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Are Recommended Daily Allowances for Vitamin C Adequate?

(ascorbic acid/diet/optimum health)

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ABSTRACT **The Recommended Dietary Allowance of vitamin C (ascorbic acid) for adults has now been set at 45 mg day^{-1} by the U.S. Food and Nutrition Board. This intake suffices to prevent scurvy in most people. It is, however, much less than the optimum intake, the intake that leads to the best of health. A larger intake decreases the incidence and severity of the common cold and other diseases. Ascorbic acid has antiviral and antibacterial activity and is required for phagocytic activity of leukocytes. Several arguments indicate that for different human beings the optimum intake lies between 250 mg day^{-1} and a much higher value, 5000 mg day^{-1} or more. It is proposed that the present Recommended Dietary Allowance of 45 mg day^{-1} of vitamin C for adults be renamed the Minimum Dietary Allowance, defined as the amount needed to prevent scurvy, and that, after consideration of the evidence about intake and the best of health, there be formulated another category of values, the Recommended Daily Intake, with the suggested range of 250 mg day^{-1} to 4000 mg day^{-1} of ascorbic acid for an adult.**

The Recommended Dietary Allowance (RDA) of ascorbic acid (vitamin C) has now been set at 45 mg day^{-1} for adults (35 for infants, 60 for pregnant women, and 80 for lactating mothers) by the Food and Nutrition Board of the National Academy of Sciences–National Research Council (1). (These values are about 25% lower than those recommended in 1968.) The question of whether an intake of about 45 mg day^{-1} is adequate for the good health of most people was raised in 1949 by Bourne (2), who suggested that 1000 or 2000 mg day^{-1} might be the correct amount. In 1966, Stone (3, 4) concluded that the optimum rate of intake is 3–5 g day^{-1} for most people, and in 1970 I supported this estimate (5).

The ratio of these quantities to the official RDA is about 50 but does not represent a great difference of opinion about the interpretation of the evidence, because, in fact, two different questions are being discussed. First, are the RDA's for vitamin C adequate to prevent overt manifestations of scurvy? Second, what intake of vitamin C leads to the best of health?

A discussion of whether the RDA's for vitamin C are adequate has recently been published in these PROCEEDINGS by Jukes (6). He does not state what he means by adequate; he gives arguments bearing on both of the above questions, and seems to conclude that the RDA's are adequate for both. Some of his arguments are discussed below.

The meaning of RDA

The Food and Nutrition Board has stated in its reports that the RDA's are the amounts of vitamin C and other nutrients that protect against overt manifestations of scurvy and other deficiency diseases, and are not the amounts that lead to the best of health. This point has been recently emphasized by Harper, the chairman of the Committee on Recommended Dietary Allowances of the Food and Nutrition Board (7). He quotes the statement by the chairman of the first committee on RDA's that they "are not recommendations for the ideal diet," and also the statement of another nutritionist (Hegsted) that the term "recommended allowance" was adopted "*to avoid* any implication of finality or ... optimal requirements."

The prevention of scurvy

The recent decrease in the RDA from 60 to 45 mg day^{-1} for ascorbic acid was made largely from consideration of the work of Hodges *et al.* (8), who studied six subjects, and concluded, in agreement with earlier investigators, that 10 mg day^{-1} is probably enough to prevent scurvy in most people. Although the number of subjects in all studies of experimental scurvy is small and little information about individual differences is available, it seems likely that the present RDA is adequate to prevent scurvy.

The optimum intake of vitamin C

The Requirements of Animals. It is unlikely, because of the burden of the machinery, that animals would synthesize more ascorbic acid than the amount required for optimum health (9). The amounts made by mammals when calculated for 70 kg body weight are 3–19 g day^{-1} and similar amounts may be near the optimum for man. The animals studied range in weight from the mouse (20 g body weight) with a rate of synthesis of 10 g day^{-1}/70 kg to the goat (50 kg) with a rate of synthesis of 13 g day^{-1}/70 kg (10). Values for the rat under various conditions of stress range from 3 to 15 g day^{-1}/70 kg (11–13).

The recommended purified diets (14) for the guinea pig and the monkey, animals requiring exogenous vitamin C, contain 1100 mg and 1250 mg of ascorbic acid per 10,000 kJ of food energy (corresponding to a 70-kg man), and a diet adequate for almost all animals contains 4100 mg/10,000 kJ (15). These values presumably approximate the optimum intake, and may well be pertinent to man.

Yew (16) reported that growth rate and other measures of good health indicate an optimum intake of 3.5 g day^{-1}/70 kg for guinea pigs. Jukes criticized her conclusion that the value suggests a similar value of the optimum intake for man, because of the great difference in size. The constancy of rate of synthesis on a weight basis by other animals indicates, however, that the extrapolation to man is significant. Yew's observations accordingly provide additional support for the

Abbreviation: RDA, Recommended Dietary Allowance; RDI, Recommended Daily Intake.

conclusion that the optimum rate of intake for man is in the range of a few grams/day.

The Evolution Argument. Ascorbic acid differs from other vitamins in that an exogenous source is required by only a few animal species. It has been pointed out (17, 2) that this fact indicates that the amount contained in a diet of raw natural plant food is less than the optimum intake. If the amount of an essential substance contained in the available food is greater than the optimum requirement, a mutant that had lost the machinery for manufacturing the essential substance would have an advantage over the wild type of the species, in that it would have been relieved of the burden of developing and operating the machinery. [This effect has been verified by Zamenhof and Eichhorn (18) by experiments involving competition between different strains of microorganisms.] For ascorbic acid, the average value for 110 raw natural plant foods is 2.3 g/day per amount of food for 70 kg body weight (range 0.6–16 g, except for nuts and grains, which contain none) (17). Animals of many species must surely have lived for long periods of time on a diet providing 2.3 g day^{-1} or more of ascorbic acid (per 70 kg of body weight), yet only a few species have lost the ability to synthesize this important substance. Hence this value probably represents a lower limit to the optimum intake. The loss of the ability to manufacture ascorbic acid by a few species of animals, including the primates, presumably occurred while the primitive ancestor was living in an environment that provided an especially large amount of the substance.

Jukes (6) has criticized this argument, but his criticisms seem to have little weight. He suggested "that loss of ascorbic-acid-synthesizing power in man was probably a neutral change when it occurred, because primates in 'natural' conditions have diets that contain adequate amounts of vitamin C, and that the mutation entered the genome by genetic drift." This idea fails, however, to explain why similar "genetic drift" did not occur for many other species. He states also that "loss of ascorbic-acid-synthesizing ability would be extremely unlikely to take place as an evolutionary change unless the ascorbic acid requirement were comparatively small, for the change would greatly restrict the environmental niche that humans could inhabit if their requirement were high." There is an obvious flaw in this argument. The loss of the ability to synthesize ascorbic acid occurred in the common ancestor of man and the other primates (presumably in a region where the food was especially rich in this substance). Jukes suggests that the process of evolutionary change in that region and at that time was influenced by the possibility that descendants of that ancestor, millions of years later, would broaden their environmental niche by moving into temperate and subarctic areas. This argument cannot be accepted. Considerations of possible effects in the distant future began to determine events only after man's intelligence and foresight had been developed.

Protection Against Disease. The evidence is strong that an increased intake of vitamin C decreases the amount of illness associated with the common cold. Among the earlier studies, which have been discussed before (5, 19), I mention that of Cowan, Diehl, and Baker (20), who reported a 31% decrease in respiratory illness per subject when they received 200 mg day^{-1} of ascorbic acid as compared to those receiving a placebo, and that of Ritzel (21), who reported a 63% decrease in illness for subjects receiving 1000 mg day^{-1}. More recent studies are those of Anderson, Reid, and Beaton (22), who reported a 30% decrease in illness when subjects received 1 g day^{-1} plus an additional 3 g day^{-1} for first 3 days of a cold, Charleston and Clegg (23), who reported a 58% decrease when subjects received 1 g day^{-1}, and Coulehan *et al.* (24), who reported a 30% decrease in illness for younger children receiving 1 g day^{-1}, and a 36% decrease for older children receiving 2 g day^{-1}. Very little protective effect was observed when a suspension containing large numbers of cold viruses was instilled into the nasal cavities of subjects receiving 3 g day^{-1} (Walker, Bynoe, and Tyrrel, 25); probably the protective effect of ascorbic acid can be overwhelmed by a massive exposure to the virus.

The amount of illness with other diseases is also decreased. Anderson, Reid, and Beaton (22) reported a decrease in amount of illness in subjects receiving 1 g day^{-1} of ascorbic acid, relative to those receiving a placebo, of 40% for nonrespiratory diseases, as well as 30% for respiratory diseases. Greenwood (26), from a study of over 500 patients, concluded that "a significant number of patients with disc lesions were able to avoid surgery by the use of large doses of vitamin C." The intake of his subjects was 1 g day^{-1}. The effectiveness of ascorbic acid in controlling vertebral disc lesions may be attributed to its essential role in the synthesis of collagen. The same property is presumably responsible for the recognized value of an increased intake of the vitamin in facilitating the healing of wounds, fractures, and burns (references are given in ref. 19).

The Antiviral Activity of Ascorbic Acid. Many investigators have studied the inactivation of viruses *in vitro* by ascorbic acid. Jungeblut in 1935 (27) reported that ascorbic acid inactivates poliomyelitis virus. Jungeblut and others (references given by Stone in ref. 19) also reported inactivation by ascorbic acid of herpes virus, vaccinia virus, hoof-and-mouth virus, rabies virus, tobacco mosaic virus, and bacterial viruses. A thorough study of inactivation of bacterial viruses by ascorbic acid has been made by Murata and his coworkers (28, 29), who have shown that several bacterial viruses are 99% inactivated by exposure for 60 min to ascorbate concentrations that can be reached in the blood by a large intake. Murata and Kitagawa (30) found that the inactivation does not occur in the absence of oxygen. From this and other observations they concluded that it results from single-strand scissions of phage DNA by free radicals formed during the autoxidation of ascorbic acid.

Some protection against viral diseases (poliomyelitis, hepatitis, fever blisters, shingles, virus pneumonia, measles, chicken pox, virus encephalitis, mumps, infectious mononucleosis) has been reported by several investigators. References are given by Stone (19).

There is evidence that viruses are involved in some human cancers. Vitamin C might provide some protection against these cancers, through its antiviral activity. Moreover, an increased intake of the vitamin increases the strength of the intercellular cement and hence should increase the resistance of tissues to invasion by metastases and infiltration by malignant tumors (31).

The Antibacterial Activity of Ascorbic Acid. The inactivation *in vitro* of diphtheria toxin by ascorbic acid was reported in 1935 by Jungeblut and Zwemer (32). Jungeblut and others

later reported inactivation of tetanus toxin, staphylococcus toxin, and dysentery toxin (references given by Stone in ref. 19). Bacteriostatic and bactericidal action of ascorbic acid, 2 mg dl^{-1}, against *Staphylococcus aureus* and several other bacteria was observed by Gupta and Guha in 1941 (33) and also by others (19). Some success in controlling various bacterial infections in man by an increased intake of ascorbic acid has been reported (references given by Stone in ref. 19). The possibility that an increased intake of vitamin C has some general protective effect against both bacterial and viral diseases should not be rejected.

One of the most potent defense mechanisms of the body is phagocytosis by blood leukocytes and the macrophages of the reticuloendothelial system. It has been known for 30 years that ascorbic acid is needed for effective phagocytic activity of leukocytes (34), the concentration needed being about 20 μg per 10^8 cells. It is known that wounds, infections, and other stresses lead to a decrease in the serum and leukocyte concentrations of ascorbic acid. Hume and Weyers (35) found that the average concentration of ascorbic acid for subjects receiving an ordinary Scottish diet was 20.0 (SD $\pm$3.3) μg per 10^8 cells. On the first day of a cold, the concentration dropped to 10.3 (SD $\pm$0.3) μg, and remained below the phagocytically effective level for 3 days. A regular intake of 1 g of ascorbic acid per day plus 6 g/day for 3 days when a cold is contracted sufficed to keep the concentration high, above 23.9 μg per 10^8 cells. An intake of 200 mg day^{-1} was not sufficient; the concentration on the first 3 days of a cold fell into the range of 8–14 μg per 10^8 cells. The evidence is strong that an intake of ascorbic acid much larger than the RDA is needed to provide protection against the secondary bacterial infections that often accompany the common cold, as well as against other bacterial infections, which often are incurred under conditions of stress.

It is likely that the bactericidal effect of ascorbic acid takes place by way of free radicals formed during oxidation of ascorbic acid in the presence of hydrogen peroxide. Hydrogen peroxide is formed during the reaction of ascorbic acid and oxygen (50), and macrophages lack peroxidase. It has been shown that ascorbic acid and hydrogen peroxide together have a pronounced bactericidal effect, which is increased by a small concentration of copper ions (36, 37). The presence of free radicals has been demonstrated by electron-spin resonance spectroscopy (38), and the bactericidal activity is completely inhibited by free-radical inhibitors (37).

Vitamin C and Serum Cholesterol. The evidence for a negative correlation between intake of ascorbic acid and concentration of cholesterol in the blood for both guinea pigs and humans has been reviewed by Krumdieck and Butterworth (39). The mechanism of this effect seems to be that an increase in concentration of ascorbic acid leads to an increase in the rate of conversion of cholesterol to bile acids (40). The recognized correlation between the serum cholesterol level and the incidence of coronary heart disease indicates that an increased intake of vitamin C should be of value in providing some protection against heart disease.

This conclusion is supported by the results of correlation analysis between mortality ratios of ischemic heart disease, cerebrovascular accidents, and other causes of death, and the intakes of ascorbic acid and other nutrients, reported by Knox (41). Large negative correlations were found between ascorbic acid intake and ischemic heart disease ($r = -0.49$) and also cerebrovascular disease ($r = -0.68$); the latter was the largest negative correlation found in the analysis. Krumdieck and Butterworth, in their discussion of the pathogenesis of atherosclerosis (39), conclude that "vitamin C seems to occupy a position of unique importance by virtue of its involvement in two systems: the maintenance of vascular integrity and the metabolism of cholesterol to bile acids," and suggest that it is pertinent to consider the adequacy of the present recommended dietary allowances.

Vitamin C, Mental Alertness, and Well-Being. Many people have referred to an increase in mental alertness and general feeling of well-being accompanying an increased intake of vitamin C, although some have reported a failure to observe such an effect. One carefully planned and executed study about vitamin C and mental alertness is that of Kubala and Katz (42). The subjects were schoolchildren and college women from four schools. The blood plasma concentration of ascorbic acid was determined, and the subjects were divided into two groups, less than or greater than 1.10 mg dl^{-1}. Subjects in each school were matched in pairs on a series of socioeconomic indicators, and the matched groups were compared with respect to average intelligence quotients (IQ). In each of the four schools, the average IQ was higher for the high-ascorbic-acid group than for the other group; the difference for the combined groups (4.51 IQ units) was statistically significant at the level $P < 0.05$. All the subjects then received a supplementary glass of orange juice (90 mg of ascorbic acid) each day for about 4 months, and the IQ was again measured. The average increase in IQ was 0.02 for the high-ascorbic-acid group and 3.54 for the low group, the difference being statistically significant at the level $P < 0.05$. Two further tests were made, after periods without and with supplementary orange juice. There is an approximately linear relationship between the average IQ and the average plasma concentration of ascorbic acid for the four values of average IQ (p. 35 of ref. 5). Kubala and Katz suggest that the higher values of the measured IQ result from an increase in "alertness" or "awareness" caused by the improved nutritional state, and that the subjects with plasma concentration of ascorbic acid less than 1.1 mg dl^{-1} were functioning at less than maximum capacity. These observations accordingly indicate that an intake of vitamin C that does not provide a plasma concentration greater than 1.1 mg dl^{-1} is not adequate, in that it does not permit the person to function at maximum capacity. The daily intake required to reach this level is about 110 mg.

A study of the general state of health in relation to intake of vitamin C has been reported by Cheraskin and Ringsdorf (43). The 1086 subjects were physicians or dentists and their wives, who were followed over a period of 8 years. The number of clinical symptoms and signs of imperfect health was determined (Cornell Medical Index Health Questionnaire), and the intake of vitamin C was obtained through a 7-day survey. (For all subjects the average intake was 140 mg day^{-1}.) It was found that for each age group the number of clinical symptoms and signs decreased with increase in the intake of vitamin C. The average values for all subjects were 17.7 symptoms and signs when intake was less than 100 mg day^{-1}, 15.9 when 100–199 mg day^{-1}, and 14.6 when 200 mg day^{-1} or more. There is clear indication that some improvement in health is associated with an increase in intake from below 100 mg day^{-1} to between 100 and 200 mg day^{-1}, and a further

improvement with further increase to more than 200 mg day^{-1}.

The average numbers of symptoms and signs for all subjects with age less than 40, 40 to 49, and 50 or more are 14.6, 16.7, and 18.0, respectively, the increase representing the effect of aging on the state of health. These numbers cover the range 3.4, as compared with the range 3.1 for change in intake of vitamin C.

In fact, the average numbers of symptoms and signs for high intake, age 50 or more (17.1), medium intake, age 40 to 49 (16.8), and low intake, age less than 40 (16.6) are nearly the same. From this evidence, and for this population, I reach the tentative conclusion that high intake of vitamin C (more than 200 mg day^{-1}) is associated with a physiological age of about 16 years less than that associated with low intake (less than 100 mg day^{-1}). The increment in age that is associated with a doubling of morbidity and mortality is 8 years; hence there is indication here that age-specific morbidity and mortality may be decreased by as much as 75% by changing from a low to a high intake of vitamin C.

The Significance of the Renal Tubular Reabsorption of Ascorbic Acid. Ascorbate ion is small, and it passes readily through the pores of the renal glomerular filters. When the serum concentration is small, almost all of the ascorbate is returned to the blood by the process of tubular reabsorption. The mechanism of tubular reabsorption is saturated when the serum concentration reaches about 1.6 mg dl^{-1} (the value is somewhat different for different people, with a range of about 1.0–2.5 mg dl^{-1}). The ascorbic acid above this serum concentration is rapidly eliminated in the urine. Below the level of saturation of tubular reabsorption the serum concentration in mg dl^{-1} is about 1% of the intake in mg day^{-1} (range 0.4–2%), and above this level it continues to increase, with slope of about 1.4×10^{-4} mg dl^{-1} per mg day^{-1}; that is, about 1.4% of the slope observed for low intake (44–46). The concentration in leukocytes and tissues increases with increase in the serum concentration.

It has been customary to say that the serum concentration at which tubular reabsorption is saturated corresponds to saturation of the tissues, and that the increased urinary elimination of ascorbic acid above this concentration represents the effort of the body to rid itself of an unneeded excess of the vitamin. The main difference of opinion in the past has been as to whether the intake of 100–250 mg day^{-1} required for "tissue saturation" is essential to normal good health, or whether one half or one quarter of this intake might be adequate. I believe that this entire argument is fallacious. First, saturation of tubular reabsorption does not correspond to tissue saturation; instead, the concentrations in blood and tissues continue to increase with increased intake above this level, although at a much lower rate, and there is much evidence that the increased intake improves health. Moreover, not all of the large intake is excreted in the urine, but only a fraction, about 60%, and some of the retained vitamin may be put to good use. Second, I believe that the concentration corresponding to the saturation of the mechanism of tubular reabsorption is a lower limit for the optimum concentration, and hence for the intake of the vitamin, because this mechanism involves a burden on the organism; because this mechanism is a burden, it would not have been developed an unneeded excess capacity during the course of evolution. Instead, it would have been developed to a lower capacity, thus representing a compromise between the benefit of additional conservation of the vitamin and the burden of the additional machinery that would be needed for this additional conservation (9, 47).

Conclusion

The recommended daily intake of ascorbic acid for an adult male was set by the Food and Nutrition Board in 1943 at 75 mg day^{-1}. It was later reduced to 60 mg day^{-1}, and in 1973 to 45 mg day^{-1}. The principal consideration in setting these values has been the prevention of scurvy. The value for Britain was set in 1969 at 30 mg day^{-1}. In a book (48) coauthored by the chairman (Passmore) of the British Panel on Recommended Allowances of Nutrients, there is the following statement: "The chief argument against the desirability of full saturation is that few people in Britain ever achieve it. It would need a revolution in British habits to eat sufficient fruit and vegetables to provide the vitamin at a level comparable to that needed by the guinea pig." It is likely that similar considerations have been involved in decisions of the U.S. Food and Nutrition Board. The decreased availability of foods of high quality in recent decades may have been in part responsible for the decision to decrease the RDA.

It is, I believe, misleading to call these small intakes the Recommended Dietary Allowances, permitting them to be interpreted, as is often done, as the intakes that lead to the best of health. I suggest that instead they be called the Minimum Dietary Allowances.

In addition, I suggest that the Food and Nutrition Board consider formulating recommendations about the ranges of intakes of vitamin C and other nutrients that, on the basis of the available evidence, include the optimum intakes for most people. These ranges could properly be described as recommended; they might be called the Recommended Daily Intakes (RDI). For vitamin C, I suggest that the RDI for an adult be 250 mg day^{-1} to 4000 mg day^{-1}. The lower limit, 250 mg day^{-1}, is suggested by several considerations. First, it would lead to saturation of the mechanism of renal tubular reabsorption for most people, and hence would include the intakes at which ingested ascorbic acid most efficiently increases the concentration in blood and tissues. Moreover, Cheraskin and Ringsdorf's observations (43) indicate that for the population studied by them an intake of 200 mg day^{-1} or more is associated with better health than an intake of 100–199 mg day^{-1}. Some other reported benefits of an intake of about 200 mg day^{-1} of vitamin C in addition to that in the usual diet have been mentioned above. The upper limit remains uncertain. Although ascorbic acid is described as having very low toxicity, concern has been expressed about increased production of oxalic acid following an increased intake of the vitamin. A careful study (49) showed, however, that for normal males the ingestion of less than 4 g day^{-1} of ascorbic acid resulted in a negligible increase in urinary oxalate. Many people have ingested 4 g day^{-1} or more of ascorbic acid over long periods of time, with no serious side effects, and this intake may be judged to be as safe as many other dietary and prophylactic measures. The upper limit, 4 g day^{-1}, of the recommended range accordingly seems reasonable.

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