dripping away. But I am an "N of 1" anecdote and not an "N of 1" experiment; I was never "blind" and there was never an A-B-A, A-B-B-A, or any other variant design. As might be expected, there are other members of my family and friends who are converts to this tasty remedy.

Imagine how intrigued I was when Linus Pauling published his first book on vitamin C and colds.[1] Pauling self-treated with mega-doses of vitamin C ranging up to 18,000 mg/d. After reading an initial portion of this book, I must admit I only skimmed the rest. I felt as if Pauling was trying to sell his ideas rather than trying to provide an unbiased view of the topic. I was not surprised when I read the correspondence between Pauling and two reviewers of his book, Beaton and Whalen.[2–4] The latter were critical of his conclusions; Pauling dealt with this by claiming they misrepresented his views; they in turn made counterclaims and denied his accusations of misrepresentations.

Many things trouble me about the study of vitamin C supplementation for prevention and treatment of the common cold. Among them are the following: (1) the common cold is a phenotype; it is not just a single entity with a single viral etiology; coronavirus, parainfluenza virus, respiratory syncytial virus, and rhinovirus have been causally identified, and other nonidentified viruses are also implicated; (2) studies do not require either a prespecified number of events per unit of time or stratification of patients into cohorts with similar histories; thus, there is no way to assess homogeneity of variance; (3) the prevalence and incidence of colds varies from year to year and by season; (4) there is no standardization of the source of vitamin C across studies; most is derived from corn, but other sources are acerola, red algae, bilberry, blueberries, chlorella, cranberries, and rose hips; (5) there is no effort to assess other dietary sources of vitamin C that may be ingested during studies; (6) when ascorbic acid concentrations in blood are measured, time of blood drawing is often not specified and it may not be consistent; (7) when a placebo group is involved, there often is no assurance that the taste attributable to ascorbic acid does not compromise the "blinding" of the study; (8) when sodium ascorbate is the precursor source of ascorbic acid, there are no adjustments made for how intrapatient or interpatient variations in gastric acidity may influence its reprotonation and bioavailability; and (9) vitamin C is water soluble, and excess amounts are eliminated once saturation is achieved—differential effects from mega-doses are not established.

In 1974, Coulehan et al[5] published a study in the *New England Journal of Medicine* (*NEJM*) on vitamin C prophylaxis against URIs in 666 resident children at a Navajo boarding school. Parental consent was obtained,

and 641 children completed the 14-week study. There is no statement that assent was obtained from the children who ranged in age from 6 to 15 years. Treatment arms were ascorbic acid 500 mg twice daily (AA1) for children age 6 to 10 years, AA at 500 mg times 2 (1000 mg) twice daily (AA2) for children age 11 to 15 years, or placebo (PBO) for both cohorts matched to numbers dispensed, appearance, and, importantly, to taste. Unfortunately, there is no description of how the latter was accomplished. The study results were (1) no difference between cohorts in number of URIs; (2) there were less days with symptoms (26%) among girls and boys in the AA1 versus PBO analysis, and 33% fewer in the girls in the AA2 versus PBO analysis; (3) no differences were found for the AA2 boys; and (4) for subcohorts in whom AA levels were determined, higher AA levels were associated with symptom reduction. Curiously, the lack of value in the AA2 boys was consistent with another study published 1 year earlier.[6]

After reading the study by Coulehan et al,[5] I realized that there was a problem with the investigators' statistical handling of their data. I discussed my ideas with two statistician colleagues. They concurred with my concerns, and we wrote a Letter to the Editor of the *NEJM*. The *NEJM* did not publish the letter, so we decided to publish it elsewhere as a standalone article.[7] For the record, I have previously mentioned this experience.[8] Essentially, we pointed out how large N studies can produce statistical significance in the absence of clinical significance. We also raised questions about the use of the Mann-Whitney *U* test, a distribution-free test, and of nonparametric χ^2 analyses, and we also discussed the lack of corrections for multiple comparisons. We concluded that the authors did not demonstrate a prophylactic effect for vitamin C.

In 1996, Hemilä,[9] a strong supporter of therapeutic roles for vitamin C, challenged the conclusions by several National Institutes of Health authors[10,11] that a placebo effect colored the interpretation of their findings. Nevertheless from 2000 to 2007, the Cochrane Collaboration issued three reports, all of which concluded with some variation of this statement: Long-term supplementation with large daily doses of vitamin C does not appear to prevent colds.[12–14] Hemilä contributed to the 2004 and 2007 reports.

The latest Cochrane Collaboration report on vitamin C is by Hemilä and Chalker.[15] The following are some relevant sentences contained in their report. "Vitamin C (ascorbic acid) for preventing and treating the common cold has been a subject of controversy for 70 years … Regular ingestion of vitamin C had no effect on common cold incidence in the ordinary population, based on 29 trial comparisons involving 11,306 participants … The failure of vitamin C supplementation to reduce the incidence of colds in the general population indicates that routine vitamin C supplementation is not justified … Nevertheless, given the consistent effect of vitamin C on the duration and severity of colds in the regular supplementation studies … it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them. Further therapeutic RCTs [randomized controlled trials] are warranted."

Another claim for vitamin C is a beneficial effect in asthma. A 2001 report from the Cochrane Collaboration and its 2004 and 2009 updates conclude that there is insufficient evidence for the usefulness of vitamin C in asthma.[16–18] These conclusions were once again challenged by Hemilä.[19] One of Hemilä's arguments is that numerous smaller sample studies show beneficial effects from vitamin C. He is essentially taking a nonparametric view of cumulative data. Although he does not use an actual sign test,[20] his implication is that the sheer number of positive, small-sample reports prove his case. In a rare occurrence, the 2001 Cochrane report was withdrawn and replaced, although the conclusions did not change.[21,22]

There are unresolved issues with vitamin C for the common cold and for asthma that are methodologic, statistical, and interpretive. We can only ask that future prevention and intervention studies be conducted by researchers who are free of bias and have learned from the flaws in prior reports. This could bring clarity to this highly obfuscated topic.

To conclude my observations about vitamin C, let us look at an Internet comment that, to me, epitomizes how mixed up this whole subject is, despite the time, dollars, and scholarship devoted to it. In 2013, a woman known only as Sheila posted the following remarks on the Internet: "Linus Pauling did not die naturally at the grand old age of 93, he was murdered whilst in hospital by injection of a lethal dose (read up on it) was it because he revealed and knew to [*sic*] much?? there are evil powers in the world that will do ANYTHING to keep their power, positions and most of all money and have no real care about the health of the public, recommending

minute doses of vitamins. we should be taking in grams just enough to keep us ok but not enough to keep us from getting ill as there is alot [*sic*]of money to be made from the whole sickness industry."[23] Pauling died in 1994 from prostate cancer. He claimed, without proof, that his long-term use of mega-doses of vitamin C delayed its onset.

An additional study design issue occurred to me as I was developing this *Note*. Different issues arise when one is investigating prophylaxis for a contagious versus a noncontagious illness. Perhaps the prophylactic difference noted above between the effects of vitamin C on girls compared with boys can be explained as follows. Cold viruses are often transmitted through hand contact. Is it possible that, in a contained environment, girls are more likely than boys to walk hand-in-hand? If so, then perhaps spread could more readily be prevented in girls than in boys. But here is the rub—the opposite could also be true. Prevention might work better when there are fewer events to stop.

Vitamin D has also been implicated as a causal factor for the common cold. Two observations point in this direction. Colds are more frequent in the winter when vitamin D levels are generally lower, and patients with chronic obstructive pulmonary disease who have lower levels of vitamin D have more URIs. Citing the role of vitamin D, Gindi et al[24] found that the number of recent URIs was inversely related to serum 25(OH)D levels; this linkage was stronger in patients with preexisting respiratory tract disease. A supplementation study lasting 18 months conducted by Murdoch et al[25] comparing 161 subjects given vitamin D_3 tablets with 161 subjects on PBO revealed no difference in the occurrence of URIs. Again, we can only conclude that the role for vitamin D supplementation for colds and other URIs is still unresolved. One important factor may be that in the study by Murdoch et al,[25] their subjects did not have deficient 25(OH)D levels. On a more positive note, the Cochrane Collaborators review of vitamin D for asthma is quite encouraging. Martineau et al[26] stated that they were "… confident that vitamin D reduced the risk of asthma exacerbation in these trials …[but] research is needed to clarify whether there is a difference in effect between adults and children and with respect to asthma severity, baseline vitamin D status and doses."

Before concluding this *Note* I want to remind our readers about a few selected facts about vitamin D, a fat-soluble vitamin. There are two forms of vitamin D, cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). The latter is derived from fungi and plants, some of which we ingest. D_2 has a few therapeutic uses (eg, hypoparathyroidism, hypophosphatemia, and rickets). Vitamin D_3 is important for the incorporation of calcium into bone. We synthesize it when our skin is exposed to sunlight (UVA and UVB rays). We can also ingest vitamin D_3 in vitamin supplements, mostly derived from the lanolin in sheep skin glands or from fish oil (eg, cod liver oil) or fish skin (eg, salmon).[27] It is important to remember that heating may cause loss of vitamin D from foods. Cooking losses are highly variable and are determined by the specific food and the method of cooking.[28] Inadequate levels of vitamin D are present in approximately one billion people worldwide.[29] No age cohort or nationality is spared. From the public health perspective, this is indeed unfortunate; treatment is both straightforward and inexpensive.

Our monthly Topic Update was organized by Dr. Theoharis Theoharides, our Topic Editor for Allergy, Asthma, and Immunology. His Update focuses on the all-important role of vitamin D in immunity.[30–35]

Richard I. Shader, MD
Editor-in-Chief

REFERENCES

1. Pauling LC. Vitamin C and the Common Cold. San Francisco: WH Freeman; 1970.
2. Beaton GH, Whalen S. Vitamin C and the common cold. *Can Med Assoc J*. 1971;105:355–357.
3. Pauling L. Vitamin C and the common cold. *Can Med Assoc J*. 1971;105:448. (correspondence).
4. Beaton GH, Whalen S. Vitamin C and the common cold. *Can Med Assoc J*. 1971;105:450. (correspondence).
5. Coulehan JL, Reisinger KS, Rogers KD, et al. Vitamin C prophylaxis in a boarding school. *N Engl J Med*. 1974;290:6–10.
6. Wilson CWM, Loh HS. Common cold and Vitamin C. *Lancet*. 1973;1:638–641.

7. Shader RI, Harmatz J, La Brie R. Vitamin C prophylaxis and some problems of statistical inference. *Curr Ther Res Clin Exp*. 1974;16:655–658.
8. Shader RI. Statistics and evaluating the elderly for surgery. *Clin Ther*. 2015;37:2609–2611.
9. Hemilä H. Vitamin C, the placebo effect, and the common cold: a case study of how preconceptions influence the analysis of results. *J Clin Epidemiol*. 1996;49:1079–1084. discussion 1085, 1087.
10. Karlowski TR, Chalmers TC, Frenkel LD, et al. Ascorbic acid for the common cold. A prophylactic and therapeutic trial. *JAMA*. 1975;231:1038–1042.
11. Chalmers TC. Effects of ascorbic acid on the common cold. An evaluation of the evidence. *Am J Med*. 1975;58:532–536.
12. Douglas RM, Chalker EB, Treacy B. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev*. (2):CD000980, 2000.
13. Douglas RM, Hemila H, D'Souza R, et al. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev*. (4):CD000980, 2004.
14. Douglas RM, Hemilä H, Chalker E, et al. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev*. (3):CD000980, 2007.
15. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev*. (1):CD000980, 2013.
16. Kaur B, Rowe BH, Ram FS. Vitamin C supplementation for asthma. *Cochrane Database Syst Rev*. (4):CD000993, 2001.
17. Ram FS, Rowe BH, Kaur B. Vitamin C supplementation for asthma. *Cochrane Database Syst Rev*. (3):CD000993, 2004.
18. Kaur B, Rowe BH, Arnold E. Vitamin C supplementation for asthma. *Cochrane Database Syst Rev*. (1):CD000993, 2009.
19. Hemilä H. The effects of Vitamin C on asthma should also be studied. *BMJ*. 2014;349:g5517. http://www.bmj.com/content/349/bmj.g5517/rr/797361. Accessed April 1, 2017.
20. Wikipedia. Sign test. https://en.wikipedia.org/wiki/Sign_test. Accessed April 1, 2017.
21. Kaur B, Rowe BH, Stovold E. WITHDRAWN: Vitamin C supplementation for asthma. *Cochrane Database Syst Rev*. (10):CD000993, 2013.
22. Milan SJ, Hart A, Wilkinson M. Vitamin C for asthma and exercise-induced bronchoconstriction. *Cochrane Database Syst Rev*. (10):CD010391, 2013.
23. Sheila. Linus Pauling did not die a natural death. *Medical News Today*. http://www.medicalnewstoday.com/opinions/4681. Accessed April 1, 2017.
24. Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2009;169:384–390.
25. Murdoch DR, Slow S, Chalmers ST, et al. Effect of Vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. *JAMA*. 2012;308:1333–1339.
26. Martineau AR, Cates CJ, Urashima M, et al. Vitamin D for management of asthma. *Cochrane Database Syst Rev*. (9):CD011511, 2016.
27. DifferenceBetween.net. Difference between Vitamin D and Vitamin D3. http://www.differencebetween.net/science/difference-between-vitamin-d-and-vitamin-d3/ixzz4akdwC6aL. Accessed April 1, 2017.
28. Jakobsen J, Knuthsen P. Stability of vitamin D in foodstuffs during cooking. *Food Chem*. 2014;148:170–175.
29. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.
30. Theoharides TC. Vitamin D and atopy. *Clin Ther*. 2017;39:880–883.
31. Chirumbolo S, Bjorklund G, Sboarina A, Vella A. The role of vitamin D in the immune system as a pro-survival molecule. *Clin Ther*. 2017;39:894–916.
32. Pandolfi F, Franza L, Mandolini C, Conti P. Immune modulation by Vitamin D: special emphasis on its role in prevention and treatment of cancer. *Clin Ther*. 2017;39:884–893.
33. Hall SC, Agrawal DK. Vitamin D and bronchial asthma: an overview of the last five years. *Clin Ther*. 2017;39:917–929.
34. Murugesan H, Selvara P. Influence of Cdx-2 and Taq I gene variants on vitamin D3 modulated intracellular chemokine positive T-cell subsets in pulmonary tuberculosis. *Clin Ther*. 2017;39:946–957.
35. Lang PO, Aspinall R. Vitamin D status and the host resistance to infections: what is currently (not) understood. *Clin Ther*. 2017;39:930–945.

This month's Allergy, Asthma, and Immunology Update is a special feature which is available as FREE ACCESS content on the journal's website. One of the previous Allergy, Asthma, and Immunology Updates, entitled "Alarmins," was published in Volume 38, Number 5 of Clinical Therapeutics. To view the previous Update, see the articles below:

1. Theoharides TC. Danger Signals and Inflammation.
2. Arshad MI, Khan HA, Noel G, Piquet-Pillorce C, Samson M. Potential Therapeutic Aspects of Alarmin Cytokine Interleukin 33 or Its Inhibitors in Various Diseases.
3. Pandolfi F, Altamura S, Frosali S, Conti P. Key Role of DAMP in Inflammation, Cancer, and Tissue Repair.
4. Magna M, Pisetsky DS. The Alarmin Properties of DNA and DNA-associated Nuclear Proteins.
5. Nie Y, Yang D, Oppenheim JJ. Alarmins and Antitumor Immunity.
6. Ledderose C, Bao Y, Kondo Y, Fakhari M, Slubowski C, Zhang J, Junger WG. Purinergic Signaling and the Immune Response in Sepsis: A Review.
7. Weng Z, Zhang B, Tsilioni I, Theoharides TC. Nanotube Formation: A Rapid Form of "Alarm Signaling"?

http://dx.doi.org/10.1016/j.clinthera.2017.04.001