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# Vitamin C: Is Supplementation Necessary for Optimal Health?

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## Abstract

***Background:*** Consumption of vitamin C is essential for life in humans because the body does not synthesize it. Numerous studies have demonstrated that supplementation with vitamin C enhances the immune system, avoids DNA damage, and significantly decreases the risk of a wide range of pathologies, such as cancers, and degenerative and chronic diseases. Moreover, it has been demonstrated that modern crop production, transport, and food storage severely impair the quality of food and provoke a loss in micronutrients, such as vitamin C.

***Objectives:*** In this paper, we report that the Recommended Daily Allowance (RDA) in vitamin C is lower than the bodily needs. In fact, it does not seem to ensure true health protection and it appears difficult to reach an effective dose of vitamin C only through food consumption. Furthermore, the literature shows that vitamin C intake higher than the RDA is safe. Therefore, in order to achieve optimal health and avoid a number of diseases, we suggest that, in the present situation, vitamin C supplementation is required.

***Conclusions:*** According to the current literature, we would like to emphasize that to ensure an optimal allowance of vitamin C, we advise 1 g daily intake of vitamin C supplementation, accompanied by a diet rich in fruits and vegetables.

## Introduction

Vitamin C, also known as ascorbate or ascorbic acid, is synthesized by all animals except humans, monkeys, guinea pigs, bats, and several bird species.[1] Biologically, ascorbate is synthesized from glucose in a series of steps catalyzed by enzymes. In humans, the gene that codes for the terminal step in ascorbate synthesis, gulonolactone oxidase, is damaged and has stopped functioning.[2,3] The cause of this genetic damage is unknown, although it has been suggested that it was due to radiation exposure.[2] Expanding on an earlier hypothesis, the gene may have been mutated by a virus: specifically, a retrovirus has been proposed.[4]

The Recommended Daily Allowance (RDA) of ascorbic acid for human adults was set by the Food and Nutrition Board in 1943.[5] Since the creation of the RDAs, numerous studies have been conducted, even including a Nobel prizewinner (Linus Pauling), but they have failed to agree on daily appropriate doses of vitamin C intake that are needed.[6,7] The RDA for vitamin C was increased (2000) from 60 to 90 mg per day.[8] Many studies have demonstrated that higher doses than the RDA for vitamin C can improve the immune system and can prevent as well as treat a wide range of pathologies.[9–12] Moreover, over the past several decades, the literature has shown a significant loss of micronutrients, such as vitamin C, as a result of modern farming.[13] Consequently, the aim of this review is to compare the findings of scientific studies with the RDA, while hypothesizing a necessity for vitamin C supplementation.

## Functions of Vitamin C

Vitamin C is required for the maintenance of normal connective tissue and wound healing. Vitamin C also is needed for bone remodeling because of the presence of collagen in

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the organic matrix. A number of other metabolic reactions require vitamin C to act as a cofactor. Notable among those are the synthesis of epinephrine from tyrosine, and the synthesis of the bile acids. Furthermore, vitamin C involvement is suspected in the process of adrenal steroidogenesis. Other putative biochemical uses of vitamin C include a role in thyroxine synthesis, amino acid metabolism, and aiding in the absorption of iron.[14] Vitamin C can quench aqueous reactive species,[15] plays an important role in the antioxidant defense system and immunocompetence,[16] and in strengthening resistance to infection.[17,18] In addition, vitamin C fights against deoxyribonucleic acid (DNA) mutations[19] and might be of clinical value in the treatment of certain types of cancer and other diseases.[5,20–23]

### Recommended Dietary Allowance of Vitamin C

People vary widely in their requirements for vitamin C.[24] The RDA for vitamin C is based on twice the amount of vitamin C needed to prevent scurvy as well as on the threshold of the vitamin C needed to spill vitamin C into urinary excretion.[5,7] Moreover, the RDA for vitamin C is based on estimates of vitamin C absorption, on losses associated with food preparation, and on estimated rates of depletion, turnover, and catabolism.[8,7] Levine et al.[6] postulated in their paper that to establish an RDA for a vitamin, it is necessary to determine vitamin concentrations in plasma and tissues in relation to vitamin dose for a wide range of doses, true bioavailability or vitamin absorption at each dose, vitamin urinary excretion at each dose, and potential toxicity. In theory, these data could be obtained from nutrition depletion–repletion studies in combination with pharmacokinetic principles. For vitamin C, however, the information is unavailable, incomplete, or flawed. Consequently, the aim of the work of by Levine et al.[6] was to measure vitamin C depletion–repletion pharmacokinetics in 7 healthy inpatient volunteers by using 7 doses of vitamin C from 30 to 2500 mg. The U.S. Food and Nutrition Board has prepared RDAs since 1941. Initially, the RDA for vitamin C was based on the amount needed to prevent people from getting scurvy with a safety margin,[5,6,8] but this may not lead to optimal health.[5] Consequently, Pauling suggested that the RDA might be better called the Minimum Dietary Allowance.[5] Currently, vitamin C RDA requirements differ between countries, with the highest value being close to 110 mg/day.[8,25] Stone[26,27] concluded that the optimum intake rate should be 3000–5000 mg per day for most people based on the production of ascorbic acid from rats based on body weight. However, extrapolating the need in humans based on the amounts per kilogram of another animal may not be accurate. Pauling[5,24] suggested the range of 250–4000 mg as recommended daily intake of ascorbic acid. By accounting for the differences among people only in terms of weight, age, and sex, the RDAs remain an anachronistic and simplistic standard. Therefore, Challem[28] concluded that the RDAs might be seriously inadequate guidelines for health. However, high doses of vitamin C consumption, as proposed by previous authors, are not supported by all the literature. Indeed, a recent meta-analysis on a potential effect of vitamin C on the common cold conducted by Douglas et al.[29] showed that there seems no justification for routine megadose vitamin C supplementation, 1–3 g/day, in the normal population. Nevertheless, prophylaxis may be justified in those exposed to severe physical exercise or cold stress or both. Moreover, without reaching the megadoses of vitamin C consumption, numerous reviews suggest that intakes of vitamin C much higher than the RDA may reduce the risk or risk factors for chronic diseases such as heart disease and certain types of cancer.[7,30–33] In the same way, two studies demonstrated that current RDA for vitamin C should be reevaluated and increased to 200 mg daily.[6,34]

### Bodily Needs in Vitamin C

Vitamin C enhances the immune system.[9] Levine et al.[6] found that white blood cells became saturated at a dose of 100 mg of vitamin C. It is important to point out that data concerning plasma concentrations do not necessarily indicate that all tissues would be saturated at this dose. Indeed, specific transporters allow the accumulation of vitamin C by many tissues. Different vitamin C transporters are specialized in the epithelial system, such as intestine, kidney, and liver, while others are focused in the brain, eye, and other organs.[35–38] However, affinity, velocity, and other specific properties for ascorbic acid present significant differences between transporters.[39,40] White blood cells, which have specific requirements for vitamin C in fighting infection, store high quantities of vitamin C even when levels in the surrounding plasma are low.[41,42] An increase in vitamin C intake simultaneously induced an increase in plasma and leukocyte vitamin C concentration.[16,43] In fact, vitamin C has been defined as a stimulant of leukocyte function, especially of neutrophil and monocyte movement.[44] Vitamin C supplementation was shown to improve many indices of human immune responses, such as antimicrobicidal and natural killer cell activities, lymphocyte proliferation, chemotaxis, and delayed-type hypersensitivity (DTH) response, and the concentration of vitamin C is high in activated neutrophils and macrophages.[45–50] Indeed, vitamin C supplements (1–3 g/day, over 1 week for each dose) have been shown to enhance neutrophil chemotaxis in healthy adults.[51] In addition, 1 g/day of ascorbic acid over 28 days was given to healthy adults; they responded with immune system stimulation through enhanced T-lymphocyte proliferation in response to infection, thus increasing cytokine production and synthesizing immunoglobulins.[52] This study also demonstrated that combined supplementation with vitamins C and E (1 g/day and 400 mg/day, respectively, for 28 days) has a more prominent effect on immunity than supplementation with either vitamin alone. Different intakes of vitamin C (5–250 mg/day for 92 days) were tested in healthy men. A deficient diet (5–20 mg/day) showed that plasma and leukocyte vitamin C concentrations were decreased by about 50%, and the DTH responses to several antigens were decreased, whereas lymphocyte proliferation was not affected. In contrast, doses of 60–250 mg/day were shown to have normalized the DTH responses.[45] Moreover, in older people (>70 years), known to have reduced vitamin C plasma and leukocyte concentrations, vitamin C supplementation (500 mg/day for 1 month) enhanced the proliferative response of T lymphocytes.[47] Furthermore, in healthy people and patients, with higher concentrations of ascorbate (1 g/day), white blood cells became more active and could move toward infection or inflammation more quickly.[53–55]

Glutathione deficiency can seriously impair immune function.[56] Nevertheless, Lenton et al.[57] demonstrated that intracellular glutathione and ascorbate protected human lymphocytes against oxidative DNA damage. Furthermore, glutathione and ascorbate are directly correlated in human lymphocytes,[58] and Lenton et al.[59] demonstrated that 13 weeks of vitamin C supplements (500 or 1000 mg/day) induced the ability of vitamin C to increase lymphocyte glutathione, suggesting that vitamin C may also be of value in the treatment of diseases or conditions involving glutathione deficiency. For example, during aging, ascorbate and glutathione in lymphocytes decreases, and low concentrations induce a higher risk of cancer, particularly lung cancer, and chronic illnesses such as ischemic heart disease, diabetes, cataract, chronic renal failure, and leukaemia.[60,61]

Levine et al.[6,25] measured the absorption, blood levels, and excretion of vitamin C. Levine's papers recommend 200 mg per day for vitamin C and stipulated that doses above 400 mg provide no additional benefit. In their works, these authors determined the steady-state plasma and white blood cell concentration of vitamin C and its excretion in healthy subjects. However, they did not investigate the effects on function. Levine et al.[6] gave a dose of vitamin C, waited until it had been excreted, and then measured the blood levels and concluded that plasma vitamin C had plateau at a plasma level of 75–80 $\mu$mol/L, at the dose of 200 mg. Moreover, in that study, the authors claimed that plasma was saturated at a dose around 1 g/day. However, it appeared that plasma level of vitamin C increased for all doses. Indeed, the subjects studied (6 samples were obtained from 7 subjects studied) showed a rise in plasma levels with doses ranging between 400 mg and 1000 mg, and with doses between 400 mg and 2500 mg, but only 3 samples were obtained at these latter ranges. Furthermore, in healthy subjects, a later paper demonstrated that oral doses of 3 g 6 times daily led to a predicted plasma vitamin C concentration of 220 $\mu$mol/L.[62] In addition, Benke[63] demonstrated that vitamin C concentration in plasma depended on the dosage and method of administration. The author showed that 0.5, 1, and 2 g oral doses of vitamin C ingested once daily increased plasma concentration, reaching an increase of 100% with 2 g, with a peak value after 3 hours following the ingestion, and decreased linearly over 24 hours. Nevertheless, if this dose is administered at regular intervals of less than 1.5 hour, a higher average level of plasma concentration during 24 hours can be maintained. Hence, the literature shows that frequent repeated oral doses (2–3 g per 1–4 hours) allow sustained high plasma levels close to 220 $\mu$mol/L.[62–64] However, in their works, Levine et al[6,25] administered half the dose chosen (30, 60, 100, 200, 400, 1000, 2500 mg) twice daily. Consequently, we could hypothesize that this interval of vitamin C intake and size of doses were not adequate enough to enhance plasma vitamin C concentration from the subjects' normal level. Levine et al.[6] recommended 200 mg daily of vitamin C, according to their results in white blood cell saturation, calculated at 100 mg, and vitamin C bioavailability measured at 200 mg. These authors concluded that there was no benefit exceeding a vitamin C level of 400 mg. Nevertheless, their recommendation of taking 200 mg of vitamin C daily was determined in only 7 healthy men aged 20–26 years, which may not represent the general population. By using the identical experimental methods, the same authors recommended 90 mg daily for young women ($n = 15$).[25] Consequently, they did not include older and younger subjects, smokers, pregnant women, and sick people. Hickey and Roberts,[65] who analyzed Levine's recommendations, noted that the requirement for many individuals could be considerably greater than 200 mg and might be 2500 mg to ensure that everyone approached plasma saturation. In spite of these limitations in their study, Levine et al.[6] brought a more scientific approach to the recommended daily vitamin C allowance and demonstrated that the official RDA is considerably lower than that recommended in their paper.

### Vitamin C Consumption Higher than the RDA

Vitamin C can be taken orally and intravenously. Nevertheless, oral absorption of vitamin C cannot achieve plasma concentrations comparable to those obtained by intravenous administration.[62] Intravenous doses were administered, as an alternative therapy, in order to treat patients with advanced cancer.[62,66–68] This can be explained by the fact that intravenous doses raise plasma concentrations as high as 14,000 $\mu$mol/L, with doses of 50–100 g daily, and concentrations of 1000–5000 $\mu$mol/L are selectively cytotoxic to tumor cells but not to normal cells *in vitro*.[69–73] It must be specified that these latter doses cannot be tolerated by oral consumption.[62]

Higher oral doses of vitamin C (2500 mg daily) resulted in greater vitamin C levels in the blood.[6,25] Presumably, bioavailability, or gastrointestinal absorption, declined at vitamin C doses above 200 mg.[6,34] Bioavailability was 100% up to 200 mg but decreased to close to 33% or lower after a single dose of 1250 mg[6] and could result in gastrointestinal upset. However, the findings by Levine et al.[6] also did not demonstrate that more vitamin C was available with 200 mg than with higher doses, nor does it mean that an equivalent amount of vitamin C was available at lower doses.

High levels of vitamin C protect against damage to blood vessels[74] and very significantly reduce mortality rates in the elderly.[75] Indeed, Fletcher et al.[75] have measured that men (mean age 80 years) with 100 mg daily vitamin C intake presented a mortality risk nearly half that compared to peer men with a consumption of 50 mg/day. Moreover, men with low serum ascorbate concentrations may have an increased risk of mortality.[60] A large body of evidence demonstrates that high dietary vitamin C supplementation (between 1 and 10 g/day or more, according to some studies) can enhance resistance to and improve recovery from infectious, degenerative diseases, and certain types of cancer,[17,18,20,23] as well as prevent and treat a wide range of diseases.[10–12,68,76–78] Many biological, clinical, and epidemiological studies have indicated that higher intakes of vitamin C, 1–3 g daily doses, may be required to reduce risk of chronic diseases such as cardiovascular disease, cancer, or cataract.[23,79,80] Furthermore, the oxidative stress associated with many diseases may increase ascorbate requirements.[81,82] Large doses of ascorbate have been found to reduce cardiovascular disease risk, lengthen the lifespan of patients with cancer,[83] and, epidemiologically, to lengthen lifespan in general.[84] Moreover, daily supplementation with 1000 mg of ascorbic acid results in a significant decrease of blood-lead levels associated with the general population.[85] If these associations are related causally, ascorbic acid intake may have public health impli-

cations for lead neurotoxicity control.[86] A recent study has shown that vitamin C supplementation (1000 mg twice daily, for a maximum of 2 months) in infertile men might improve sperm count, sperm motility, and sperm morphology and might have a place as an additional supplement to improve the semen quality leading to conception.[87] Researchers and clinicians have suggested that large quantities of supplemental ascorbate (on average 1–10+ g/day) may compensate for the lack of endogenous ascorbate.[88]

Supplements compensate for the inability to produce endogenous ascorbate, and various researchers and clinicians have accordingly recommended the consumption of large supplemental doses of ascorbate.[88] A recent study showed that, in a population reporting cold and flu symptoms, hourly doses of 1000 mg of vitamin C for the first 6 hours and 3 times daily thereafter decreased flu and cold symptoms by 85% compared with a control group.[89] However, Audera et al.[90] demonstrated that doses of vitamin C, 1 g or 3 g daily taken shortly after onset of a cold, did not reduce the duration or severity of cold symptoms in healthy adults when compared with a vitamin C dose of 30 mg/day. In the same way, a more recent study showed that vitamin C supplementation of 0.5 g/day versus 50 mg/day had no apparent effect on the duration or severity of the common cold, but significantly reduced the frequency of the latter.[91] Concerning the common cold, the meta-analysis by Douglas et al.[29,78] indicated that the trials in which vitamin C was introduced as a therapy at the onset of colds did not show any benefit in doses up to 4 g daily, but one large trial reported equivocal benefit from an 8-g therapeutic dose at the onset of symptoms.

For the moment, no one study can indicate the exact needs of all healthy individuals. Particularly because most studies have small subject numbers and specific subgroups studied, it is difficult to make conclusions about standardized daily doses for all categories of the population. The vitamin C needs might change according to age, sex, level of activity, and whether subjects smoked or not.

The recommended daily vitamin C allowance should range from 250 mg to 4000 mg for an adult, as suggested by Pauling,[5] and should be 2500 mg according to the recommendations of Hickey and Roberts.[65] In spite of some studies concluding that vitamin C with doses of 1–3 g daily had no prophylactic influence, specifically on common colds,[29] recent reviews have demonstrated the considerable benefits and safety of vitamin C intake greater than the RDA in healthy adults.[10,30,79,92] Moreover, the literature has demonstrated that men might consume more vitamin C than women[16,93] and that the elderly might require more ascorbate than younger people.[94–96] Based on the currently available literature, we suggest that, in healthy subjects, a minimum vitamin C consumption of 1 g daily is necessary, in order to complete a prevention program for many diseases.

### Vitamin C Doses in Diet Supplement and Food

Oral administration of vitamin C induced peak values of plasma close to 220 $\mu$mol/L, when 3 g 6 times daily were used.[62] However, the study by Padayatty et al.[62] showed that single supplement gram doses produced transient peak plasma concentrations that were at most two or threefold higher than those from vitamin C contained in five to nine daily servings of fruits and vegetables, which only produced a plasma concentration of 80 $\mu$mol/L.

Based on cancer prevention, the U.S. department of Agriculture and the National Cancer Institute recommend that five servings of fruits and vegetables are to be eaten daily,[97] even if recent analysis has suggested that this consumption should be higher.[98] If these recommendations are followed, daily vitamin C intake will be 210 to 280 mg, depending on food cofactors.[7] Furthermore, amounts >500 mg/day would be difficult to obtain from dietary sources alone and would require supplements.[99] However, the conventional farming system, using toxic chemical products in order to carry out intensive production, presents a great health hazard and severely decreases food quality.[100–103] Indeed, analysis of fruits and vegetables has shown a significant loss of minerals and trace elements in modern diets compared to that of a few decades ago.[13,104,105] Moreover, a considerable loss of nutrients in the modern diet has been observed during food processing, long transporting, and incorrect food storage.[106–108] Indeed, vitamin C in foods is irreversibly oxidized by exposure to light, oxygen, and/or heat, and reports suggest that fresh produce or juice may lose 50%–100% of its vitamin C content due to handling and processing.[109–111] Hence, the increased processing of the food supply may be impacting the level of dietary vitamin C available to consumers.[112]

### Safety of Vitamin C Supplementation

It has been suggested that vitamin C alone or mixed with *N*-acetyl-cysteine could be toxic, acting as a pro-oxidant.[113,114] However, the literature shows evidence that ascorbic acid is not a pro-oxidant *in vivo*, even with iron co-supplementation.[23,115] Because vitamin C assists in the absorption of dietary iron, some research has focused on whether increased vitamin C intake inopportunely increases iron stores. Supplementary doses of 500 mg/day have been shown to have little effect on iron bioavailability.[116] Moreover, most published studies on the subject strongly indicate that vitamin C doses up to 2000 mg/day do not increase body iron stores enough to produce any clinically significant adverse effects.[117,118] The literature has also evoked the potential adverse effects of high doses of vitamin C, especially as regards the increase in oxalate and kidney stone formation.[6,7] Indeed, Auer et al.[119] demonstrated that 8 g/day, divided into four doses of 2 g, for 8 consecutive days, can cause harmful calcium oxalate crystalluria secondary to relative hyperoxaluria in persons who have a predisposition for increased crystal aggregation. Nevertheless, these authors specified that these individual's response to vitamin C ingestion is probably rare. Wandzilak et al.[120] observed a modest increase in urinary oxalate after experimental administration of high doses of vitamin C (5 and 10 g/day for 5 days). However, these results appear to be due to *in vitro* conversion of ascorbate to oxalate during the analytical procedure rather than *in vivo* conversion. Consequently, these authors concluded that no genuine increase in urinary oxalate was demonstrable despite a greatly increased ascorbate intake. Moreover, other work by Auer et al.,[121] but using 4 g/day of ascorbic acid for 5 days, concluded that ingestion of these doses did not affect the principal risk factors associated with calcium oxalate kidney stone formation. Furthermore, large doses of vitamin C (1.5 g or more) did not

produce kidney stones and the doses of vitamin C above 1.5 g in fact reduced the risk of kidney stones.[122–124] These authors stated that the restriction of higher doses of vitamin C because of the possibility of kidney stones is unwarranted. Evidence indicates that high intakes of vitamin C do not increase oxalate excretion or induce the potential formation of kidney stones.[30,92,125] Moreover, no effect of high-dose ascorbic acid ingestion was found on the daily urinary excretion of uric acid.[126] Gastrointestinal distress seems to be the most common adverse effect of high vitamin C intakes.[127] When these symptoms occur, the vitamin C dosage is usually >2 g/day. The symptoms generally disappear within a week or 2 with no further consequences, and may have been produced by other components such as sorbitol.[128] Harmful effects have been mistakenly attributed to vitamin C, including hypoglycemia, rebound scurvy, infertility, mutagenesis, and destruction of vitamin $B_{12}$. Health professionals should recognize that vitamin C does not produce these effects.[129] Other studies showed evidence that large doses of vitamin C are safe.[11,130–133] A recent review demonstrated that vitamin C supplements of ≤2000 mg/day are safe for most adults.[92] These authors also supported the claim that intakes of up to 4000 mg/day are well tolerated in the general population. No consistent and compelling data demonstrating serious adverse effects of vitamin C in humans have been established,[79] although the tolerable upper limit intake has been estimated at 2 g/day.[8]

## Conclusions

The literature has shown evidence of vitamin C benefits in terms of prevention and treatment of a large panel of diseases. However, RDA for vitamin C does not cover the need for vitamin C in daily bodily functions. Numerous studies have demonstrated that vitamin C consumption higher than the RDA enhances the immune system and decreases the risk of DNA damage. Vitamin C greater than 400 mg/day can improve protection against oxidative stress, certain cancers, and degenerative and chronic diseases. Nevertheless, modern farming leads to a lowering in food quality, inducing a considerable loss of micronutrients, and not allowing a sufficient intake of vitamin C simply through food consumption. Consequently, even if vitamin C requirements vary greatly among individuals, it is suggested that vitamin C supplementation is not only totally safe but also necessary to achieve optimal health. Therefore, in agreement with the current literature, we advise healthy people to consume five servings of fruits and vegetables daily, added to 1 g of vitamin C supplementation divided in two or three doses during the day, in order to ensure an optimal allowance in vitamin C.

## Disclosure Statement

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## References


1. Linster CL, Van Schaftingen E. Vitamin C: Biosynthesis, recycling and degradation in mammals. FEBS J 2007;274:1–22.
2. Nishikimi M, Yagi K. Molecular basis for the deficiency in humans of gulonolactone oxidase, a key enzyme for ascorbic acid biosynthesis. Am J Clin Nutr 1991;54:1203S–1208S.
3. Nishikimi M, Fukuyama R, Minoshima S, et al. Cloning and chromosomal mapping of the human nonfunctional gene for L-gulono-gamma-lactone oxidase, the enzyme for L-ascorbic acid biosynthesis missing in man. J Biol Chem 1994;269:13685–13688.
4. Challem JJ. Did the loss of endogenous ascorbate propel the evolution of Anthropoidea and Homo sapiens? Med Hypotheses 1997;48:387–392.
5. Pauling L. Are recommended daily allowances for vitamin C adequate? Proc Natl Acad Sci U S A 1974;71:4442–4446.
6. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: Evidence for a recommended dietary allowance. Proc Natl Acad Sci U S A 1996;93:3704–3709.
7. Levine M, Rumsey SC, Daruwala R, et al. Criteria and recommendations for vitamin C intake. JAMA 1999;281: 1415–1423.
8. Food and Nutrition Board IoM. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. A Report of the Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Washington, DC: National Academy Press, 2000.
9. Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. Ann Nutr Metab 2007;51:301–323.
10. Bendich A, Langseth L. The health effects of vitamin C supplementation: A review. J Am Coll Nutr 1995;14:124–136.
11. Hemila H. Vitamin C supplementation and common cold symptoms: Factors affecting the magnitude of the benefit. Med Hypotheses 1999;52:171–178.
12. Yeom CH, Jung GC, Song KJ. Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration. J Korean Med Sci 2007;22:7–11.
13. Davis DR, Epp MD, Riordan HD. Changes in USDA food composition data for 43 garden crops, 1950 to 1999. J Am Coll Nutr 2004;23:669–682.
14. Whitney EN, Catalo CB, Rolfes SR. Understanding normal and clinical nutrition. Belmont, CA: Wadsworth/Thompson Learning, 2002:335–341.
15. Cathcart RF 3rd. Vitamin C: The nontoxic, nonrate-limited, antioxidant free radical scavenger. Med Hypotheses 1985; 18:61–77.
16. Jacob RA. Assessment of human vitamin C status. J Nutr 1990;120(suppl 11):1480–1485.
17. Hemila H. Vitamin C and the common cold. Br J Nutr 1992;67:3–16.
18. Hemila H. Does vitamin C alleviate the symptoms of the common cold? A review of current evidence. Scand J Infect Dis 1994;26:1–6.
19. Sweetman SF, Strain JJ, McKelvey-Martin VJ. Effect of antioxidant vitamin supplementation on DNA damage and repair in human lymphoblastoid cells. Nutr Cancer 1997;27: 122–130.
20. Hoffer A, Pauling L. Hardin Jones biostatistical analysis of mortality data for a second set of cohorts of cancer patients with a large fraction surviving at the termination of the study and a comparison of survival times of cancer patients receiving large regular oral doses of vitamin C and other nutrients with similar patients not receiving these doses. Orthomol Med 1993;8:157–167.
21. Prasad KN, Kumar R. Effect of individual and multiple antioxidant vitamins on growth and morphology of human

nontumorigenic and tumorigenic parotid acinar cells in culture. Nutr Cancer 1996;26:11–19.
22. Ames BN. Micronutrients prevent cancer and delay aging. Toxicol Lett 1998;102–103:5–18.
23. Carr A, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr 1999;69:1086–1107.
24. Pauling L. Evolution and the need for ascorbic acid. Proc Natl Acad Sci U S A 1970;67:1643–1648.
25. Levine M, Wang Y, Padayatty SJ, Morrow J. A new recommended dietary allowance of vitamin C for healthy young women. Proc Natl Acad Sci U S A 2001;98:9842–9846.
26. Stone I. Hypoascorbemia, the genetic disease causing the human requirement for exogenous ascorbic acid. Perspect Biol Med 1966;10:133–134.
27. Stone I. On the genetic etiology of scurvy. Acta Genet Med Gemellol (Roma) 1966;15:345–350.
28. Challem JJ. Toward a new definition of essential nutrients: Is it now time for a third "vitamin" paradigm? Med Hypotheses 1999;52:417–422.
29. Douglas R, Hemila H, Chalker E, Treacy B. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2007:CD000980.
30. Hathcock JN. Vitamins and minerals: Efficacy and safety. Am J Clin Nutr 1997;66:427–437.
31. Ames BN. A role for supplements in optimizing health: The metabolic tune-up. Arch Biochem Biophys 2004;423: 227–234.
32. Ames BN. Increasing longevity by tuning up metabolism: To maximize human health and lifespan, scientists must abandon outdated models of micronutrients. EMBO Rep 2005;6(spec no):S20–S24.
33. Ames BN. Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. Proc Natl Acad Sci U S A 2006;103:17589–17594.
34. Graumlich JF, Ludden TM, Conry-Cantilena C, et al. Pharmacokinetic model of ascorbic acid in healthy male volunteers during depletion and repletion. Pharm Res 1997;14: 1133–1139.
35. Daruwala R, Song J, Koh WS, et al. Cloning and functional characterization of the human sodium-dependent vitamin C transporters hSVCT1 and hSVCT2. FEBS Lett 1999;460: 480–484.
36. Tsukaguchi H, Tokui T, Mackenzie B, et al. A family of mammalian Na+-dependent L-ascorbic acid transporters. Nature 1999;399:70–75.
37. Wang Y, Mackenzie B, Tsukaguchi H, et al. Human vitamin C (L-ascorbic acid) transporter SVCT1. Biochem Biophys Res Commun 2000;267:488–494.
38. Takanaga H, Mackenzie B, Hediger MA. Sodium-dependent ascorbic acid transporter family SLC23. Pflugers Arch 2004;447:677–682.
39. Liang WJ, Johnson D, Jarvis SM. Vitamin C transport systems of mammalian cells. Mol Membr Biol 2001;18:87–95.
40. Corpe CP, Lee JH, Kwon O, et al. 6-Bromo-6-deoxy-L-ascorbic acid: An ascorbate analog specific for Na+-dependent vitamin C transporter but not glucose transporter pathways. J Biol Chem 2005;280:5211–5220.
41. Hornig D. Distribution of ascorbic acid, metabolites and analogues in man and animals. Ann N Y Acad Sci 1975;258:103–118.
42. Moser U. Uptake of ascorbic acid by leukocytes. Ann N Y Acad Sci 1987;498:200–215.
43. Omaye ST, Skala JH, Jacob RA. Plasma ascorbic acid in adult males: Effects of depletion and supplementation. Am J Clin Nutr 1986;44:257–264.
44. Maggini S, Wintergerst ES, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. Br J Nutr 2007;98(suppl 1):S29–S35.
45. Jacob RA, Kelley DS, Pianalto FS, et al. Immunocompetence and oxidant defense during ascorbate depletion of healthy men. Am J Clin Nutr 1991;54:1302S–1309S.
46. Panush RS, Delafuente JC, Katz P, Johnson J. Modulation of certain immunologic responses by vitamin C: III. Potentiation of *in vitro* and *in vivo* lymphocyte responses. Int J Vitam Nutr Res 1982;23(suppl):35–47.
47. Kennes B, Dumont I, Brohee D, et al. Effect of vitamin C supplements on cell-mediated immunity in old people. Gerontology 1983;29:305–310.
48. Washko P, Rotrosen D, Levine M. Ascorbic acid in human neutrophils. Am J Clin Nutr 1991;54:1221S–1227S.
49. Wolf G. Uptake of ascorbic acid by human neutrophils. Nutr Rev 1993;51:337–338.
50. May JM, Huang J, Qu ZC. Macrophage uptake and recycling of ascorbic acid: Response to activation by lipopolysaccharide. Free Radic Biol Med 2005;39:1449–1459.
51. Anderson R, Oosthuizen R, Maritz R, et al. The effects of increasing weekly doses of ascorbate on certain cellular and humoral immune functions in normal volunteers. Am J Clin Nutr 1980;33:71–76.
52. Jeng KC, Yang CS, Siu WY, et al. Supplementation with vitamins C and E enhances cytokine production by peripheral blood mononuclear cells in healthy adults. Am J Clin Nutr 1996;64:960–965.
53. Anderson R. Ascorbate-mediated stimulation of neutrophil motility and lymphocyte transformation by inhibition of the peroxidase/H2O2/halide system *in vitro* and *in vivo*. Am J Clin Nutr 1981;34:1906–1911.
54. Anderson R. Assessment of oral ascorbate in three children with chronic granulomatous disease and defective neutrophil motility over a 2-year period. Clin Exp Immunol 1981;43:180–188.
55. Anderson R. Effects of ascorbate on normal and abnormal leukocyte functions. In: Vitamin C: New Clinical Applications in Immunology, Lipid Metabolism and Cancer. A. Hank Huber, Bern: Germany; 1982; pp. 23–24.
56. De Rosa SC, Zaretsky MD, Dubs JG, et al. N-acetylcysteine replenishes glutathione in HIV infection. Eur J Clin Invest 2000;30:915–929.
57. Lenton KJ, Therriault H, Fulop T, et al. Glutathione and ascorbate are negatively correlated with oxidative DNA damage in human lymphocytes. Carcinogenesis 1999;20: 607–613.
58. Lenton KJ, Therriault H, Cantin AM, et al. Direct correlation of glutathione and ascorbate and their dependence on age and season in human lymphocytes. Am J Clin Nutr 2000;71:1194–1200.
59. Lenton KJ, Sane AT, Therriault H, et al. Vitamin C augments lymphocyte glutathione in subjects with ascorbate deficiency. Am J Clin Nutr 2003;77:189–195.
60. Loria CM, Klag MJ, Caulfield LE, Whelton PK. Vitamin C status and mortality in US adults. Am J Clin Nutr 2000;72:139–145.
61. Kharb S, Singh V, Ghalaut PS, et al. Glutathione levels in health and sickness. Indian J Med Sci 2000;54:52–54.

62. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: Implications for oral and intravenous use. Ann Intern Med 2004;140:533–537.
63. Benke KK. Modelling ascorbic acid level in plasma and its dependence on absorbed dose. J Aust Coll Nutr Environ Med 1999;18:11–12.
64. Hickey S, Roberts H. Misleading information on the properties of vitamin C. PLoS Med 2005;2:e307; author reply e309.
65. Hickey S, Roberts H. Ascorbate: The Science of Vitamin C. Napa, CA: Lulu Press, 2004.
66. Cameron E, Pauling L. Cancer and Vitamin C. Philadelphia: Camino Books, 1993.
67. Riordan NH, Riordan HD, Meng X, et al. Intravenous ascorbate as a tumor cytotoxic chemotherapeutic agent. Med Hypotheses 1995;44:207–213.
68. Padayatty SJ, Riordan HD, Hewitt SM, et al. Intravenously administered vitamin C as cancer therapy: Three cases. CMAJ 2006;174:937–942.
69. Benade L, Howard T, Burk D. Synergistic killing of Ehrlich ascites carcinoma cells by ascorbate and 3-amino-1,2,4,-triazole. Oncology 1969;23:33–43.
70. Bram S, Froussard P, Guichard M, et al. Vitamin C preferential toxicity for malignant melanoma cells. Nature 1980;284:629–631.
71. Leung PY, Miyashita K, Young M, Tsao CS. Cytotoxic effect of ascorbate and its derivatives on cultured malignant and nonmalignant cell lines. Anticancer Res 1993;13: 475–480.
72. Casciari JJ, Riordan NH, Schmidt TL, et al. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre *in vitro* tumours. Br J Cancer 2001;84:1544–1550.
73. Chen Q, Espey MG, Krishna MC, et al. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues. Proc Natl Acad Sci U S A 2005;102:13604–13609.
74. Ruiz E, Siow RC, Bartlett SR, et al. Vitamin C inhibits diethylmaleate-induced L-cystine transport in human vascular smooth muscle cells. Free Radic Biol Med 2003;34: 103–110.
75. Fletcher AE, Breeze E, Shetty PS. Antioxidant vitamins and mortality in older persons: Findings from the nutrition add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community. Am J Clin Nutr 2003;78:999–1010.
76. Hemila H. Vitamin C intake and susceptibility to the common cold. Br J Nutr 1997;77:59–72.
77. Hemila H. Vitamin C supplementation and respiratory infections: A systematic review. Mil Med 2004;169:920–925.
78. Douglas RM, Hemila H, D'Souza R, et al. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2004:CD000980.
79. Frei B, Trabe MG. The new US Dietary Reference Intakes for vitamins C and E. Redox Rep 2001;6:5–9.
80. Li Y, Schellhorn HE. New developments and novel therapeutic perspectives for vitamin C. J Nutr 2007;137: 2171–2184.
81. Harman D. Free-radical theory of aging. Increasing the functional life span. Ann N Y Acad Sci 1994;717:1–15.
82. Mezzetti A, Lapenna D, Romano F, et al. Systemic oxidative stress and its relationship with age and illness. Associazione Medica "Sabin". J Am Geriatr Soc 1996;44:823–827.
83. Cameron E, Pauling L. Cancer and Vitamin C. Palo Alto, CA: Linus Pauling Institute of Science and Medicine, 1979.
84. Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. Epidemiology 1992;3:194–202.
85. Dawson EB, Evans DR, Harris WA, et al. The effect of ascorbic acid supplementation on the blood lead levels of smokers. J Am Coll Nutr 1999;18:166–170.
86. Simon JA, Hudes ES. Relationship of ascorbic acid to blood lead levels. JAMA 1999;281:2289–2293.
87. Akmal M, Qadri JQ, Al-Waili NS, et al. Improvement in human semen quality after oral supplementation of vitamin C. J Med Food 2006;9:440–442.
88. Cathcart RF. Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy. Med Hypotheses 1981;7:1359–1376.
89. Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. J Manipulative Physiol Ther 1999;22: 530–533.
90. Audera C, Patulny RV, Sander BH, Douglas RM. Megadose vitamin C in treatment of the common cold: A randomised controlled trial. Med J Aust 2001;175:359–362.
91. Sasazuki S, Sasaki S, Tsubono Y, et al. Effect of vitamin C on common cold: Randomized controlled trial. Eur J Clin Nutr 2006;60:9–17.
92. Hathcock JN, Azzi A, Blumberg J, et al. Vitamins E and C are safe across a broad range of intakes. Am J Clin Nutr 2005;81:736–745.
93. VanderJagt DJ, Garry PJ, Bhagavan HN. Ascorbate and dehydroascorbate: Distribution in mononuclear cells of healthy elderly people. Am J Clin Nutr 1989;49:511–516.
94. Blanchard J, Conrad KA, Mead RA, Garry PJ. Vitamin C disposition in young and elderly men. Am J Clin Nutr 1990;51:837–845.
95. Blanchard J. Depletion and repletion kinetics of vitamin C in humans. J Nutr 1991;121:170–176.
96. Heseker H, Schneider R. Requirement and supply of vitamin C, E and beta-carotene for elderly men and women. Eur J Clin Nutr 1994;48:118–127.
97. Lachance P, Langseth L. The RDA concept: Time for a change? Nutr Rev 1994;52:266–270.
98. Guenther PM, Dodd KW, Reedy J, Krebs-Smith SM. Most Americans eat much less than recommended amounts of fruits and vegetables. J Am Diet Assoc 2006;106:1371–1379.
99. Levine M, Dhariwal KR, Welch RW, et al. Determination of optimal vitamin C requirements in humans. Am J Clin Nutr 1995;62:1347S–1356S.
100. Belpomme D, Irigaray P, Hardell L, et al. The multitude and diversity of environmental carcinogens. Environ Res 2007;105:414–429.
101. He ZL, Yang XE, Stoffella PJ. Trace elements in agroecosystems and impacts on the environment. J Trace Elem Med Biol 2005;19:125–140.
102. Lal R. Soil management in the developing countries. Soil Sci 2000;165:57–72.
103. Lal R. Cropping systems and soil quality. J Crop Production 2003;8:33–52.
104. Thomas D. A study on the mineral depletion of the foods available to us as a nation over the period 1940 to 1991. Nutr Health 2003;17:85–115.
105. Mayer AM. Historical changes in the mineral content of fruits and vegetables. Br Food J 1997;99:207–211.
106. Reddy MB, Love M. The impact of food processing on the nutritional quality of vitamins and minerals. Adv Exp Med Biol 1999;459:99–106.

107. Kramer A. Effect of storage on nutritive value of food. J Food Qual 1977;1:23–55.
108. Vanderslice JT, Higgs DJ. Vitamin C content of foods: Sample variability. Am J Clin Nutr 1991;54:1323S–1327S.
109. Severi S, Bedogni G, Zoboli GP, et al. Effects of home-based food preparation practices on the micronutrient content of foods. Eur J Cancer Prev 1998;7:331–335.
110. Gil MI, Ferreres F, Tomas-Barberan FA. Effect of postharvest storage and processing on the antioxidant constituents (flavonoids and vitamin C) of fresh-cut spinach. J Agric Food Chem 1999;47:2213–2217.
111. Johnston CS, Bowling DL. Stability of ascorbic acid in commercially available orange juices. J Am Diet Assoc 2002;102:525–529.
112. Johnston CS. Strategies for healthy weight loss: From vitamin C to the glycemic response. J Am Coll Nutr 2005;24: 158–165.
113. Podmore ID, Griffiths HR, Herbert KE, et al. Vitamin C exhibits pro-oxidant properties. Nature 1998;392:559.
114. Childs A, Jacobs C, Kaminski T, et al. Supplementation with vitamin C and *N*-acetyl-cysteine increases oxidative stress in humans after an acute muscle injury induced by eccentric exercise. Free Radic Biol Med 2001;31:745–753.
115. Gomez-Cabrera MC, Domenech E, Romagnoli M, et al. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. Am J Clin Nutr 2008;87: 142–149.
116. Hunt JR, Gallagher SK, Johnson LK. Effect of ascorbic acid on apparent iron absorption by women with low iron stores. Am J Clin Nutr 1994;59:1381–1385.
117. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: A randomised placebo-controlled trial. Lancet 2002;360:23–33.
118. Cook JD, Watson SS, Simpson KM, et al. The effect of high ascorbic acid supplementation on body iron stores. Blood 1984;64:721–726.
119. Auer BL, Auer D, Rodgers AL. Relative hyperoxaluria, crystalluria and haematuria after megadose ingestion of vitamin C. Eur J Clin Invest 1998;28:695–700.
120. Wandzilak TR, D'Andre SD, Davis PA, Williams HE. Effect of high dose vitamin C on urinary oxalate levels. J Urol 1994;151:834–837.
121. Auer BL, Auer D, Rodgers AL. The effect of ascorbic acid ingestion on the biochemical and physicochemical risk factors associated with calcium oxalate kidney stone formation. Clin Chem Lab Med 1998;36:143–147.
122. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Intake of vitamins B6 and C and the risk of kidney stones in women. J Am Soc Nephrol 1999;10:840–845.
123. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of the intake of vitamins C and B6, and the risk of kidney stones in men. J Urol 1996;155:1847–1851.
124. Gerster H. No contribution of ascorbic acid to renal calcium oxalate stones. Ann Nutr Metab 1997;41:269–282.
125. Hoffer A. Ascorbic acid and kidney stones. Can Med Assoc J 1985;132:320.
126. Schmidt KH, Hagmaier V, Hornig DH, et al. Urinary oxalate excretion after large intakes of ascorbic acid in man. Am J Clin Nutr 1981;34:305–311.
127. Miller DR, Hayes KC. Vitamin excess and toxicity. In: Hathcock JN, ed. Nutritional Toxicology. Vol 1. New York: Academic Press, 1982:81–133.
128. Hill RE, Kamath KR. "Pink" diarrhoea: Osmotic diarrhoea from a sorbitol-containing vitamin C supplement. Med J Aust 1982;1:387–389.
129. Levine M. New concepts in the biology and biochemistry of ascorbic acid. NEJM 1986;314:892–902.
130. Hanck A. Tolerance and effects of high doses of ascorbic acid: *Dosis facit venenum*. Int J Vitam Nutr Res 1982; 23(suppl):221–238.
131. Johnston CS. Biomarkers for establishing a tolerable upper intake level for vitamin C. Nutr Rev 1999;57:71–77.
132. Garewal HS, Diplock AT. How 'safe' are antioxidant vitamins? Drug Saf 1995;13:8–14.
133. Diplock AT. Safety of antioxidant vitamins and beta-carotene. Am J Clin Nutr 1995;62:1510S–1516S.

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