

MEGA DOSES OF VITAMIN C:

Useful or Useless?

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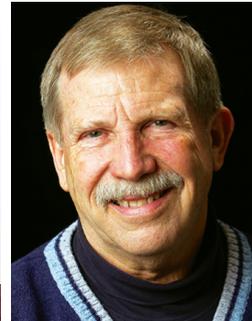
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INTRODUCTION

Vitamin C, L-ascorbic acid, plays an important role in the body as an antioxidant, as a critical component of collagen synthesis, and in the production of neurotransmitters. Since large amounts of vitamin C are required daily, most vertebrate species can synthesize it, though some species – including primates, guinea pigs, and some bat species – have lost that capability, possibly because early in their history their diets were rich in vitamin C, making endogenous vitamin C superfluous.

Humans ingest, on average, <100 mg/day of vitamin C, proportionally much less than the amounts synthesized by capable species. In recent years, and now more specifically in the midst of the current COVID-19 pandemic, there has been widespread controversy concerning the consumption of vitamin C for the prevention of both acute infectious and chronic diseases, specifically cancer and heart disease.

This theory was initially proposed in 1970 by Linus Pauling, PhD (1901-1994), in his book, *Vitamin C and the Common Cold*. Pauling, who received the Nobel Prize for Chemistry in 1954 for the application of quantum mechanics to the understanding of chemical bonding, recommended mega doses of vitamin C, i.e. 1,000 - 2,000 mg/day (12 - 24 mg/kg) to ward off colds and lessen their symptoms. He cautioned that some individuals could remain in good health, including freedom from colds, by ingesting only 250 mg/day (3.0 mg/kg), whereas others might require $\geq 5,000$ mg/day (60 mg/kg) or more.¹

In 2013 Harvard Health reviewed 29 randomized trials of vitamin C with more than 11,000 subjects. Though the risk of getting a cold was cut in half in extremely active individuals who took the recommended dietary allowance (RDA) of 200 mg/day (2.4 mg/kg) of vitamin C, there didn't seem to be any such effect in the general population. On the other hand, 2,000 mg/day (24 mg/kg) reduced the duration of cold symptoms an average of 8% in adults and 14% in children.² As of this writing, at least 51 clinical trials are underway in which vitamin C's efficacy is being evaluated for COVID-19,

some with doses 10 times the RDA of 200 mg/day.³

In 1979, Pauling further proposed that vitamin C could be effective in the prevention of cancer, and he later stated that mega doses of vitamin C could help control heart disease and other chronic diseases associated with aging.^{4,5} These doses were in stark contrast to the American Medical Association's original RDA for vitamin C of 60 mg/day (0.7 mg/kg), established in 1989 as the amount required to prevent clinical scurvy, which was only increased to 100 - 200 /day (1.2 - 2.4 mg/kg) in 1999.^{6,7} In contrast to Pauling, the American Medical Association further advised that vitamin C doses of $\geq 1,000$ mg/day could have adverse consequences in some people, and physicians should counsel patients to avoid these high doses.⁷

CONSIDERATIONS RELEVANT TO LINUS PAULING AND HIS HYPOTHESIS

Linus Pauling, the Scientist

Linus Pauling was one of the founders of the fields of quantum chemistry and molecular biology, and one of only four persons to be awarded two Nobel prizes (Chemistry, 1954; Peace, 1962). His contributions to molecular biology and quantum chemistry were many and varied. His use of X-ray crystallography to elucidate the structure of biological molecules, and his description of the alpha helix in protein structure, directly inspired James Watson, Francis Crick, Maurice Wilkins, and Rosalind Franklin's elucidation of the double helix structure of DNA.⁸ As a biochemist, with his knowledge and understanding of organic processes and their interaction with living organisms, he stood out as one of the true geniuses of 20th century science. His opinions on scientific matters, especially those related to molecular biology, merit careful consideration at the very least.

As discussed below, Pauling himself ingested enormous (by clinical standards) amounts of vitamin C. He died in 1994 at the age of 93 of prostate cancer. His father had died of a perforated ulcer at the age of 36, and his mother at the age of 45.

Vitamin C (L-ascorbic acid) and its Role in the Human Body

As is well known, vitamin C is an essential nutrient, required to prevent scurvy,⁹ a disease in which the body's collagen breaks down, because vitamin C is essential in the biosynthesis of collagen. It is also important for the neutralization of highly reactive oxidizing free radicals, and can regenerate other antioxidants, specifically vitamin E, thus playing an important role in immune functions.¹⁰

Synthesis of Vitamin C in Vivo

Vitamin C can be synthesized by most mammals, with the exception of primates (humans, monkeys, and apes), the guinea pig, and a few species of bats (Fig. 1).¹¹

Synthesis of vitamin C begins in the liver. Through four enzymatic steps, D-glucose circulating in the blood is transformed into L-ascorbic acid (Fig. 2). The final enzyme in this biosynthesis is L-gulonolactone oxidase, a product of the GULO gene, present in all mammals except primates, humans, guinea pigs, and some bats.

Obviously, animals that lack the GULO gene, including humans, must ingest vitamin C for survival. The U.S. Office of Dietary Supplements advises that men older than 19 years consume 90 mg/day (~1.0 mg/kg), and women older than 19 years consume 75 mg/day (~1.0 mg/kg).¹²

In earlier times humans ate a more plant-based diet, and consumed much larger amounts of vitamin C. While wild primates require only 3-6mg/kg/day of vitamin C to prevent scurvy, they still take in much higher levels in their diet of fruits and leaves. It is estimated that Panamanian howler monkeys consume >600 mg/day (90

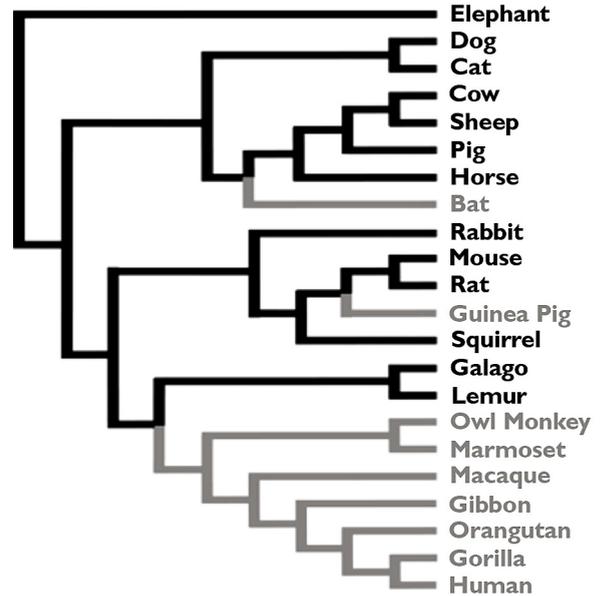


Fig. 1. Phylogenetic distribution of the Ability to Synthesize Vitamin C in Mammals. Black lines indicate lineages able to synthesize vitamin C. Gray lines show those that are incapable¹⁰

mg/kg) of vitamin C, and Panamanian spider monkeys consume >700 mg/day (>100 mg/kg), more than 100 times the amount per kg of the RDA in humans. Wild gorillas consume approximately 9 kg. of wild green foods per day, and take in more than 4,000 mg/day (25 mg/kg) of vitamin C. Similarly high vitamin C intake seems unavoidable for wild chimpanzees, orangutans, as well as many other monkeys, with their strong focus on ripe fruits in the diet.¹³ For species with such diets, it would seem that an inability to synthesize vitamin C confers no evolutionary disadvantage.

Guinea pigs require between 10-30 mg/kg/day but take in ~100 mg/kg/day in the wild.^{14,15} Katharine Milton, at the University of California, Berkeley, has suggested that just as wild primate diets are very high in vitamin C, diets eaten by early humans were also rich in vitamin C.¹³ Pauling estimated that early humans probably had an intake of vitamin C between 2,500 and 9,000 mg/day (100 - 360 mg/kg).⁵

CONSIDERATIONS FOR SUGGESTED VITAMIN C INTAKE IN HUMANS

From diet studies, Pauling concluded that humans could not be

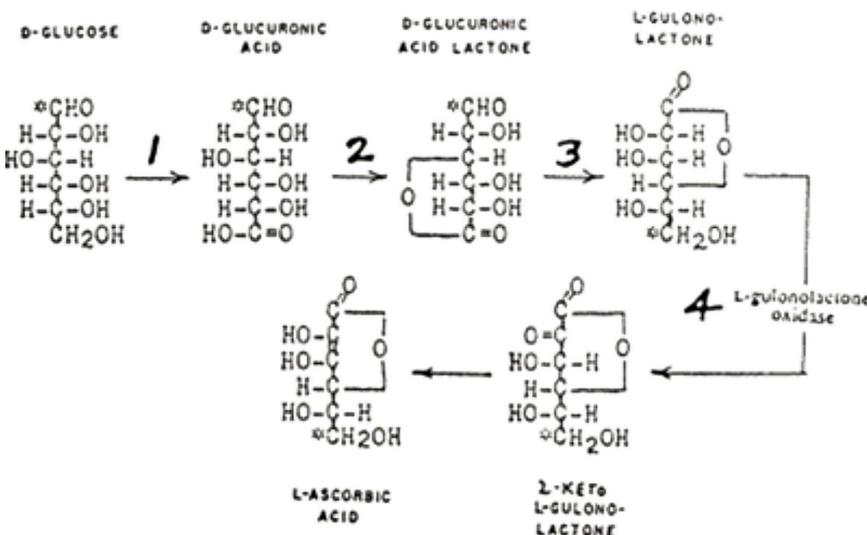


Fig. 2. Man has first three enzymes in liver, but is missing the fourth enzyme L-gulonolactone oxidase.

so much different from other mammals, and for humans to ingest much less vitamin C than other animals do, could not be beneficial. He then hypothesized that the human requirement for vitamin C might lie in the range of 20 - 50 mg/kg/day. Many other scientists, however, feel that these amounts seem high, since the basic food values of vitamin C extracted from food seldom exceeds 140 mg per food item, or a total of 250 mg of vitamin C per meal.⁵ More conservative scientists, therefore, while accepting the essence of Pauling's reasoning, suggest an intake of 600 - 1,200 mg/day (7.3 - 14.5 mg/kg), based on extrapolations from the early human herbivore diet.¹² Table 1 provides a comparison of the human intake of vitamin C with that of other mammals.

Potential Complications of High-Dose Vitamin C

Concerns have been advanced that ingesting more than the RDA of vitamin C would provoke kidney stones, but this result has not been demonstrated, only hypothesized, and linked specifically to urinary oxalate excretion.¹⁶ The two largest population-based studies to date examining urinary oxalate excretion (one consisting of 94 healthy adults and the other consisting of 186 calcium oxalate stone formers), found no statistically significant relation between dietary and urinary oxalate.^{17,18}

Extremely high doses of vitamin C given to rats, mice, and guinea pigs for several days showed little or no sign of toxicity.¹⁹ Since vitamin C is water soluble and excess amounts are excreted in the urine, the only adverse effects are anecdotal reports of kidney stones that were linked by the authors to oxalate excretion and oxalate kidney stones.

Mega Doses of Vitamin C in Cancer

The potential benefits for cancer prevention of a diet containing abundant fruits and vegetables and rich in vitamin C, have been difficult to assess. A relatively recent review of epidemiological studies concluded that "the possibility that fruits and vegetables may help to reduce the risk of cancer has been studied for over 30 years, but no protective effects have been firmly established."²⁰

This statement does not mean there are no benefits to be derived from a diet rich in fruits and vegetables, but rather - as this comprehensive review indicates - the overriding influence on cancer risk of obesity, smoking, and high alcohol consumption makes it difficult, if not impossible, to conduct epidemiological studies that adequately control for those variables. Further, none of those dietary studies assessed the benefits of the very high vitamin C intake that Pauling advocated.

Aside from the many inconclusive epidemiological studies, however, there have been important clinical and

laboratory studies of vitamin C's potential benefit for cancer. Lewis Cantley and Jihye Yun provided a review of the conflicting studies in a 2020 report from the NCI that is a must-read for anyone who wants the full history of studies of vitamin C and cancer.²¹

In brief, early studies that showed cancer patients to be deficient in vitamin C led to the postulate that vitamin C might prevent cancer by increasing collagen synthesis.²² Ascorbate could also suppress cancer development by inhibiting hyaluronidase, which otherwise weakens the extracellular matrix and enables cancer to metastasize. In 1976, Ewan Cameron and Linus Pauling published a study of 100 patients with terminal cancer treated with ascorbate. Compared with 1,000 retrospective control patients who were matched for age, sex, type of cancer, and clinical stage, patients treated with vitamin C had improved quality of life and a four-fold increase in their mean survival time.²³

With these and other promising outcomes, the Mayo Clinic conducted a double-blind randomized trial of high dose vitamin C in cancer patients, which failed to show any positive effects.²⁴ Their reports in the *New England Journal of Medicine* seemed to discredit the Cameron-Pauling trials, and for a long time dampened enthusiasm for vitamin C as a cancer therapy.

However, as Cantley and Yun point out in their review,²¹ there were crucial differences between the two studies. First, the Mayo Clinic trials abruptly stopped administering ascorbate and switched to traditional chemotherapy when the patient developed signs of tumor progression, so the median time of vitamin C treatment in the Mayo Clinic trials was only 2.5 months. Pauling and Cameron treated patients for the duration of the entire study period, or as long as 12 years.

Secondly, the Mayo Clinic trials administered 10 g of daily ascorbate to patients orally, while the Cameron and Pauling trials administered their vitamin C both orally and intravenously. This difference in the two dosage routes proved highly consequential.

The oral vitamin C doses used in the Mayo Clinic studies would have produced peak plasma concentration of less than 200 µM. In contrast, the same dose given intravenously, as in the Pauling studies, would produce peak plasma concentrations of nearly 6 mM, more than 25 times higher. When given orally, vitamin C concentration in human plasma is tightly controlled by multiple mechanisms, but intravenous administration bypasses these controls. A phase I clinical study revealed that ascorbate concentrations could safely reach 25-30 mM with intravenous infusion of 100 g of

Animal	Vitamin C Synthesized	Vitamin C Ingested in Diet (Average)	Vitamin C Dosage Recommended	Vitamin C Recommended by Linus Pauling
Early Humans	???mg/day data unavailable	2,500-9,000mg/day (100.0 – 360.0 mg/kg) ³	NA	NA
Human Male	0mg/day	≤100mg/day (<1.1 mg/kg) ¹³	90mg/day (1.0 mg/kg) ⁹	1,750-3,500mg/day (19.7 – 39.4 mg/kg) ³
Human Female	0mg/day	≤100mg/day (<1.1 mg/kg) ¹³	75mg/day (1.0 mg/kg) ⁹	1,750-3,500mg/day (22.9 – 45.8 mg/kg) ³
Chimpanzees & Orangutans	0mg/day	~4,000mg/day (~25.2 mg/kg) ²⁴	NA	NA
Gorillas	0mg/day	~4,000mg/day (~25.2 mg/kg) ²⁹	NA	NA
Guinea Pigs	0mg/day	~100mg/day (~100 mg/kg) ^{16,17}	100mg/day (100 mg/kg) ^{16,17}	NA
Cows, goats, sheep, mice, squirrels, gerbils, rabbits, cats, dogs	All synthesized, and as much as 13,000 mg/day in goats (166.7 mg/kg) ²⁶	NA, but herbivores consume vitamin C in their diets	NA	

Table 1. Vitamin C Ingestion in Various Mammalian Species

vitamin C,²⁵ and plasma concentrations around 10 mM were sustained for at least 4 hours which, based on preclinical studies, is sufficient to kill cancer cells.

Cantley and Yun's review concluded that since patients were only treated with vitamin C orally in the Mayo Clinic studies, those studies do not disprove high dose vitamin C's efficacy as a cancer treatment.

With this new understanding of past studies, there have been a number of recent phase I/II clinical trials and reports on the safety and efficacy of high dose vitamin C as a treatment for cancer – either as monotherapy or in combinational therapy. These were reviewed in 2018.²⁶ Virtually all studies show improved quality of life for cancer patients by minimizing pain and protecting normal tissues from toxicity caused by chemotherapy. Additionally, vitamin C showed synergistic effects when combined with radiation and standard chemotherapies. Since these studies were not designed as large-scale, randomized controlled trials, the efficacy of high dose vitamin C therapy remains to be determined.

The mechanisms by which vitamin C can affect cancer cells remain only partially elucidated. In a recent review article, Cantley and coworkers discussed the possible mechanisms and reported work in his laboratory on the effect of vitamin C on colorectal cancer cells with the BRAF or KRAS mutations.²⁷ Cancer cells with these mutations are highly dependent on glycolysis. At the high pharmacological levels of ascorbate achieved with intravenous injection,

and in the presence of catalytic metal ions, ascorbate can induce oxidative stress through the generation of hydrogen peroxide (H₂O₂).²⁸ Other investigators have also reviewed the potential cellular mechanisms by which vitamin C could be cytotoxic for cancer cells.^{29,30}

In Cantley's studies, administration of daily high dose vitamin C injections to mice engineered to develop KRAS-driven colon tumors, resulted in the mice developing fewer and smaller colon tumors compared with the control mice. It is noteworthy that the dose of vitamin C used intravenously in these studies was equivalent to a person eating 300 oranges (~15,330 mg of vitamin C), and as discussed earlier, oral intake of even such a massive dose could not achieve the same blood level.

Other investigators have studied intravenous vitamin C in clinical studies of pancreatic cancer, a typically lethal cancer driven by KRAS mutations.²⁸ Pharmacological ascorbate also inhibits the growth of pancreatic tumor xenografts and displays synergistic cytotoxic effects when combined with gemcitabine in pancreatic cancer. Phase I trials of pharmacological ascorbate in pancreatic cancer patients have demonstrated safety and potential efficacy.

Withal the above, no proven therapeutics have emerged, despite decades of effort. One of the problems with this area of research is that vitamin C is not patentable, so there is no incentive for pharmaceutical manufacturers to support investigations in this field.

Vitamin C and Health

Epidemiological studies of vitamin C and E, the most prevalent natural antioxidant vitamins, suggest that supplement users have a lower rate of mortality. In 1992 Enstrom conducted a cohort study of 11,348 adults, and found that the men who consumed the most vitamin C (≥ 300 mg/day; 3.6 mg/kg) had a 42% lower death rate from all causes and lived up to 6 years longer than men in the lowest vitamin C intake group, who consumed ~ 60 mg/day (~ 0.7 mg/kg). Women in the high intake group had a 10% lower overall death rate.³¹

A study of 13,421 Spanish university graduates followed for a mean of 11 years found that cardiovascular mortality was lower in the tertile with the highest vitamin C intake.³²

Why is Scurvy Uncommon?

Although scurvy results from inadequate intake of vitamin C, clinical scurvy is uncommon; even after vitamin C is removed from the diet, scurvy takes weeks to occur because of autoregulatory mechanisms that maintain blood levels.

When plasma concentrations of vitamin C fall below 70 $\mu\text{mol/L}$ (around the saturation level of plasma), vitamin C is reabsorbed in the kidneys through sodium dependent transporter SCVT-1. When plasma concentrations rise above 70 $\mu\text{mol/L}$, SCVT-1 is turned off, and vitamin C is no longer passively reabsorbed but rapidly excreted, leading to a plasma half-life in that situation of about 2 hours.^{33,34}

Moreover, vitamin C exists in the body in both a reduced form (ascorbic acid – the most common) and an oxidized form (dehydroascorbic acid). Erythrocytes can recycle the oxidized form back to the reduced form, thus maintaining plasma levels of ascorbic acid. Because of the ability to recycle the oxidized form, and reabsorption from SCVT-1, the half-life of plasma vitamin C has been reported to be between 8 and 40 days when under the saturation level.

Though early explorers knew nothing of these pharmacokinetics, they knew that scurvy would only appear after prolonged ocean voyages. Dr. James Lind is credited with conducting the first controlled clinical trial in 1747. He divided 12 scorbutic sailors into 6 groups of 2 sailors each, and gave different dietary supplements to each; only the pair that received citrus fruits recovered well. Nonetheless, inertia and skepticism prevailed then as they do now, and it was not until around 1800 that citrus juice became a mandatory supplement in the British Navy. British sailors have been called “Limeys” ever since.

DISCUSSION

Because there have been so many conflicting reports in the scientific literature about the benefits of vitamin C, most physicians probably regard Linus Pauling’s ideas about vitamin C’s abilities to prevent cancer and the common cold with skepticism. However, epidemiological studies are complicated by the multiple variables that are hard to control for.

Pauling considered our inability to manufacture vitamin C to be the evolutionary legacy of our previously fruit-rich diet. Genetically, it is due to a deletion mutation of the GULO gene that is necessary for the final step in biosynthesis, and this appears to be the result of the accumulation of random mutations that would have conferred no evolutionary disadvantage provided adequate amounts were ingested. Indeed, other primates that do not manufacture vitamin C, such as gorillas and orangutans, eat a diet exclusively of fruits, leaves, and vegetables.

Although some animals are known to have a very low incidence of cancer (e.g. elephants, chimpanzees, mole rats, and bowhead whales), this is not attributed to a diet rich in vitamin C, but rather to specific genetic properties.³⁵

The human RDA for vitamin C has been increased from the original 60 mg/day (0.7 mg/kg) to 90 mg/day (1.0 mg/kg) for males, and 75 mg/day (1.0 mg/kg) for females; others have suggested an intake of up to 200 mg/day (2.4 mg/kg).^{2,10,13} This amount does not adequately reflect the early vitamin C-rich diet of man as an herbivore, or the vitamin C-rich diet of wild primates.

If one concludes from the conflicting studies in the literature that large doses can be beneficial, the question then remains: how much should one eat every day to assure homeostasis or complete saturation?

Granted that it is virtually impossible to achieve with oral ingestion the plasma levels obtainable with intravenous injection, large oral doses pose little risk to humans because we are able to excrete excess vitamin C in the urine. It is notable that our mammalian counterparts that have also lost the ability to synthesize vitamin C ingest far more than the minimal requirement, but do so by eating more or less continuously throughout the day.

Pauling chose to ingest a total of 18,000 mg/day (220 mg/kg), taken at different times, to achieve this saturation state.⁵ The key phrase in that policy may be “taken at different times.” Instead of taking 5,000 mg/day (60 mg/kg) at once, perhaps we should be taking 1,000 mg (12 mg/kg), five times throughout the day. This may be inconvenient, but perhaps this is how to obtain the benefits of a high intake of vitamin C.

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