
Vitamin C and Infectious Diseases

HARRI HEMILÄ

University of Helsinki, Helsinki, Finland

INTRODUCTION

In the early part of this century it was thought that low vitamin C intake may decrease resistance to infections (1–6). Nevertheless, the precise role of vitamin C in infectious diseases is still poorly understood. The purpose of this chapter is to review the literature relating vitamin C intake to the susceptibility to and severity of infections. Two exhaustive searches of the old literature on studies about vitamin C and infections have been carried out, but the data of the original publications were not thoroughly analyzed in either of these reviews (7,8).

VITAMIN C AND THE COMMON COLD

In the early 1970s Linus Pauling suggested that vitamin C supplementation may decrease the incidence and severity of common cold infections (9,10). His conclusions were based on earlier studies in which groups supplemented with vitamin C showed some benefit. Since Pauling has made the issue popular, a large number of studies have been carried out to examine whether vitamin C supplementation has an effect on colds (8,11–15).

Severity of Common Cold Episodes

There are eight published studies that have examined the effect of high-dosage (≥ 2 g/day) regular vitamin C supplementation on the duration and severity of common cold episodes (Table 1) (16–25). Each of these studies found a statistically significant decrease in at least one outcome. If the p values found in the eight studies are combined by the Fisher method (28,29), a very small combined p value results. Thus it is unlikely that the published differences in favor of vitamin C are caused by chance alone. All of the eight studies were placebo-controlled, double-blind studies and five of them were randomized (16,20,21

Table 1 Vitamin C and Common Cold Symptoms^a

Ref.	Subjects, country	No. of episodes in vitamin C group	Dose (g/day)	Effect on duration or severity ^b	p (1 - t)	$-2 \times \ln(p)$
16	Military recruits, USA	37 ^c	2	-72 ^d	0.016	8.27
17	Adults, USA	4 ^e	2	-50 ^f	0.023	7.55
18	Adults, USA	11 ^e	3	-30 ^g	0.005	10.60
19	Schoolchildren, USA	16	2	-29	0.006 ^h	10.23
20	Schoolchildren, Chile	38	2	-24	0.041	6.39
21,22	Adults, Canada	561	1 + 3 ⁱ	-21 ^j -5	0.008	9.66
23,24	Adults, USA	76	3 + 3 ⁱ	-17	0.025	7.38
25	Military recruits, USA	600	2	-5 ^f -3	0.012	8.85
Total:		1343	Median	-26	χ^2 (16 df) = 68.9 combined $p(1 - t) =$ 0.00000001	
			Mean	-31		
			Weighted mean	-15		

^aStudies in which ≥ 2 g/day of vitamin C was regularly administered were selected. In the case of short-term studies supplementation was initiated before the symptoms started and continued after the symptoms ended. For a more comprehensive list of the original data see Table 1 in Ref. 14. Anderson's 1972 study (26) was included as the dose was 4 g/day during the episodes although the regular dose was 1 g/day. Anderson's 1974 study was excluded since there is bias in the distribution of subjects in the study groups (26,27). In the case of the studies by Anderson (21) and Pitt and Costrini (25) the days indoors and the severity of symptoms, respectively, were selected as outcomes in the calculations. The weighted mean was calculated using the number of episodes in the vitamin C groups as the weight. The p values were recalculated when appropriate data were available. The combined p value was calculated by the Fisher method (28,29).

^bThe outcome is the duration of cold symptoms except when otherwise indicated.

^cThe number of subjects; the number of episodes is not given in the report.

^dDays of morbidity for sore throats.

^eInduced rhinovirus infection.

^fSeverity of symptoms.

^gSeverity of symptoms at the fourth day after challenge.

^h p Value for comparing the sickness days between the groups.

ⁱAt the onset of a cold episode an additional 3 g/day was given for 3-5 days.

^jDays indoors due to a cold episode.

23,25). Consequently it is unlikely that biases between the study groups or the placebo effect would cause the consistent differences in favor of vitamin C.

From the published studies it is clear that vitamin C has physiological effects on common cold symptoms. Nevertheless, there have been great quantitative differences in the effects (Table 1; 14,15), and it is not clear what the practical significance of vitamin C supplementation in the treatment of colds is. Most of the controlled studies have administered vitamin C regularly, whereas in the treatment of symptoms it would appear more reasonable to start supplementation immediately after the first symptoms, but it is not clear whether the effects of therapeutic supplements are comparable to those found with regular supplements (Table 1).

Incidence of the Common Cold

If high vitamin C doses decreased common cold incidence substantially, the most convincing evidence should be seen in studies using large vitamin doses and recording large numbers of cold episodes. However, none of the four largest studies using ≥ 1 g/day of vitamin C found a significant decrease in cold incidence (Table 2; 21,25,30,31). Furthermore, the pooled estimate does not suggest any real difference between vitamin C and placebo groups. Consequently, high-dose vitamin C supplementation has no meaningful preventive effect on cold episodes in subjects comparable to those used in the four major studies.

Nonetheless, although the major studies show that a high vitamin C dose per se does not prevent colds to any meaningful extent in large segments of the general population, this should not be interpreted as definite evidence that vitamin C intake can have no effects on cold incidence in any conditions. A number of smaller studies have found a statistically significant decrease in cold incidence in subjects supplemented with vitamin C. It is possible that some of the positive results are caused by the use of different kinds of subjects or by other differences in the experimental conditions compared to the major studies in Table 2. In a recent metaanalysis of three studies using subjects under acute heavy physical stress it was calculated that the pooled risk ratio (RR) of cold episodes in vitamin C groups was 0.50 (90% confidence interval [CI]: 0.37, 0.66; $p(1 - t) = 0.00003$), suggesting that vitamin C intake can affect cold incidence in certain specific conditions (33).

Furthermore, it is possible that some of the positive results are not due to the high vitamin C dose used, but to the correction of marginal deficiency in the control group. In this respect the randomized double-blind study by Baird et al. (34) is particularly interesting as the dietary vitamin C intake was rather low, 50 mg/day, and the supplement dose was also small, 80 mg/day. This study is relevant to the question of whether marginally low intake in the control group (50 mg/day) increases susceptibility to colds compared to the

Table 2 Vitamin C and Common Cold Incidence^a

Ref.	Subjects, country	Vitamin C dose (g/day)	Duration (months)	No. of episodes		RR	90% CI
				Vitamin C	Placebo		
21	Adults, Canada	1	3	561	609	0.93	0.84, 1.03
30	Women, UK	1	3	627	690	0.93	0.85, 1.03
25	Military recruits, USA	2	2	600	619	1.00	0.91, 1.10
31	Schoolchildren, Sweden	1	3	657	622	1.08	0.98, 1.19
Totals:				2,445	2,540	RR _{pool} : 0.99	0.94, 1.03

^aStudies in which ≥ 1 g/day of vitamin C was regularly administered and >300 cold episodes were recorded were selected. The smaller studies using ≥ 1 g/day of vitamin C excluded from this table contain approximately 1500 episodes in all (cf. Table 1 in Ref. 14) and thus their weight is small compared to that of the studies included. Anderson's 1974 study is excluded since there is bias in the distribution of subjects in the study groups (26,27). The RR and CI values were calculated with the normal approximation of the Poisson distribution and the pooled values were calculated using the inverses of variances as weights (32). RR, relative risk; CI, confidence interval.

somewhat higher intake (130 mg/day). There were 184 and 135 cold episodes among the 133 and 61 male subjects administered vitamin C and placebo, respectively. Thus, among Baird's male subjects receiving higher vitamin C intake (130 mg/day) the RR of cold episodes was 0.63 (90% CI: 0.52, 0.75; $p(1 - t) = 0.00002$). A few other studies are also consistent with the suggestion that low vitamin C intake increases the susceptibility to colds (34a). Even if the association of vitamin C intake and common cold susceptibility were largely limited to the marginal deficiency region, this could be of great importance globally. For example, vitamin A supplementation has been shown to decrease the mortality rate of children in several developing countries in which dietary vitamin A intakes are low (35); in developed countries vitamin A supplementation has no comparable effects.

Subgroup Differences in the Effects of Vitamin C on Cold Severity

Some of the common cold studies have compared the effects of vitamin C supplementation on different subgroups (Table 3; 21,36,37). Anderson et al. (21,36) carried out two studies with adults, both of which compared various subgroups. However, the experimental protocols of his studies differed considerably. In the first, subjects were given 1 g/day of vitamin C regularly over the entire study period and 3 g/day extra for 3 days during cold episodes (21). In the other study 1.5 g was administered on the first day of the cold episode and 1 g/day on 4 consecutive days (36); these subjects were also administered a regular dose of 0.5 g per week (i.e., 0.07 g/day), which is such a small dose that it should not affect the results. Thus the former study (21) may be considered one with regular supplementation (1–4 g/day), whereas the latter (36) may be considered one with therapeutic supplementation (1–1.5 g/day), i.e., supplementation starting only after the onset of cold symptoms.

In both studies Anderson found that vitamin C supplementation was more beneficial for subjects who had a low intake of fruit juices, which are a major dietary source of vitamin C (Table 3). This finding is biologically reasonable as supplementation should be most beneficial for people with low dietary intake. The effect of vitamin C status on cold duration was also studied by Coulehan, who determined the plasma vitamin C level in selected subjects administered placebo or vitamin C and divided the subjects of both study groups into three subgroups on the basis of vitamin C plasma levels (Table 4). Coulehan found that the duration of colds gradually decreased while the vitamin C level in plasma increased; however, the subjects with the highest plasma levels had the longest colds (Table 4; 38). Thus it appears possible that 1 g/day of vitamin C supplementation produced plasma levels that were too high for a subgroup of subjects. Still, there are no other data indicating that excessive vitamin C intakes or plasma levels could increase the duration of colds. Two studies comparing two different vitamin C doses found a greater decrease in the duration of colds in the group given the higher vitamin dose (19,23,24). The significance of Coulehan's puzzling observation thus remains unclear.

Children are an important source of common cold infections in the community (39), and therefore Anderson's observation in both studies that vitamin C is more beneficial to adults having contact with children is noteworthy (Table 3). Anderson also found other subgroup differences, but these were not consistent between the studies. For example, regular supplementation was more beneficial to people frequently in crowds, but this subgroup difference was not found in the therapeutic study (Table 3). It is possible that some of the further subgroup differences are caused by chance; however, different protocols in the two

Table 3 Effect of Vitamin C Supplementation on Colds in Certain Subgroups

	Effect on the "total days indoors"	
	1972 Study (21) regular supplement	1975 Study (36) therapeutic supplement
Anderson et al. studies (21,36)		
Daily juice		
0-3 oz	-48%	-33%
4+ oz	-22%	-22%
Contact with young children		
Yes	-46%	-40%
No	-17%	-13%
Frequently in crowds		
Yes	-34%	-25%
No	-17%	-29%
Smoker		
Yes	-30%	-31%
No	-31%	-22%
Sex		
Male	-36%	-25%
Female	-26%	-27%
Age (years)		
<25	-30%	<30 -37%
≥25	-31%	≥30 -15%
Student		
No	-39%	—
Yes	-18%	—
Usual colds		
2+	-43%	—
0-1	-13%	—
	Effect on the symptom	
	"Duration"	"Severity"
Carr et al. study (37)		
Twins living		
Together	+1%	+6%
Apart	-35%	-35%

studies (regular/therapeutic) can also determine which groups show the greatest benefits from supplements.

Carr et al. found that vitamin C had a considerable effect on twins living apart, but no effect on twins living together (Table 3). An obvious explanation of the difference is that twins living together exchanged their tablets to great extent. Two other studies with children found an increase in plasma (19) and urine (40) vitamin C levels in the placebo [sic!] groups, a finding which even more directly shows that tablet exchange may take place among playful children under study conditions. It is also noteworthy that in Carr's study

Table 4 Plasma Vitamin C Level and the Duration of Colds

Vitamin C level in plasma	Episodes (no.)	Mean duration (days)	Difference from low-placebo
Placebo group			
Low	20	5.6	0%
Middle	18	4.5	-20%
High	10	4.4	-21%
Vitamin C group (1 g/day)			
Low	22	4.0	-29%
Middle	15	2.7	-52%
High	13	6.8	+21%

Source: Ref. 38.

(37) the average duration of colds in both groups of twins living together (5.4 days) was intermediate between that of the vitamin C (4.9 days) and placebo (7.5 days) groups of twins living apart, also consistent with the notion that tablets were exchanged by twins living together. Carr's subgroup analysis is important in suggesting that in some studies with children the mischief of the subjects may have confounded the results and the observed difference may underestimate the true physiological effect.

Some Problems in the Interpretation of the Common Cold Studies

Many people have drawn more or less inappropriate conclusions about the vitamin C-common cold studies. From the studies published so far it is clear that Pauling (9,10) was correct in his general conclusion that vitamin C has effects on colds, on both their severity and incidence. Nevertheless, quantitatively he was substantially overoptimistic. Pauling based his quantitative conclusions (10) on the study by Ritzel on schoolchildren in a skiing school in the Swiss Alps (41,42), but such children are not a good representative sample of the general population. Thus, when Pauling implicitly extrapolated the results to all people (i.e., children at school and adults), he took a bold step and went wrong. Furthermore, Pauling's conclusion (10) that the 45% decrease in cold incidence in the vitamin group in Ritzel's study was caused by the high vitamin C dose (1 g/day) per se was also hasty. It is possible that the effect was due to the correction of marginal vitamin C deficiency in the control group, in which case a much smaller dose could have produced a similar effect. This interpretation is supported, for example, by Baird's study (34), as noted. The lack of effect of high vitamin C doses in the major studies (Table 2) also suggests that if the vitamin affects cold incidence it is in the low-intake range rather than in the high-intake range.

Several reviewers have drawn quite different conclusions about the effects of vitamin C on colds than Pauling. However, there are profound problems in many reviews of the topic. In one major review (43) there were data inconsistent with the original publications and the data were analyzed improperly (27,44). In another major review (45) some data were misrepresented and some other relevant data were not presented at all (44,46,47). In a brief review of vitamin C and colds in a major medical journal (48) a few explicit statements

were gravely inconsistent with the data in the original reports (44). Furthermore, the vitamin C–common cold trial carried out at the National Institutes of Health (NIH) in the middle of the 1970s (23), which appears to be the most influential study so far, was interpreted inappropriately (24). However, overtly negative conclusions from the original data are not a problem that appeared after Pauling made the issue popular, since in some earlier studies the authors' conclusions were much more negative than objective interpretation of the findings would have permitted (13).

It appears quite clear that the great quantitative variation in the results (Table 1; 14,15) has been an important factor hampering the conclusion that vitamin C has real effects on the severity of colds. However, it seems that there are also much deeper conceptual reasons for prejudice against vitamin C at the paradigm level, to use Thomas Kuhn's terminology (44,49–51).

There is a widespread belief that the sole physiological role of vitamin C is to prevent scurvy, and evidently this belief has generated strong prejudices against all other observed physiological effects of the vitamin (44,49,50). Nevertheless, vitamin C participates in the function of several enzymes that are unrelated to connective tissue metabolism (52–55), and as a major physiological antioxidant it can have numerous nonspecific biochemical effects. Consequently, there are no biochemical reasons to assume that the physiological effects of vitamin C are strictly limited to the prevention of overt scurvy. None of the three major reviews (43,45,48) discussed the possible effects of vitamin C on the immune system to provide a background to the examination of whether the effects of vitamin C on the common cold make any sense biologically. This is important as the evaluation of the effectiveness of a therapeutic method usually depends greatly on the possibility of rationalizing the method biologically, and not just on the interpretation of experimental results (56,57).

Furthermore, if a treatment bypasses the medical establishment and is marketed directly to the public there may be a temptation in the medical community to accept the first bad news that comes along uncritically without considering the entire body of relevant data (57). Vitamin C is of great interest among nonprofessionals and therefore such psychological effects may be pertinent. Finally, there are numerous obviously erroneous claims about the effects of vitamin C supplementation and a vast commercial exploitation of such claims. In the minds of critical people not engaged with vitamin C in particular, this kind of background may lead to a biased view of vitamin C in general.

VITAMIN C AND THE IMMUNE SYSTEM

The common cold studies suggest implicitly that vitamin C intake affects the immune system. There are many experimental data indicating that vitamin C has effects on the immune system, but the experimental data have been inconsistent to a large extent (58–61). Although the role of vitamin C in the immune system still is not clear, there are certain effects that may be physiologically relevant.

Protection Against Oxidants Produced During Infection

Phagocytes have an enzyme system which produces superoxide, hypochlorite, and other oxidants with the purpose of killing viruses and bacteria. Many of these oxidants may be harmful to the host cells if they are released into the extracellular medium (62,63).

Moreover, oxidants produced during viral infections may play some role in the appearance of symptoms (64–69). Vitamin C is an efficient reducing agent (antioxidant), and it may protect various kinds of cells against harmful oxidants (14,70–76).

Functions of the Phagocytes

The concentration of vitamin C in the phagocytes and lymphocytes is over 10 times higher than in plasma (77–83), suggesting that the vitamin has functional roles in these immune system cells. A decrease in the intracellular concentration of vitamin C occurs when phagocytes are activated in vitro (84,85) and during common cold infections (86).

Low vitamin C intake has been reported to decrease the phagocytic activity in guinea pigs (87–93) and monkeys (94), although no changes in phagocytosis were found in some studies (85,95,96). Vitamin C may also affect the chemotactic responsiveness of phagocytes (92–94,96–106). It seems possible that the effects of vitamin C on the phagocytes are mediated by antioxidant effects (107), as oxidants have been shown to suppress phagocyte functions (108–110). Furthermore, vitamin C has been reported to decrease neutrophil dysfunctions caused by corticosteroids (111–113).

The physiological significance of vitamin C intake to the function of human phagocytes in vivo is not clear. In certain pathological conditions vitamin C supplementation has been reported to normalize the functions of phagocytes (114–134), suggesting that vitamin C intake may be important in some situations. However, some of these effects could not be repeated (135), and in one study the ability of phagocytes to kill *Escherichia coli* in vitro was decreased when a healthy subject was administered 2 g/day of the vitamin (136).

Proliferation of T Lymphocytes

A number of studies have found that a higher vitamin C concentration increases the proliferative responses of T lymphocytes in vitro (124,137–144). Vitamin C supplementation has increased T-cell proliferative responses in some animal species (145–148). Some studies with human subjects administered vitamin C have reported an increase in lymphocyte proliferative responses (120,124,138,149–153), while some others found no changes (135,137,138,141,154,155). It seems possible that there are real effects of vitamin C supplementation, but they may be quantitatively relevant only in some specific groups of people.

The effect of vitamin C on T cells can be a nonspecific antioxidant effect, as some other reducing agents also increase the proliferative responses of lymphocytes (156–159). Moreover, it has been suggested that physiological oxidants suppress lymphocyte proliferation (160–162), providing a biological rationale for the effects of antioxidants.

Production of Interferon

Vitamin C has been reported to increase the induced production of interferon in cell culture (163–166) and in mice (167,168). However, vitamin C had no effect on interferon production in two lymphoblastoid cell lines induced by Sendai virus (165) and in mouse embryo cells induced by Semliki Forest virus (169).

Other Possible Effects on the Immune System

A few reports have suggested that vitamin C status may affect the production of antibodies and complement components, but the data are conflicting (58,59,145–147,170–175).

In one study with hospital patients a significant positive correlation was observed between natural killer (NK) cell activity and vitamin C concentration in leukocytes (176). In a study with healthy subjects vitamin C supplementation first led to a slight suppression of NK cell activity and thereafter to a significant enhancement (177). In patients with Chédiak–Higashi syndrome NK cell activity normalized during vitamin C supplementation (138). In normal mice vitamin C supplementation did not affect NK cell activity (178).

Several studies have found that vitamin C suppresses the replication of viruses in cell cultures (163,179–184), but the mechanism of this effect is not known. D-Isoascorbic acid also caused suppression of replication (180), suggesting a mechanism based on a non-specific antioxidant effect. It is not clear whether the effect is physiologically relevant. In one study vitamin C did not affect the replication of selected respiratory viruses in cell culture (185).

Under in vitro conditions vitamin C has been found to inactivate viruses and bacteria directly and to break deoxyribonucleic acid (DNA) (186–190), but the physiological significance of this effect is doubtful. Vitamin C is easily oxidized under in vitro conditions in the presence of transition metals (e.g., iron), causing the generation of reactive radicals. However, in healthy subjects the concentration of free iron ion in plasma is extremely low (191), so that such radical-forming reactions apparently do not occur to any significant extent. Furthermore, there is a problem with the nonspecificity of the reaction as the radicals produced should be as harmful to the host tissues as to the infecting agents.

Vitamin C participates in the synthesis of carnitine (52–54), and there are some data suggesting that carnitine affects the immune system (192). This may be a further way vitamin C intake affects the immune system.

In the intensive search for proteins and smaller molecules efficiently and specifically defending the body against viruses and bacteria vitamin C has not been of any particular interest. Still, it is possible that as an efficient reducing agent vitamin C has nonspecific effects on the immune system, similarly to the nonspecific effects of pH or temperature on various biological systems. If the major role of vitamin C in the immune system is that of a physiological antioxidant protecting various cells against oxidants released during an infection, it could have quantitatively meaningful effects even though the mechanisms may be nonspecific. Finally, it is also possible that there are substantial individual differences in the effects of vitamin C in humans, as has been found in the guinea pig (193–195).

INFECTIONS IN ANIMALS

If vitamin C affects the immune system in a nonspecific manner as an antioxidant, it is probable that the effects are not strictly limited to the respiratory viruses, which in fact consist of half a dozen unrelated viruses with over 100 serotypes. Consequently, it is possible that vitamin C intake affects susceptibility to and severity of infections by some of the nonrespiratory viruses and possibly by some bacteria as well.

Most mammals synthesize vitamin C in the liver. The guinea pig is one of the rare species that have lost the capability to synthesize vitamin C (196,197), and therefore it provides a good experimental model for studies dealing with the effects of low vitamin C levels on susceptibility to infections. Low vitamin C intake has been found to decrease the resistance of guinea pigs to *Mycobacterium tuberculosis* (198–205), other bacteria (2,95,206–211), Rickettsiae (212), *Endamoeba histolytica* (213), and *Candida albicans* (214). Supplementation of guinea pigs with vitamin C has been reported to increase resistance to the rabies virus (215–217). In some studies vitamin C supplementation had no

effects on bacterial infections (218–220), but there is such a large number of experimental variables of potential importance that discrepancies in results are not surprising.

In guinea pigs infected with *M. tuberculosis* vitamin C supplementation slightly increased the hemoglobin level (221). In histological studies fewer caseonecrotic lesions, more collagenous tissue within and around the tuberculous centers, and less dispersion of tubercle bacilli were observed in vitamin C-supplemented animals (202,203,222). Furthermore, in guinea pigs infected with *M. tuberculosis* there was a decrease in vitamin C level in the adrenals, the liver, and urine (223,224).

Primates lack the ability to synthesize vitamin C (196,197). In some studies with rhesus monkeys vitamin C was reported to decrease the incidence of poliomyelitis (225,226), while in one study no effect was observed (227). Nonetheless, in the latter study it was noted that many rhesus monkeys on a scorbutic diet died of spontaneous infections, chiefly pneumonia and enterocolitis, while those receiving adequate amounts of vitamin C remained well (227). In rhesus monkeys vitamin C intake affects the bacterial flora in the oral cavity (228,229). In marmosets vitamin C supplementation decreased the rates of morbidity and mortality due to parainfluenza infection (230). In macaque monkeys malarial infection decreased the vitamin C level in plasma (231).

Fishes require exogenous vitamin C (196,232). In catfish (232) and rainbow trout (233,234) vitamin C supplementation decreased the mortality rate of bacterial and parasitic infections.

Rats and mice synthesize vitamin C in the liver and consequently cannot be used to study the effects of low vitamin C intakes. However, the effect of vitamin C supplementation and the effect of infections on vitamin C metabolism can be studied in these species and in others that synthesize vitamin C. In mice infected with *Pseudomonas aeruginosa* (235) and *Candida albicans* (135) vitamin C supplementation increased the proportion of surviving animals. In mice infected with rodent malaria parasites, vitamin C depressed parasitemia and extended the mean survival time of the infected mice (236). Vitamin C inhibited the multiplication of *Mycobacterium lepra* in mouse foot pads (237). In mice infected with *Streptococcus pneumoniae* vitamin C supplementation enhanced the clearance of bacteria from the lungs, apparently through an increased influx of neutrophils to the lungs; however, the survival rate was not significantly changed in the vitamin C group (238). In rats infected with *Trypanosoma hippicum* there was a decrease in the vitamin C concentration in the liver, spleen, and adrenals, but the level of vitamin C in plasma was doubled (239). In cats vitamin C supplementation decreased the duration of rhinotracheitis (240). In chickens vitamin C supplementation increased the resistance to *Salmonella gallinarum* (241), *E. coli* (242), and viral bronchitis (243).

It is possible that the amount of the infecting agent affects the role of vitamin C intake. If vitamin C has only moderate effects on the immune system it is possible that it shows effects when the infectious dose is rather small, whereas there may be no effect when the infectious dose is very large. In rhesus monkeys vitamin C provided moderate protection when quite a small dose of polio virus was used, while it was without effect when a large dose was used (226), but the number of animals was so small that the conclusion is not strong. In a study with guinea pigs infected with bacteria, it was also pointed out that the infectious dose seemed to affect the role of vitamin C intake (206).

From the studies examining the effects of vitamin C on the immune system and on various animal infections it seems possible that vitamin C intake may have effects on the susceptibility of humans to infections other than the common cold.

INFECTIONS IN HUMANS

Most of the placebo-controlled studies that have examined the effects of vitamin C on infections have dealt with the common cold. There are few controlled studies of the role of vitamin C on other infections, although quite a large number of uncontrolled reports have suggested that vitamin C may have beneficial effects on various infections. In this section the review is restricted to studies of vitamin C and infections in which some kind of control group has been used. The type of the control group is indicated in the tables; in most cases the control group was not administered placebo. A few uncontrolled reports are briefly commented on in the next section.

Incidence of Infections

The results of all studies known to us that have reported quantitative data on the incidence of infections in two groups differing in vitamin C intake are listed in Tables 5 and 6. Table 5 contains intervention studies and Table 6, observational studies.

In Tables 5 and 6 the odds ratio (OR) is used as the measure of the effect of the difference in the vitamin C intake. When the incidence is low ($< 20\%$) the OR is a good approximation of the RR (32). Furthermore, the exact confidence interval (CI) of the OR is much more easily calculated than the exact CI of the RR, making the OR a more practical measure of an effect when there are only a few cases per group (32). The one-tailed p value was calculated since the question being considered in the present analysis was whether higher vitamin C intake decreases the incidence of infections or not; there is no theoretical or experimental reason to assume that a higher vitamin C intake would increase the incidence of infections.

Several studies have reported much lower incidence of infections in the study group receiving a larger amount of vitamin C compared to the corresponding control group. However, all of these studies are small and the results are inaccurate; i.e., the confidence intervals are wide. Furthermore, in several cases the studies have been poorly planned and/or reported, and thus it is possible that there are serious biases between the study groups. Some important aspects of the studies are listed in the tables, but for more specific technical details the reader is referred to the original references.

Three intervention studies have analyzed the relation between vitamin C intake and posttransfusion hepatitis. Morishige and Murata reported a lower frequency of hepatitis among subjects administered vitamin C (244), but the validity of this poorly described study is questionable. Nevertheless, on the assumption that the groups are comparable the difference in favor of vitamin C is significant. Banic and Kosak found only one case of hepatitis among subjects administered vitamin C but seven cases among controls not administered placebo (245). Knodell et al. found a small decrease in the incidence of hepatitis in the vitamin C group, but the confidence interval is wide because of the small number of cases (246). Furthermore, in Knodell's study the vitamin C group was transfused on average 1.29 times as much blood as the placebo group. Assuming that the risk is directly proportional to the amount of blood given there was a 45% decrease in the incidence of hepatitis (247). Accordingly, all three intervention studies are consistent with the conclusion that vitamin C supplementation decreases the incidence of posttransfusion hepatitis, but as a result of the various technical shortcomings in the studies the conclusion is not strong.

Three intervention studies and one observational study have reported on the relation of vitamin C intake and the incidence of pneumonia. Pitt and Costrini carried out a ran-

Table 5 Vitamin C Intake and the Incidence of Infections: Intervention Studies

Ref.	Vitamin C dose (g/day)	Control type ^a	Cases/Total subjects		OR (90% CI) ^b	<i>p</i> (1 - <i>t</i>)	Subjects/notes
			Vitamin C	Control			
Posttransfusion hepatitis							
244	2-6	C	3/1367	12/170	0.03 (0.009, 0.082)	<0.001	See text
245	3-10	C	1/141	7/155	0.15 (0.013, 0.78)	0.025	
246,247,248	3.2	P, DB	6/90	8/85	0.69 (0.26, 1.8)	0.26	See text
Pneumonia							
25	2	P, DB	1/331	7/343	0.15 (0.013, 0.74)	0.022	Military recruits
249	0.05-0.3	F	0/335	17/1100	0.00 (0, 0.32)	0.005	Schoolchildren
249a	0.3	C	2/114	10/112	0.18 (0.03, 0.77)	0.009	Military recruits
Tuberculosis							
250	0.02-0.37 ^c	C	1/644 ^d	10/1096 ^d	0.17 (0.015, 0.81) ^d	0.026	Blacks
Bronchitis							
41,42	1	P, DB	8/139	13/140	0.60 (0.27, 1.3)	0.14	Schoolchildren in a skiing camp
Pharyngitis, laryngitis, or tonsillitis							
41,42	1	P, DB	7/139	14/140	0.48 (0.21, 1.1)	0.062	Schoolchildren in a skiing camp
Tonsillitis							
249	0.05-0.3	F	29/335	94/1100	1.01 (0.70, 1.5)	—	Schoolboys
249	0.05-0.3	F	1/60	7/90	0.20 (0.018, 1.06)	0.057	New recruits to the school
Secondary bacterial infections after a common cold episode							
251	6	C	6/45	15/45	0.31 (0.12, 0.75)	0.014	From Table 1 in Ref. 251. See text
Rheumatic fever							
252	0.1	P	14/28	10/28	1.8 (0.72, 4.5)	—	From Table 1 in Ref. 252.
249	0.05-0.3	F	0/335	16/1100	0.0 (0, 0.34)	0.007	Schoolboys

^aType of control: C, placebo not used; F, vitamin C added to the food; P, placebo-controlled; DB, double-blind.

^b*p* Values are 1-tailed mid-*p* values and 90% CI are mid-*p* confidence intervals (32). The *p* values and the CIs were calculated with the StatXact program (Cytel Software Co., Cambridge, MA). OR, odds ratio; CI, confidence interval.

^cVitamin C doses: 0.02-0.075 g/day to children under 4 years, 0.05-0.22 g/day to children 5-12 years, and 0.075-0.375 g/day to those over 13 years. In addition to vitamin C certain other essential nutrients were administered: niacin, thiamin, riboflavin, vitamin A, Ca, Fe.

^dThe denominator is the number of person-years in the group; the OR and CI are calculated from the figures shown.

Table 6 Vitamin C Intake and the Incidence of Infections: Observational Studies

Table 6 Vitamin C intake and outcomes							
Ref.	Plasma vitamin C limit ($\mu\text{mol/L}$)	Cases/total Vitamin C levels		OR	(90% CI) ^a	<i>p</i> ^a (1 - <i>t</i>)	Subjects/notes
		High	Low				
Tuberculosis							
253	34 (6 mg/L)	0/117	27/896	0	(0, 0.46)	0.017	Mostly blacks (85%); cohort study
Acute necrotizing ulcerative gingivitis							
254	70	—	—	0.14 1.00 ^c	(0.06, 0.33) ^b	<0.001 —	Case-control study; 60 matched pairs
Postoperative pneumonia							
255	11 (2 mg/L)	10/74	7/35	0.62	(0.25, 1.6)	0.20	Hospital patients; cohort study

^aFor calculation of OR, 90% CI, and p value, see Table 5. OR, odds ratio; CI, confidence interval.

^bUnadjusted OR from logistic regression analysis calculated in the reference.

^cOR from logistic regression adjusted for social class calculated in the reference.

domized double-blind study with military recruits in a training camp (25). Their trial was primarily concerned with the role of vitamin C in relation to the common cold (cf. Tables 1 and 2), but they also reported a dramatic decrease in the incidence of pneumonia in the vitamin C group. Glazebrook and Thomson studied schoolboys in an institution and found no cases of pneumonia in the vitamin C group (249). In their study vitamin C was added to the food in the kitchen. Kimbarowski and Mokrow (249a) examined the effect of vitamin C supplementation in military recruits having upper respiratory symptoms at the start of the study, and observed a substantially lower incidence of pneumonia in subjects administered the vitamin. In an observational study with surgical patients Lund and Crandon (255) found a slightly increased risk of pneumonia in patients with the lowest vitamin C levels, but the difference is not statistically significant. Moreover, in Lund and Crandon's study there were three fatalities due to pneumonia and all of these were among subjects with high vitamin C levels, pointing out the difficulty of drawing conclusions from small studies and particularly from small observational studies.

In a placebo-controlled study Ritzel reported a decrease in the incidence of bronchitis, pharyngitis, laryngitis, and tonsillitis in schoolchildren in a skiing camp with vitamin C supplementation (41). Glazebrook and Thomson found a decrease in tonsillitis with vitamin C in schoolboys newly recruited to the school, but not in those who had remained in the school for a longer time (249). Asfora compared vitamin C to some other medications in the same subjects and reported a lower number of secondary infections after common cold episodes when vitamin C was administered (251). However, the number of cold episodes was not disclosed and it appears indirectly that the number is not the same for the two treatments, hampering the interpretation of the available data.

Glazebrook and Thomson found no cases of rheumatic fever, a complication of streptococcal infection, among the schoolboys administered vitamin C, but 16 cases in the control group (249). In contrast, an older study by Schultz showed no preventive effect of vitamin C on rheumatic fever (252). Nevertheless, there are considerable differences

between the two studies. Schultz selected as subjects children who had previous episodes of rheumatic fever, whereas Glazebrook and Thomson had no such selection. Also, the dietary vitamin C intake was particularly low in Glazebrook and Thomson's subjects at 10–15 mg/day. Schultz did not estimate the dietary intake of his subjects, but possibly it was much higher.

Two studies have reported a lower incidence of tuberculosis in subjects with higher vitamin C intake. In an intervention study by Downes (250) there was only one case of tuberculosis among subjects administered vitamin C. However, some other nutrients were also given, and therefore the difference between the groups is not specifically attributable to vitamin C (250). In a prospective cohort study Getz et al. found no cases of tuberculosis among subjects with high plasma vitamin C levels (253).

In an observational study on acute necrotizing ulcerative gingivitis caused by anaerobic oral bacteria high vitamin C intake was associated with lower risk of infection (254). However, when the social classes were included in the logistic regression model no association with vitamin C intake remained. Vitamin C intake is a strong life-style indicator, and therefore in observational studies the associations with vitamin C intake may be caused indirectly by some other life-style factors. For this reason intervention studies provide much more reliable information about the effects of vitamin C intake. It is also clear that in the case of observational studies the potential confounding factors should be carefully considered.

Two studies have reported an association between vitamin C intake and the prevalence of hemolytic streptococcus in the tonsils (Table 7; 38,256). Although the association is consistent with vitamin C's having physiological effects on the immune system, its clinical significance is not clear. For example, Coulehan (38) did not find a lower rate of secondary infections after common cold episodes in the group supplemented with vitamin C.

From the statistical point of view the studies discussed leave the role of vitamin C intake on the incidence of infections other than the common cold largely unresolved. In several studies no placebo was used nor were subjects randomly allocated to the study groups. Consequently, it is possible that there are substantial biases in the study groups. Further-

Table 7 Vitamin C Intake and the Colonization of Tonsils with Hemolytic Streptococci

Ref.	Cases/total		OR (90% CI) ^a	<i>p</i> ^a (1 - <i>t</i>)	Subjects/notes
	Vitamin C levels				
	High	Low			
Intervention study:					
38	6/57	13/57	0.40 (0.16, 0.97)	0.043	Children
Observational study: limit:					
256	4/32	30/64	0.16 (0.06, 0.42)	<0.001	From table 1 in Ref. 256. Children referred to tonsillectomy

^aFor calculation of OR, 90% CI, and *p* value, see Table 5. OR, odds ratio; CI, confidence interval.

more, in many studies the number of cases was so small that the studies had no reasonable statistical power. For example, it is quite amazing that in two intervention studies the incidence of hepatitis (245) and pneumonia (25) was >80% lower in the vitamin C group, yet the differences between the vitamin C and control groups are barely statistically significant when employing the conservative two-tailed test. Such lack of statistical power has been a persistent problem in medical studies. The number of subjects are sometimes so small that the results are practically meaningless. Freiman et al. (257) surveyed 71 studies published in the medical literature that had reported a "negative result." They calculated that 50 of the studies would, from the statistical point of view, have missed a 50% improvement from the therapy tested. Still, such an effect can often be clinically relevant if it is real.

Pauling (247) explicitly pointed out the lack of statistical power in the study of Knodell et al. on posttransfusion hepatitis (246), which was presented by the authors as definitely proving that vitamin C has no effect on patients undergoing blood transfusion. However, the 90% CI of Knodell's results is also consistent with an OR as low as 0.26. It is clear that Knodell's data do not support the conclusion that vitamin C intake has no physiological effect on the incidence of posttransfusion hepatitis. Nevertheless, it is a question of subjective interpretation whether the study provides weak evidence for benefit from vitamin C supplementation, or whether such a small-scale study lacking any reasonable statistical power should simply be disregarded. We prefer to see Knodell's study and many other small-scale studies in Table 5 as consistent with the hypothesis that vitamin C has effects on infections other than the common cold. However, because of various technical shortcomings the conclusion is not strong. Neither is it clear what the specific infections on which vitamin C intake may have the greatest effects are. In any case, as regards the great apparent reduction in the incidence of various infections as reported in several studies in Table 5, it would seem worthwhile carrying out well-planned studies that do not suffer from a similar lack of statistical power and other experimental defects as many studies in the table do.

Vitamin C Metabolism During Infections

A large number of studies have reported a decrease in vitamin C levels in plasma, white blood cells, or urine during infections. Tuberculosis has been studied most extensively (258–272), but low levels have also been reported in patients with other infections (271, 273–282). Several reports have noted that more severe forms of tuberculosis (263–272) and other infections (280) are often associated with lower vitamin C levels than the milder forms. It is noteworthy that plasma, leukocyte, and urine vitamin C levels are also decreased in the common cold (18,86,283–285).

The reasons for the lower vitamin C status in patients with infections have been considered in some of the papers. The dietary vitamin C intake of the patients may have been rather low in some studies (261,274,275). However, in some other studies the dietary vitamin C intake was comparable for the infectious patients and the healthy controls, suggesting that low dietary intake cannot be the only cause of reduced vitamin C levels in the patients (258,264,265,268). Furthermore, several studies have found differences in the metabolism of vitamin C test doses in patients compared to healthy control subjects (258,264,266–268,270,274,277,280).

Banerjee et al. reported that the decrease in the reduced vitamin C (ascorbate) level in plasma and urine is associated with a concomitant increase in the oxidized form (dehydroascorbate) (259,271,279). Their assay method found that in normal healthy people 5%–10% of the vitamin C is in the dehydroascorbate form, while 65%–80% was in the oxidized

form in patients who later died of meningococcal meningitis, tetanus, pneumonia, or typhoid fever (271). This observed increase in dehydroascorbate level is consistent with the idea that the role of vitamin C in infections is particularly that of a reducing agent (antioxidant) protecting against oxidants produced during an infection. Furthermore, the change in the oxidation level also indicates that the low levels of reduced vitamin C in patients with infections are not caused by poor diet alone, but are partially caused by physiological changes resulting from the infections.

The decrease in vitamin C levels in infected patients is no proof that supplementation would benefit the patients. Nonetheless, the consistent benefit of vitamin C supplementation on the severity of the common cold, along with the changes in the vitamin C metabolism in various infections including the common cold, provides a sound reason to wonder whether large doses of vitamin C might also have beneficial effects on other infections than the common cold.

The Severity of Infections

A number of studies have directly or indirectly assessed the effects of vitamin C supplementation on the severity of various infections (Table 8; 246–249,270,286–293). The severity of a disease is a much more poorly defined variable than the incidence of the disease. Various measures of severity yield numerical values that are not meaningfully comparable. For example, changes in the red blood cell sedimentation rate (RBC SR) or in the numbers of various blood cells may indicate true physiological effects of vitamin C, but such changes are not easy to interpret as a real benefit to the patient. Consequently, an estimate of the effect was not calculated in Table 8, but the original results in the two study groups and the *p* value for the difference are presented.

There are great experimental differences among the studies in Table 8. Some of the observations come from therapeutic studies in which vitamin C administration was commenced only after the onset of the disease. In some other studies vitamin C was administered regularly and the episodes occurring were affected by regular vitamin administration. As regards the question of whether vitamin C intake has any real physiological effects on the severity of the infections, both types of studies can yield relevant information. Nevertheless, it is possible that the quantitative effects of regular and therapeutic supplementation are not similar, and this is a further reason for not calculating any explicit estimates of benefit. In this analysis the primary interest is in the question of whether the level of vitamin C intake has any physiological effects on the severity of infections, rather than on the quantitative estimate of its potential effects.

In a double-blind placebo-controlled study Terezhalmay et al. (286) observed a significant decrease in the duration of herpes labialis infections among subjects administered 0.6–1.0 g/day of vitamin C and a similar amount of bioflavonoids. A significant decrease in the formation of vesicles was also found.

In a double-blind placebo-controlled study with elderly patients admitted to hospital with bronchitis or bronchopneumonia, Hunt et al. (286a) found a significantly greater decrease in respiratory symptoms in subjects administered vitamin C.

Glazebrook and Thomson (249) did not observe any marked effect of vitamin C on the incidence of tonsillitis (cf. Table 5); however, significantly fewer tonsillitis cases in the vitamin C group were sent to a hospital, suggesting that on average the infections were milder (Table 8). Furthermore, among the children who were sent to a hospital the stay was significantly shorter among those who had been administered vitamin C.

Ganguly and Waldman (287,288) studied the effect of orange juice on the symptoms of

an experimental infection with attenuated rubella virus. They found a significant decrease in the number of subjects in whom respiratory symptoms developed in the orange juice group using nasal inoculation. Also, the antibodies against the rubella virus developed more rapidly in the subjects administered orange juice. In subjects inoculated subcutaneously no significant effect on respiratory symptoms or on the emergence of antibodies was observed. The control group was administered placebo tablets as part of a double-blind study evaluating an antiviral drug, so that the control group thought that they might receive an effective antiviral substance and accordingly the placebo effect is not an obvious explanation of the difference between the groups. Orange juice is an important source of vitamin C and while the observed benefit may be due to vitamin C, there are other substances in the orange juice as well.

Knodell et al. (246) administered vitamin C for 2 weeks to patients undergoing blood transfusion, while the hepatitis infections occurred on average 7 weeks after blood transfusion. The mean serum glutamic-oxaloacetic transaminase (SGOT) level was lower in the hepatitis cases administered vitamin C, and there were fewer cases of chronic hepatitis among the vitamin C group. Furthermore, the incubation period was longer in the vitamin C-supplemented group. Although none of Knodell's observations was significant statistically, the consistency in the results is striking and the pattern is not easy to interpret as purely a result of chance.

Several studies have reported that vitamin C has some effects on subjects with tuberculosis. All of these studies are old and technically more or less deficient. In some reports there are no data that allow calculation of the *p* value corresponding to the reported mean differences. A number of the tuberculosis studies have reported statistically significant differences between the vitamin C and control groups, but it is likely that the differences are caused at least in part by the placebo effect and biases between the study groups.

A few German and Swiss studies suggested that vitamin C supplementation may decrease the duration of epidemic hepatitis and poliomyelitis (294–298). There are various shortcomings in these controlled studies and they do not have much weight in considering whether vitamin C intake affects the severity of infections.

In a cohort study with human immunodeficiency virus (HIV)-infected subjects the relative hazard of progression to acquired immunodeficiency syndrome (AIDS) was 0.55 in subjects with the highest level of vitamin C intake (299).

In the case of common cold severity there are some data suggesting that the effect of vitamin C is not saturated by 1 g/day (15,19,24). In this respect most of the studies in Table 8 used rather small doses. Nonetheless, Terezhalmay et al. (286) found that 0.6 and 1.0 g/day produced comparable effects on herpes infections, indicating that the effect of vitamin C may reach saturation with doses of 0.6 g/day or lower. Nevertheless, 10 mg/day of vitamin C prevents scurvy and 60 mg/day is the recommended dietary allowance (RDA) recommendation for vitamin C (300); thus Terezhalmay's results are not trivial even though the effect could be reproduced with doses somewhat smaller than 600 mg/day.

In the treatment of infections one factor that may be important is the promptness of initiating vitamin C supplementation. In the case of the common cold Asfora (251) reported that the greatest benefit from therapeutic vitamin C (6 g/day) was obtained when the treatment was initiated within 24 h of the onset of symptoms. Terezhalmay et al. also found time dependency in the case of herpes labialis (286). In their study in 6 of 26 subjects (23%) herpes vesicles developed when supplementation was initiated within 24 h of the onset of the symptoms, whereas vesicles developed in 8 of 12 subjects (67%) with later initiation. It is unlikely that the difference is caused by chance ($p(2 - t) = 0.02$).

In therapeutic studies the observer bias and the placebo effect may be much greater

Table 8 Vitamin C Intake and the Severity of Infections

Ref.	Vitamin C (g/day)	Control type ^a	No. of cases		Outcome value		p^b (1 - t)	Outcome ^c
			Vitamin C	Control	Vitamin C	Control		
Herpes labialis 286	0.6 ^d	P, DB	19	10	1.7 ± 0.6	3.5 ± 0.8 (SD)	<0.001	Pain (days)
					4.2 ± 1.7	9.7 ± 2.8 (SD)	<0.001	Healing (days)
	1.0 ^d	P, DB	19	10	1.3 ± 0.6	3.5 ± 0.8 (SD)	<0.001	Pain (days)
					4.4 ± 3.9	9.7 ± 2.8 (SD)	<0.001	Healing (days)
	0.6–1 ^d	P, DB	38	10	37% (14)	100% (10)	<0.001	PCTG with vesicle formation
Bronchitis 286a	0.2	PL, DB	28	29	3.4 ± 1.8	2.3 ± 2.5 (SD)	0.027	Decrease in respiratory clinical scores in four weeks
Tonsillitis 249	0.05–0.3	F	29	94	62% (18)	88% (83)	0.002	PCTG admitted to hospital
249	0.05–0.3	F	18	83	10.1 ± 7.0	16.7 ± 11.9 (SD)	0.013	Stay in hospital (days)
Rubella infection, inoculated by nose drops 287,288	0.3 ^e	P	11	13	27% (3)	77% (10)	0.011	PCTG with respiratory symptoms
					100% (11)	31% (4)	<0.001	PCTG with antibody appearing <28 days after inoculation
Rubella infection, inoculated subcutaneously 287,288	0.3 ^e	P	22	9	32% (7)	22% (2)	—	PCTG with respiratory symptoms

Posttransfusion hepatitis 246,247,248	3.2 ^f	P, DB	6	8	474 ± 386 33% (2) 7.6 ± 2.0	759 ± 907 (SD) 62% (5) 6.9 ± 2.1 (SD)	0.25 0.17 0.27	SGOT (unit) PCTG with chronic liver disease Incubation period
Tuberculosis 289	0.2–1.0	C	19	6	42% (8)	0% (0)	0.035	RBC SR decreased at least 5 mm ,
270,290	0.25	C	28 ^g	57 ^g	70%	53%	—	PCTG with decrease in RBC SR at 3 months
291	0.2	C	101	101	79% (80) 49% (49)	65% (65) 33% (33)	0.010 0.012	PCTG feeling better PCTG with decrease in sputum
292	0.15	P	82	77	58% (48)	48% (37)	0.10	PCTG clinically improved
292	0.15	P	45	37	51% (23)	30% (11)	0.028	PCTG with improved mucous membrane lesions in tuberculous tracheobronchitis
293	0.2	C	37 ^g	37 ^g	90% 72%	25% 25%	— —	PCTG feeling better PCTG with increase in hemoglobin

^aType of control: C, placebo not used; F, vitamin C added to food; P, placebo-controlled; DB, double-blind.

^bFor dichotomous data the mid-*p* value was calculated (cf. Table 5) and for continuous variables the *t*-test was used.

^cPCTG, percentage of patients with the characteristic indicated. RBC SR, red blood cell sedimentation rate. SGOT, serum glutamic-oxaloacetic transaminase. Not all outcomes from the studies are listed.

^dTerezhalmay et al. also gave their patients bioflavonoids (0.6–1 g/day).

^eVitamin C was given as orange juice.

^fVitamin C was administered for 2 weeks after the blood transfusion, i.e., it was terminated before the occurrence of the episodes.

^gThe approximate numbers are deduced from the total number of subjects given in the publication; the precise number per group was not published.

problems than in studies on incidence. An observer or a patient faithfully believing in a new method of treatment may easily form the impression that the severity of a disease is slightly decreased even if there are no real physiological effects. In contrast, for an initially healthy person it may be much more difficult to prevent an episode of illness merely by wishing. Therefore, the lack of the double-blind placebo-control method is a much more dangerous shortcoming in the therapeutic studies (Table 8) than in studies on incidence (Table 5). Nevertheless, the differences between the vitamin and control groups have been so great in some studies listed in Table 8 that they justify further work with better experimental features.

UNCONTROLLED REPORTS ON THE USE OF VITAMIN C

Case reports and experience of individual physicians are not good evidence when considering whether a method of treatment has any real physiological effects. It is clear that for a better understanding of the role of vitamin C on various infectious diseases well-planned studies are required. However, placebo-controlled studies are a rigid means of seeking the best modifications of a treatment. They are at their best when testing whether there is any physiological effect at all, but in a double-blind study the treatment cannot easily be adjusted individually if there are substantial individual differences or if the treatment should be modified depending on the response to it.

The reports by physicians who have been interested in vitamin C may provide worthwhile information on the various possible ways of using vitamin C in the treatment of infectious diseases. Nevertheless, the literature on uncontrolled reports on vitamin C and infections is not thoroughly reviewed in this section apart from a few of the more interesting papers. Previously Stone (7) and Briggs (8) carefully surveyed the literature on vitamin C and infections and provided much longer lists of references on the uncontrolled reports.

Cathcart suggested that for the treatment of various infections the optimum oral vitamin C dose should be determined individually for each patient (301,302). He reported that patients with severe bacterial and viral diseases can ingest over 100 g/day of vitamin C without problems, while healthy people usually have diarrhea or other gastrointestinal symptoms with 4–15 g/day. Cathcart's approach is to increase the dose to a level causing mild gastrointestinal discomfort and thereafter use somewhat lower doses for the treatment. This approach is a good example of treatments that are not easy to test rigorously by the double-blind method.

Some other physicians have administered large doses of vitamin C to their patients by intravenous (IV) infusion (303–306). The vitamin C level in plasma increases instantaneously and there is no loss of vitamin C in the intestines, and in this respect the IV infusion may be more efficient than oral administration. Vitamin C has also been used in the form of nose drops in the treatment of the common cold (307).

Some physicians studying the effects of vitamin C supplementation on immunological parameters have reported clinical benefit for patients (117–123,126,128,133a). Although there are no control groups in these studies, the immunological changes observed give greater weight to the reported benefits.

CONCLUSIONS

The role of vitamin C in infections was studied quite extensively in the first part of this century but much less actively thereafter. Several of the studies reported highly favorable

results but had various technical deficiencies. The topic was not ignored because of carefully conducted studies showing no effects from vitamin C. Rather, there appear to be two major reasons for the general disregard of the early studies. Antibiotics were introduced in the 1940s and because of their highly specific effects on microbes they have obviously been a much more rational choice of drugs for patients with infections than vitamin C. A second reason for the rejection of the issue apparently was the notion that the true physiological effect of vitamin C is simply the prevention of scurvy. Evidently it has not been reasonable to think that a substance that participates in the synthesis of collagen would have effects on infections. However, the biochemical characteristics of vitamin C are complex. It participates in the function of several enzymes unrelated to collagen metabolism (52–55), and as one of the major biological antioxidants it can have a large number of nonspecific effects that may be physiologically important. Although vitamin C is not a specific agent against any infection it possibly has moderate effects on general resistance to infections.

The effect of vitamin C supplementation on the common cold has been most extensively studied, and it is the only case in which certain unequivocal conclusions can be drawn, although it is unknown what the best dosage, the maximal effect, and the characteristics of subjects who benefit most are. Nevertheless, the role of vitamin C in colds was not studied for any specific biological reason, but because of the wide publicity aroused by Pauling. Apparently some people wanted to show that he was either right or wrong, while still others just wanted to study a topic on which a Nobel Prize winner had put his credibility on the line.

From the conflicting results from controlled studies published so far, it seems clear that vitamin C is no panacea against infections, in either prevention or therapy. Nevertheless, a few intervention studies have found such considerable effects that the issue should be investigated in more detail. Furthermore, vitamin C is a safe nutrient (13,308,309) costing only pennies per gram, so that even quite modest effects may be worth exploitation.

ACKNOWLEDGMENT

This work was supported by the Academy of Finland.

REFERENCES

1. Hess AF. Infantile scurvy. *V. Am J Dis Child* 1917; 14:337–353.
2. Höjer JA. Studies in scurvy: scurvy and infection. *Acta Paediatr* 1924; 3(suppl):115–122.
3. Hess AF. Diet, nutrition and infection. *N Engl J Med* 1932; 207:637–644.
4. Clausen SW. The influence of nutrition upon resistance to infection. *Physiol Rev* 1934; 14: 309–350.
5. Robertson EC. The vitamins and resistance to infection: vitamin C. *Medicine* 1934; 13: 190–206.
6. Perla D, Marmorston J. Role of vitamin C in resistance. *Arch Pathol* 1937; 23:543–575, 683–712.
7. Stone I. *The Healing Factor: Vitamin C Against Disease*. New York: Grosset & Dunlap, 1972.
8. Briggs M. Vitamin C and infectious disease. In: Briggs MH, ed. *Recent Vitamin Research*. Boca Raton, FL: CRC Press, 1984:39–81.
9. Pauling L. *Vitamin C and the Common Cold*. San Francisco: Freeman, 1970.
10. Pauling L. The significance of the evidence about ascorbic acid and the common cold. *Proc Natl Acad Sci USA* 1971; 68:2678–2681.

11. Kleijnen J, Riet G, Knipschild PG. Vitamin C and the common cold. *Ned Tijdschr Geneesk* 1989; 133:1532–1535.
12. Kleijnen J, Knipschild P. The comprehensiveness of Medline and Embase computer searches. *Pharmaceutisch Weekblad Scientific edition* 1992; 14:316–320.
13. Pauling L. *How to Live Longer and Feel Better*. New York: Freeman, 1986.
14. Hemilä H. Vitamin C and the common cold. *Br J Nutr* 1992; 67:3–16.
15. Hemilä H. Does vitamin C alleviate the symptoms of the common cold? A review of current evidence. *Scand J Infect Dis* 1994; 26:1–6.
16. Elliott B. Ascorbic acid: efficacy in the prevention of symptoms of respiratory infection on a *Polaris* submarine. *Int Res Commun Syst Med Sci* 1973; 1(3):12.
17. Mink KA, Dick EC, Jennings LC, Inhorn SL. Amelioration of rhinovirus colds by vitamin C supplementation (abstr). *Med Virol* 1988; 7:356.
18. Schwartz AR, Togo Y, Hornick RB, et al. Evaluation of the efficacy of ascorbic acid in prophylaxis of induced rhinovirus 44 infection in man. *J Infect Dis* 1973; 128:500–505.
19. Coulehan JL, Reisinger KS, Rogers KD, Bradley DW. Vitamin C prophylaxis in a boarding school. *N Engl J Med* 1974; 290:6–10.
20. Bancalari A, Seguel C, Neira F, et al. Prophylactic value of vitamin C in acute respiratory infections of schoolchildren. *Rev Med Chile* 1984; 112:871–876.
21. Anderson TW, Reid DB, Beaton GH. Vitamin C and the common cold. *Can Med Assoc J* 1972; 107:503–508.
22. Anderson TW, Reid DB, Beaton GH. Vitamin C and the common cold (correction). *Can Med Assoc J* 1973; 108:133.
23. Karlowski TR, Chalmers TC, Frenkel LD, et al. Ascorbic acid for the common cold. *JAMA* 1975; 231:1038–1042.
24. Hemilä H. Vitamin C, the placebo effect, and the common cold: a case study of how preconceptions influence the analysis of results. *J Clin Epidemiol* 1996; 49:1079–1084, 1087.
25. Pitt HA, Costrini AM. Vitamin C prophylaxis in marine recruits. *JAMA* 1979; 241:908–911.
26. Anderson TW, Suranyi G, Beaton GH. The effect on winter illness of large doses of vitamin C. *Can Med Assoc J* 1974; 111:31–36.
27. Hemilä H, Herman ZS. Vitamin C and the common cold: a retrospective analysis of Chalmers' review. *J Am Coll Nutr* 1995; 14:116–123.
28. Fisher RA. *Statistical Methods for Research Workers*. 7th ed. London: Oliver & Boyd, 1938:104–106.
29. Wolf FM. *Meta-Analysis: Quantitative Methods for Research Synthesis*. London: Sage, 1986.
30. Elwood PC, Lee HP, Leger AS, et al. A randomized controlled trial of vitamin C in the prevention and amelioration of the common cold. *Br J Prev Soc Med* 1976; 30:193–196.
31. Ludvigsson J, Hansson LO, Tibbling G. Vitamin C as a preventive medicine against common colds in children. *Scand J Infect Dis* 1977; 9:91–98.
32. Rothman KJ. *Modern Epidemiology*. Boston: Little, Brown, 1986.
33. Hemilä H. Vitamin C and common cold incidence: a review of studies with subjects under heavy physical stress. *Int J Sports Med* 1996; 17:379–383.
34. Baird IM, Hughes RE, Wilson HK, et al. The effects of ascorbic acid and flavonoids on the occurrence of symptoms normally associated with the common cold. *Am J Clin Nutr* 1979; 32:1686–1690.
- 34a. Hemilä H. Vitamin C intake and susceptibility to the common cold. *Br J Nutr* 1997; 77:59–72.
35. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality. *JAMA* 1993; 269:898–903.
36. Anderson TW, Beaton GH, Corey PN, Spero L. Winter illness and vitamin C. *Can Med Assoc J* 1975; 112:823–826.
37. Carr AB, Einstein R, Lai LYC, et al. Vitamin C and the common cold. *Acta Genet Med Gemellol* 1981; 30:249–255.

38. Coulehan JL, Eberhard S, Kapner L, et al. Vitamin C and acute illness in Navajo school-children. *N Engl J Med* 1976; 295:973–977.
39. Monto AS. Studies of the community and family. *Epidemiol Rev* 1994; 16:351–373.
40. Miller JZ, Nance WE, Norton JA, et al. Therapeutic effect of vitamin C. *JAMA* 1977; 237: 248–251.
41. Ritzel G. Critical analysis of the role of vitamin C in the treatment of the common cold. *Helv Med Acta* 1961; 28:63–68.
42. Ritzel G. Ascorbic acid and the common cold (letter). *JAMA* 1976; 235:1108.
43. Chalmers TC. Effects of ascorbic acid on the common cold: an evaluation of the evidence. *Am J Med* 1975; 58:532–536.
44. Hemilä H. Vitamin C supplementation and common cold symptoms: problems with inaccurate reviews. *Nutrition* 1996; 12:804–809.
45. Dykes MHM, Meier P. Ascorbic acid and the common cold: evaluation of its efficacy and toxicity. *JAMA* 1975; 231:1073–1079.
46. Pauling L. Ascorbic acid and the common cold: evaluation of its efficacy and toxicity. Part I. *Med Tribune* 1976; 17(12):18–19.
47. Pauling L. Ascorbic acid and the common cold. Part II. *Med Tribune* 1976; 17(13):37–38.
48. Truswell AS. Ascorbic acid (letter). *N Engl J Med* 1986; 315:709.
49. Hemilä H. Nutritional need versus optimal intake. *Med Hypotheses* 1984; 14:135–139.
50. Hemilä H. A re-evaluation of nutritional goals: not just deficiency counts. *Med Hypotheses* 1986; 20:17–27.
51. Kuhn TS. *The Structure of Scientific Revolutions*. 2d ed. Chicago: University of Chicago Press, 1970.
52. Englard S, Seifter S. The biochemical functions of ascorbic acid. *Annu Rev Nutr* 1986; 6: 365–406.
53. Padh H. Cellular functions of ascorbic acid. *Biochem Cell Biol* 1990; 68:1166–1173.
54. Rebouche CJ. Ascorbic acid and carnitine biosynthesis. *Am J Clin Nutr* 1991; 54:1147S–1152S.
55. Eipper BA, Mains RE. The role of ascorbate in the biosynthesis of neuroendocrine peptides. *Am J Clin Nutr* 1991; 54:1153S–1156S.
56. Goodwin JS, Goodwin JM. Failure to recognize efficacious treatments: a history of salicylate therapy in rheumatoid arthritis. *Perspect Biol Med* 1981; 25:78–92.
57. Goodwin JS, Goodwin JM. The tomato effect: rejection of highly efficacious therapies. *JAMA* 1984; 251:2387–2390.
58. Bourne GH. Vitamin C and immunity. *Br J Nutr* 1949; 2:341–347.
59. Thomas WR, Holt PG. Vitamin C and immunity. *Clin Exp Immunol* 1978; 32:370–379.
- 59a. Gross RL, Newberne PM. Role of nutrition in immunologic function: vitamin C. *Physiol Rev* 1980; 60:255–260.
60. Beisel WR. Single nutrients and immunity: vitamin C. *Am J Clin Nutr* 1982; 35(suppl): 423–428.
61. Leibovitz B, Siegel BV. Ascorbic acid and the immune system. *Adv Exp Med Biol* 1981; 135:1–25.
62. Weiss SJ. Tissue destruction by neutrophils. *N Engl J Med* 1989; 320:365–376.
63. Smith JA. Neutrophils, host defence, and inflammation. *J Leukocyte Biol* 1994; 56:672–686.
64. Oda T, Akaike T, Hamamoto T, et al. Oxygen radicals in influenza-induced pathogenesis and treatment with pyran polymer-conjugated SOD. *Science* 1989; 244:974–976.
65. Akaike T, Ando M, Oda T, et al. Dependence on O_2^- generation by xanthine oxidase of pathogenesis of influenza virus infection in mice. *J Clin Invest* 1990; 85:739–745.
66. Christen S, Peterhans E, Stocker R. Antioxidant activities of some tryptophan metabolites. *Proc Natl Acad Sci USA* 1990; 87:2506–2510.
67. Maeda H, Akaike T. Oxygen free radicals as pathogenic molecules in viral diseases. *Proc Soc Exp Biol Med* 1991; 198:721–727.
68. Hennes T, Peterhans E, Stocker R. Alterations in antioxidant defenses in lung and liver of mice infected with influenza A virus. *J Gen Virol* 1992; 73:39–46.

69. Buffinton GD, Christen S, Peterhans E, Stocker R. Oxidative stress in lungs of mice infected with influenza A virus. *Free Radical Res Comm* 1992; 16:99–110.
70. Hemilä H, Roberts P, Wikström M. Activated polymorphonuclear leucocytes consume vitamin C. *FEBS Lett* 1984; 178:25–30.
71. Theron A, Anderson R. Investigation of the protective effect of ascorbate on the phagocyte-mediated oxidative inactivation of human alpha-1-protease inhibitor. *Am Rev Respir Dis* 1985; 132:1049–1054.
72. Anderson R, Lukey PT. A biological role for ascorbate in the selective neutralization of extracellular phagocyte-derived oxidants. *Ann NY Acad Sci* 1987; 498:229–247.
73. Halliwell B, Wasil M, Grootveld M. Biologically significant scavenging of the myeloperoxidase-derived oxidant hypochlorous acid by ascorbic acid. *FEBS Lett* 1987; 213:15–18.
74. Frei B, Stocker R, Ames BN. Antioxidant defenses and lipid peroxidation in human blood plasma. *Proc Natl Acad Sci USA* 1988; 85:9748–9752.
75. Thomas EL, Learn DB, Jefferson MM, Weatherred W. Superoxide-dependent oxidation of extracellular reducing agents by isolated neutrophils. *J Biol Chem* 1988; 263:2178–2186.
76. Hu ML, Louie S, Cross CE, et al. Antioxidant protection against hypochlorous acid in human plasma. *J Lab Clin Med* 1993; 121:257–262.
77. Crandon JH, Lund CC, Dill DB. Experimental human scurvy. *N Engl J Med* 1940; 223:353–369.
78. Vitamin C requirement of human adults. *Lancet* 1948; 254:853–858.
79. DeChatelet LR, McCall CE, Cooper MR, Shirley PS. Ascorbic acid levels in phagocytic cells. *Proc Soc Exp Biol Med* 1974; 145:1170–1173.
80. Evans RM, Currie L, Campbell A. The distribution of ascorbic acid between various cellular components of blood, in normal individuals, and its relation to the plasma concentration. *Br J Nutr* 1982; 47:473–482.
81. Washko P, Rotrosen D, Levine M. Ascorbic acid transport and accumulation in human neutrophils. *J Biol Chem* 1989; 264:18996–19002.
82. Bergsten P, Amitai G, Kehrl J, et al. Millimolar concentrations of ascorbic acid in purified human mononuclear leukocytes. *J Biol Chem* 1990; 265:2584–2587.
83. Washko PW, Wang Y, Levine M. Ascorbic acid recycling in human neutrophils. *J Biol Chem* 1993; 268:15531–15535.
84. Winterbourn CC, Vissers MCM. Changes in ascorbate levels on stimulation of human neutrophils. *Biochim Biophys Acta* 1983; 763:175–179.
85. Stankova L, Gerhardt HB, Nagel L, Bigley RH. Ascorbate and phagocyte function. *Infect Immun* 1975; 12:252–256.
86. Hume R, Weyers E. Changes in leucocyte ascorbic acid during the common cold. *Scott Med J* 1973; 18:3–7.
87. Cottingham E, Mills CA. Influence of environmental temperature and vitamin-deficiency upon phagocytic functions. *J Immunol* 1943; 47:493–502.
88. Nungester WJ, Ames AM. The relationship between ascorbic acid and phagocytic activity. *J Infect Dis* 1948; 83:50–54.
89. Merchant DJ. The effect of serum on the activity of the polymorphonuclear leukocytes of the guinea pig. *J Infect Dis* 1950; 87:275–284.
90. Chatterjee GC, Majumder PK, Banerjee SK, et al. Relationships of protein and mineral intake to L-ascorbic acid metabolism, including considerations of some directly related hormones. *Ann NY Acad Sci* 1975; 258:382–400.
91. Shilotri PG. Glycolytic, hexose monophosphate shunt and bactericidal activities of leukocytes in ascorbic acid deficient guinea pigs. *J Nutr* 1977; 107:1507–1512.
92. Ganguly R, Waldman RH. Macrophage functions in aging: effects of vitamin C deficiency. *Allerg Immunol* 1985; 31:37–43.
93. Goldschmidt MC, Masin WJ, Brown LR, Wyde PR. The effect of ascorbic acid deficiency on leukocyte phagocytosis and killing of *Actinomyces viscosus*. *Int J Vitam Nutr Res* 1988; 58:326–334.

94. Alvares O, Altman LC, Springmeyer S, et al. The effect of subclinical ascorbate deficiency on periodontal health in nonhuman primates. *J Periodontal Res* 1981; 16:628–636.
95. Werkman CH, Nelson VE, Fulmer EI. Immunologic significance of vitamins. *J Infect Dis* 1924; 34:447–453.
96. Ganguly R, Durieux MF, Waldman RH. Macrophage function in vitamin C-deficient guinea pigs. *Am J Clin Nutr* 1976; 29:762–765.
97. Goetzl EJ, Wasserman SI, Gigli I, Austen KF. Enhancement of random migration and chemotactic response of human leukocytes by ascorbic acid. *J Clin Invest* 1974; 53:813–818.
98. Sandler JA, Gallin JJ, Vaughan M. Effects of serotonin, carbamylcholine, and ascorbic acid on leukocyte cyclic GMP and chemotaxis. *J Cell Biol* 1975; 67:480–484.
99. Anderson R, Theron A. Effects of ascorbate on leucocytes. I. *S Afr Med J* 1979; 56:394–400.
100. Boxer LA, Vanderbilt B, Bonsib S, et al. Enhancement of chemotactic response and microtubule assembly in human leukocytes by ascorbic acid. *J Cell Physiol* 1979; 100:119–126.
101. Dallegrì F, Lanzi G, Patrone F. Effects of ascorbic acid on neutrophil locomotion. *Int Arch Allergy Appl Immunol* 1980; 61:40–45.
102. Gatner EMS, Anderson R. An in vitro assessment of cellular and humoral immune function in pulmonary tuberculosis. *Clin Exp Immunol* 1980; 40:327–336.
103. Patrone F, Dallegrì F, Lanzi G, Sacchetti C. Prevention of neutrophil chemotactic deactivation by ascorbic acid. *Br J Exp Pathol* 1980; 61:486–489.
104. Anderson R, Jones PT. Increased leucoattractant binding and reversible inhibition of neutrophil motility mediated by the peroxidase/H₂O₂/halide system. *Clin Exp Immunol* 1982; 47:487–496.
105. Pryzwansky KB, Schliwa M, Boxer LA. Microtubule organization of unstimulated and stimulated adherent human neutrophils in Chediak-Higashi syndrome. *Blood* 1985; 66:1398–1403.
106. Johnston CS, Huang S. Effect of ascorbic acid nutriture on blood histamine and neutrophil chemotaxis in guinea pigs. *J Nutr* 1991; 121:126–130.
107. Nath J, Gallin JJ. Effect of vitamin C on tubulin tyrosination in polymorphonuclear leukocytes. *Ann NY Acad Sci* 1987; 498:216–228.
108. Baehner RL, Boxer LA, Allen JM, Davis J. Autooxidation as a basis for altered function by polymorphonuclear leukocytes. *Blood* 1977; 50:327–335.
109. Nelson RD, McCormack RT, Fiegel VD, et al. Chemotactic deactivation of human neutrophils. *Infect Immun* 1979; 23:282–286.
110. Stendahl O, Coble BI, Dahlgren C, et al. Myeloperoxidase modulates the phagocytic activity of polymorphonuclear neutrophil leukocytes. *J Clin Invest* 1984; 73:366–373.
111. Chretien JH, Garagusi VF. Correction of corticosteroid-induced defects of polymorphonuclear neutrophil function by ascorbic acid. *J Reticuloendothel Soc* 1973; 14:280–286.
112. Olson GE, Polk HC. In vitro effect of ascorbic acid on corticosteroid-caused neutrophil dysfunction. *J Surgical Res* 1977; 22:109–112.
113. Roth JA, Kaeberle ML. In vivo effect of ascorbic acid on neutrophil function in healthy and dexamethasone-treated cattle. *Am J Vet Res* 1985; 46:2434–2436.
114. Boxer LA, Watanabe AM, Rister M, et al. Correction of leukocyte function in Chediak-Higashi syndrome by ascorbate. *N Engl J Med* 1976; 295:1041–1045.
115. Foster CS, Goetzl EJ. Ascorbate therapy in impaired neutrophil and monocyte chemotaxis. *Arch Ophthalmol* 1978; 96:2069–2072.
116. Boxer LA, Albertini DF, Baehner RL, Oliver JM. Impaired microtubule assembly and polymorphonuclear leukocyte function in the Chediak-Higashi syndrome correctable by ascorbic acid. *Br J Haematol* 1979; 43:207–213.
117. Anderson R, Theron A. Effects of ascorbate on leucocytes. III. *S Afr Med J* 1979; 56:429–433.
118. Anderson R, Dittrich OC. Effects of ascorbate on leucocytes. IV. *S Afr Med J* 1979; 56:476–480.
119. Friedenbergs WR, Marx JJ, Hansen RL, Haselby RC. Hyperimmunoglobulin E syndrome. *Clin Immunol Immunopathol* 1979; 12:132–142.

120. Anderson R, Hay I, Wyk H, et al. The effect of ascorbate on cellular humoral immunity in asthmatic children. *S Afr Med J* 1980; 58:974–977.
121. 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.
122. Weening RS, Schoorel EP, Roos D, et al. Effect of ascorbate on abnormal neutrophil, platelet, and lymphocyte function in a patient with the Chediak-Higashi syndrome. *Blood* 1981; 57:856–865.
123. Rebora A, Dallegrì F, Patrone F. Neutrophil dysfunction and repeated infections. *Br J Dermatol* 1980; 102:49–56.
124. Anderson R. Ascorbate-mediated stimulation of neutrophil motility and lymphocyte transformation by inhibition of the peroxide/H₂O₂/halide system in vitro and in vivo. *Am J Clin Nutr* 1981; 34:1906–1911.
125. Saitoh H, Komiyama A, Norose N, et al. Development of the accelerated phase during ascorbic acid therapy in Chediak-Higashi syndrome and efficacy of colchicine on its management. *Br J Haematol* 1981; 48:79–84.
126. Corberand J, Nguyen F, Fraysse B, Enjalbert L. Malignant external otitis and polymorphonuclear leukocyte migration impairment: improvement with ascorbic acid. *Arch Otolaryngol* 1982; 108:122–124.
127. Anderson R, Hay I, Wyk HA, Theron A. Ascorbic acid in bronchial asthma. *S Afr Med J* 1983; 63:649–652.
128. Patrone F, Dallegrì F, Bonvini E, et al. Disorders of neutrophil function in children with recurrent pyogenic infections. *Med Microbiol Immunol* 1982; 171:113–122.
129. Thorner RE, Barker CF, MacGregor RR. Improvement of granulocyte adherence and in vivo granulocyte delivery by ascorbic acid in renal transplant patients. *Transplantation* 1983; 35:432–436.
130. Yegin O, Sanal O, Yeralan O, et al. Defective lymphocyte locomotion in Chediak-Higashi syndrome. *Am J Dis Child* 1983; 137:771–773.
131. Boura P, Tsapas G, Papadopoulou A, et al. Monocyte locomotion in anergic chronic brucellosis patients. *Immunopharmacol Immunotoxicol* 1989; 11:119–129.
132. Vohra K, Khan AJ, Telang V, et al. Improvement of neutrophil migration by systemic vitamin C in neonates. *J Perinatol* 1990; 10:134–136.
133. Johnston CS, Martin LJ, Cai X. Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis. *J Am Coll Nutr* 1992; 11:172–176.
- 133a. Levy R, Shriker O, Porath A, et al. Vitamin C for the treatment of recurrent furunculosis in patients with impaired neutrophil functions. *J Infect Dis* 1996; 173:1502–1505.
134. Maderazo EG, Woronick CL, Hickingbotham N, et al. A randomized trial of replacement antioxidant vitamin therapy for neutrophil locomotory dysfunction in blunt trauma. *J Trauma* 1991; 31:1142–1150.
135. Gallin JI, Elin RJ, Hubert RT, et al. Efficacy of ascorbic acid in Chediak-Higashi syndrome. *Blood* 1979; 53:226–234.
136. Shilotri PG, Bhat KS. Effect of mega doses of vitamin C on bactericidal activity of leukocytes. *Am J Clin Nutr* 1977; 30:1077–1081.
137. Delafuente JC, Panush RS. Modulation of certain immunological responses by vitamin C. II. *Int J Vitam Nutr Res* 1980; 50:44–51.
138. Panush RS, Delafuente JC, Katz P, Johnson J. Modulation of certain immunologic responses by vitamin C. III. *Int J Vitam Nutr Res* 1982; (suppl 23):35–47.
139. Manzella JP, Roberts NJ. Human macrophage and lymphocyte responses to mitogen stimulation after exposure to influenza virus, ascorbic acid, and hyperthermia. *J Immunol* 1979; 123:1940–1944.
140. Joffe MI, Sukha NR, Rabson AR. Lymphocyte subsets in measles: depressed helper/inducer subpopulation reversed by in vitro treatment with levamisole and ascorbic acid. *J Clin Invest* 1983; 72:971–980.

141. Delafuente JC, Prendergast JM, Modigh A. Immunologic modulation by vitamin C in the elderly. *Int J Immunopharmacol* 1986; 8:205–211.
142. Oh C, Nakano K. Reversal by ascorbic acid of suppression by endogenous histamine of rat lymphocyte blastogenesis. *J Nutr* 1988; 118:639–644.
143. Smit MJ, Anderson R. Inhibition of mitogen-activated proliferation of human lymphocytes by hypochlorous acid in vitro. *Agents Actions* 1990; 30:338–343.
144. Standefer JC, Vanderjagt D, Anderson RE, et al. Protective effect of ascorbate on radiation-sensitive thymidine uptake by lymphocytes. *Ann NY Acad Sci* 1987; 498:519–521.
145. Siegel BV, Morton JI. Vitamin C and the immune response. *Experientia* 1977; 33:393–395.
146. Anthony LE, Kurahara CG, Taylor KB. Cell-mediated cytotoxicity and humoral immune response in ascorbic acid-deficient guinea pigs. *Am J Clin Nutr* 1979; 32:1691–1698.
147. Fraser RC, Pavlovic S, Kurahara CG, et al. The effect of variations in vitamin C intake on the cellular immune response of guinea pigs. *Am J Clin Nutr* 1980; 33:839–847.
148. Kristensen B, Thomsen PD, Palludan B, Wegger I. Mitogen stimulation of lymphocytes in pigs with hereditary vitamin C deficiency. *Acta Vet Scand* 1986; 27:486–496.
149. Yonemoto RH. Vitamin C and immune responses in normal controls and cancer patients. *Int J Vitam Nutr Res* 1979; (suppl 19):143–154.
150. 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.
151. 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.
152. O'Brien BC, McMurray DN. Human plasma lipid and immunologic responses to eggs and ascorbic acid. *Nutr Res* 1988; 8:353–366.
153. Penn ND, Purkins L, Kelleher J, et al. The effect of dietary supplementation with vitamins A, C and E on cell-mediated immune function in elderly long-stay patients. *Age Aging* 1991; 20:169–174.
154. Kay NE, Holloway DE, Hutton SW, et al. Human T-cell function in experimental ascorbic acid deficiency and spontaneous scurvy. *Am J Clin Nutr* 1982; 36:127–130.
155. Goodwin JS, Garry PJ. Relationship between megadose vitamin supplementation and immunological function in a healthy elderly population. *Clin Exp Immunol* 1983; 51:647–653.
156. Heidrick ML, Albright JW, Makinodan T. Restoration of impaired immune functions in aging animals. *Mech Ageing Dev* 1980; 13:367–378.
157. Furukawa T, Meydani SN, Blumberg JB. Reversal of age-associated decline in immune responsiveness by dietary glutathione supplementation in mice. *Mech Ageing Dev* 1987; 38:107–117.
158. Bendich A, Gabriel E, Machlin LJ. Dietary vitamin E requirement for optimum immune responses in the rat. *J Nutr* 1986; 116:675–681.
159. Meydani SN, Barklund MP, Liu S, et al. Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. *Am J Clin Nutr* 1990; 52:557–563.
160. Metzger Z, Hoffeld JT, Oppenheim JJ. Macrophage-mediated suppression. *J Immunol* 1980; 124:983–988.
161. Zoschke DC, Messner RP. Suppression of human lymphocyte mitogenesis mediated by phagocyte-released reactive oxygen species. *Clin Immunol Immunopathol* 1984; 32:29–40.
162. El-Hag A, Clark RA. Immunosuppression by activated human neutrophils. *J Immunol* 1987; 139:2406–2413.
163. Schwerdt PR, Schwerdt CE. Effect of ascorbic acid on rhinovirus replication in WI-38 cells. *Proc Soc Exp Biol Med* 1975; 148:1237–1243.
164. Siegel BV. Enhancement of interferon production by poly(rI)·poly(rC) in mouse cell cultures by ascorbic acid. *Nature* 1975; 254:531–532.
165. Dahl H, Degre M. The effect of ascorbic acid on production of human interferon and the antiviral activity in vitro. *Acta Pathol Microbiol Scand* 1976; 84B:280–284.
166. Karpinska T, Kawecki Z, Kandefer-Szerszen M. The influence of ultraviolet irradiation,

- L-ascorbic acid and calcium chloride on the induction of interferon in human embryo fibroblasts. *Arch Immunol Ther Exp* 1982; 30:33–37.
167. Siegel BV. Enhanced interferon response to murine leukemia virus by ascorbic acid. *Infect Immun* 1974; 10:409–410.
 168. Geber WF, Lefkowitz SS, Hung CY. Effect of ascorbic acid, sodium salicylate, and caffeine on the serum interferon level in response to viral infection. *Pharmacology* 1975; 13:228–233.
 169. Versteeg J. Effects of ascorbic acid on virus replication, and production and activity of interferon in vitro. *Proc Koninkl Nederl Akad Wetensch (Biol Med)* 1969; 72:207–212.
 170. Prinz W, Bortz R, Bregin B, Hersch M. The effect of ascorbic acid supplementation on some parameters of the human immunological defence system. *Int J Vitam Nutr Res* 1977; 47: 248–257.
 171. Bates CJ, Levene CI, Oldroyd RG, Lachmann PJ. Complement component C1q is insensitive to acute vitamin C deficiency in guinea pigs. *Biochim Biophys Acta* 1978; 540:423–430.
 172. Feigen GA, Smith BH, Dix CE, et al. Enhancement of antibody production and protection against systemic anaphylaxis by large doses of vitamin C. *Res Commun Chem Pathol Pharmacol* 1982; 38:313–333.
 173. Johnston CS, Kolb WP, Haskell BE. The effect of vitamin C nutriture on complement component C1q concentrations in guinea pig plasma. *J Nutr* 1987; 117:764–768.
 174. Johnston CS. Complement component C1q unaltered by ascorbate supplementation in healthy men and women. *J Nutr Biochem* 1991; 2:499–501.
 175. Tanaka M, Muto N, Gohda E, Yamamoto I. Enhancement by ascorbic acid 2-glucoside or repeated additions of ascorbate of mitogen-induced IgM and IgG productions by human peripheral blood lymphocytes. *Jpn J Pharmacol* 1994; 66:451–456.
 176. Dowd PS, Kelleher J, Walker BE, Guillou PJ. Nutrition and cellular immunity in hospital patients. *Br J Nutr* 1986; 55:515–527.
 177. Vojdani A, Ghoneum M. In vivo effect of ascorbic acid on enhancement of human natural killer cell activity. *Nutr Res* 1993; 13:753–764.
 178. Siegel BV, Morton JI. Vitamin C and immunity. *Int J Vitam Nutr Res* 1983; 53:179–183.
 179. Atherton JG, Kratzing CC, Fisher A. The effect of ascorbic acid on infection of chick-embryo ciliated tracheal organ cultures by coronavirus. *Arch Virol* 1978; 56:195–199.
 180. Bissell MJ, Hatie C, Farson DA, et al. Ascorbic acid inhibits replication and infectivity of avian RNA tumor virus. *Proc Natl Acad Sci USA* 1980; 77:2711–2715.
 181. Morigaki T, Ito Y. Intervening effect of L-ascorbic acid on Epstein-Barr virus activation in human lymphoblastoid cells and its comparison with the effect of retinoic acid. *Cancer Lett* 1982; 15:255–259.
 182. Harakeh S, Jariwalla RJ, Pauling L. Suppression of human immunodeficiency virus replication by ascorbate in chronically and acutely infected cells. *Proc Natl Acad Sci USA* 1990; 87:7245–7249.
 183. Harakeh S, Jariwalla RJ. Comparative study of the anti-HIV activities of ascorbate and thiol-containing reducing agents in chronically HIV-infected cells. *Am J Clin Nutr* 1991; 54:1231S–1235S.
 184. Schwartz RI. Ascorbate stabilizes the differentiated state and reduces the ability of Rous sarcoma virus to replicate and to uniformly transform cell cultures. *Am J Clin Nutr* 1991; 54:1247S–1251S.
 185. Walker GH, Bynoe ML, Tyrrell DAJ. Trial of ascorbic acid in prevention of colds. *Br Med J* 1967; 1:603–606.
 186. Klein M. The mechanism of the virucidal action of ascorbic acid. *Science* 1945; 101: 587–589.
 187. Miller TE. Killing and lysis of gram-negative bacteria through the synergistic effect of hydrogen peroxide, ascorbic acid, and lysozyme. *J Bacteriol* 1969; 98:949–955.
 188. Drath DB, Karnovsky ML. Bactericidal activity of metal-mediated peroxide-ascorbate systems. *Infect Immun* 1974; 10:1077–1083.

189. Samuni A, Aranovitch J, Godinger D, et al. On the cytotoxicity of vitamin C and metal ions. *Eur J Biochem* 1983; 137:119–124.
190. Wang Y, Ness BV. Site-specific cleavage of supercoiled DNA by ascorbate/Cu(II). *Nucleic Acids Res* 1989; 17:6915–6926.
191. Halliwell B. Free radicals, reactive oxygen species and human disease. *Br J Exp Pathol* 1989; 70:737–757.
192. Famularo G, Simone CD. A new era for carnitine? *Immunol Today* 1995; 16:211–213.
193. Williams RJ, Deason G. Individuality in vitamin C needs. *Proc Natl Acad Sci USA* 1967; 57:1638–1641.
194. Yew MS. Recommended daily allowances for vitamin C. *Proc Natl Acad Sci USA* 1973; 70:969–972.
195. Yew MS. Biological variation in ascorbic acid needs. *Ann NY Acad Sci* 1975; 258:451–457.
196. Chatterjee IB. Evolution and the biosynthesis of ascorbic acid. *Science* 1973; 182:1271–1272.
197. Sato P, Udenfriend S. Studies on ascorbic acid related to the genetic basis of scurvy. *Vitam Horm* 1978; 36:33–52.
198. Höjer JA. Studies in scurvy: scurvy and tuberculosis. *Acta Paediatr* 1924; 3(suppl):140–171.
199. McConkey M, Smith DT. The relation of vitamin C deficiency to intestinal tuberculosis in the guinea pig. *J Exp Med* 1933; 58:503–517.
200. DeSavitsch E, Steward JD, Hanson L, Walsh EN. The influence of orange juice on experimental tuberculosis in guinea pigs. *Natl Tuberc Assoc Transact* 1934; 30:130–135.
201. Greene MR, Steiner M, Kramer B. The role of chronic vitamin C deficiency in the pathogenesis of tuberculosis in the guinea pigs. *Am Rev Tuberc* 1936; 33:585–624.
202. Steinbach MM, Klein SJ. Vitamin C in experimental tuberculosis. *Am Rev Tuberc* 1941; 43:403–414.
203. Russell WO, Read JA, Rouse ET. Morphologic and histochemical study of the effect of scurvy on tuberculosis in guinea pigs. *Arch Pathol* 1944; 38:31–39.
204. Boyden SV, Andersen ME. Diet in experimental tuberculosis in the guinea pig. *Acta Pathol Microbiol Scand* 1955; 37:201–204.
205. Boyden SV, Andersen ME. Diet and experimental tuberculosis in the guinea pig. *Acta Pathol Microbiol Scand* 1956; 39:107–116.
206. Findlay GM. The relation of vitamin C to bacterial infection. *J Pathol Bacteriol* 1923; 26: 1–19.
207. Grant AH. Effect of the calcium, vitamin C, vitamin D ratio in diet on the permeability of intestinal wall to bacteria. *J Infect Dis* 1926; 39:502–508.
208. Rinehart JF, Mettier SR. The heart valves and muscle in experimental scurvy with superimposed infection. *Am J Pathol* 1934; 10:61–79.
209. Rinehart JF, Connor CL, Mettier SR. Further observations on pathologic similarities between experimental scurvy combined with infection, and rheumatic fever. *J Exp Med* 1934; 59: 97–114.
210. McCullough NB. Vitamin C and resistance of the guinea pig to infection with *Bacterium necrophorum*. *J Infect Dis* 1938; 63:34–53.
211. Witt WM, Hubbard GB, Fanton JW. *Streptococcus pneumoniae* arthritis and osteomyelitis with vitamin C deficiency in guinea pigs. *Lab Anim Sci* 1988; 38:192–195.
212. Zinsser H, Castaneda MR, Seastone CV. Studies on typhus fever. VI. *J Exp Med* 1931; 53: 333–338.
213. Sadun EH, Bradin JL, Faust EC. Effect of ascorbic acid deficiency on the resistance of guinea pigs to infection with *Endamoeba histolytica* of human origin. *Am J Trop Med* 1951; 31: 426–437.
214. Rogers TJ, Adams-Burton K, Mallon M, et al. Dietary ascorbic acid and resistance to experimental renal candidiasis. *J Nutr* 1983; 113:178–183.
215. Banic S. Prevention of rabies by vitamin C. *Nature* 1975; 258:153–154.

216. Banic S. Prophylactic effect of vitamin C on the incidence of rabies in guinea pigs inoculated with fixed rabies virus. *Int J Vitam Nutr Res* 1977; (suppl 16):235–244.
217. Banic S. The effect of vitamin C on the efficiency of immunization with cell culture rabies vaccine in guinea-pigs. *Int J Vitam Nutr Res* 1979; (suppl 19):35–39.
218. Heise FH, Martin GJ. Supervitaminosis C in tuberculosis. *Proc Soc Exp Biol Med* 1936; 35:337–338.
219. Heise FH, Steenken W. Vitamin C and immunity in tuberculosis of guinea pigs. *Am Rev Tuberc* 1939; 39:794–795.
220. Peck MD, Alexander JW. Survival in septic guinea pigs is influenced by vitamin E, but not by vitamin C in enteral diets. *J Parent Enter Nutr* 1991; 15:433–436.
221. Birkhaug KE. The role of vitamin C in the pathogenesis of tuberculosis in the guinea pig. III. *Acta Tuberc Scand* 1938; 12:359–372.
222. Birkhaug KE. The role of vitamin C in the pathogenesis of tuberculosis in the guinea pig. V. *Acta Tuberc Scand* 1939; 13:52–66.
223. Birkhaug KE. The role of vitamin C in the pathogenesis of tuberculosis in the guinea pig. I and II. *Acta Tuberc Scand* 1938; 12:89–104.
224. Harris LJ, Passmore R, Oxon BM, et al. Vitamin C and infection. *Lancet* 1937; 2:183–186.
225. Jungeblut CW. Further observations on vitamin C therapy in experimental poliomyelitis. *J Exp Med* 1937; 66:459–477.
226. Jungeblut CW. A further contribution to vitamin C therapy in experimental poliomyelitis. *J Exp Med* 1939; 70:315–333.
227. Sabin AB. Vitamin C in relation to experimental poliomyelitis. *J Exp Med* 1939; 69:507–515.
228. Kelly FC. Bacteriology of artificially produced necrotic lesions in the oropharynx of the monkey. *J Infect Dis* 1944; 74:93–108.
229. Goldschmidt MC. Reduced bactericidal activity in neutrophils from scorbutic animals and the effect of ascorbic acid on these target bacteria in vivo and in vitro. *Am J Clin Nutr* 1991; 54:1214S–1220S.
230. Murphy BL, Krushak DH, Maynard JE, Bradley DW. Ascorbic acid and its effects on parainfluenza type III virus infection in cotton-topped marmosets. *Lab Anim Sci* 1974; 24: 229–232.
231. McKee RW, Geiman QM. Studies on malarial parasites. V. *Proc Soc Exp Biol Med* 1946; 63:313–315.
232. Li Y, Lovell RT. Elevated levels of dietary ascorbic acid increase immune response in channel catfish. *J Nutr* 1985; 115:123–131.
233. Wahli T, Meier W, Pfister K. Ascorbic acid induced immune-mediated decrease in mortality in *Ichthyophthirius multifiliis* infected rainbow-trout. *Acta Trop* 1986; 43:287–289.
234. Waagbo R, Sandnes K, Glette J, et al. Dietary vitamin B₆ and C. *Ann NY Acad Sci* 1992; 669:379–382.
235. Rawal BD, McKay G, Blackhall MI. Inhibition of *Pseudomonas aeruginosa* by ascorbic acid acting singly and in combination with antimicrobials. *Med J Aust* 1974; 1:169–174.
236. Bourke GC, Coleman RM, Rencricca NJ. Effect of ascorbic acid on host resistance in virulent rodent malaria (abstr). *Clin Res* 1980; 28:642A.
237. Hastings RC, Richard V, Christy SA, Morales MJ. Activity of ascorbic acid in inhibiting the multiplication of *M. leprae* in the mouse foot pad. *Int J Lepr* 1976; 44:427–440.
238. Esposito AL. Ascorbate modulates antibacterial mechanisms in experimental pneumococcal pneumonia. *Am Rev Respir Dis* 1986; 133:643–647.
239. Nyden SJ. Changes in ascorbic acid metabolism of the rat during infection with *Trypanosoma hippicum*. *Proc Soc Exp Biol Med* 1948; 69:206–210.
240. Edwards WC. Ascorbic acid for treatment of feline rhinotracheitis. *Vet Med Small Anim Clin* 1968; 63:696–698.
241. Hill CH, Garren HW. The effect of high levels of vitamins on the resistance of chicks to fowl typhoid. *Ann NY Acad Sci* 1955; 63:186–194.

242. Gross WB. Effect of environmental stress on the responses of ascorbic acid treated chickens to *E. coli* challenge infection. *Avian Dis* 1988; 32:432–436.
243. Davelaar FG, Bos J. Ascorbic acid and infectious bronchitis infections in broilers. *Avian Pathol* 1992; 21:581–589.
244. Morishige F, Murata A. Vitamin C for prophylaxis of viral hepatitis B in transfused patients. *J Int Acad Prev Med* 1978; 5(1):54–58.
245. Banic S, Kosak M. Prevention of post-transfusion hepatitis by vitamin C. *Int J Vitam Nutr Res* 1979; (suppl 19):41–44.
246. Knodell RG, Tate MA, Akl BF, Wilson JW. Vitamin C prophylaxis for posttransfusion hepatitis: lack of effect in a controlled trial. *Am J Clin Nutr* 1981; 34:20–23.
247. Pauling L. Vitamin C prophylaxis for posttransfusion hepatitis. *Am J Clin Nutr* 1981; 34:1978–1979.
248. Sutnick MR. Vitamin C prophylaxis for posttransfusion hepatitis. *Am J Clin Nutr* 1981; 34:1980–1981.
249. Glazebrook AJ, Thomson S. The administration of vitamin C in a large institution and its effects on general health and resistance to infection. *J Hyg* 1942; 42:1–19.
- 249a. Kimbarowski JA, Mokrow NJ. Farbige Ausfällungsreaktion des Harns nach Kimbarowski, als index der Wirkung von Ascorbinsäure bei Behandlung der Virusgrippe. *Dtsch Gesundheitsw* 1967; 22:2413–2418.
250. Downes J. An experiment in the control of tuberculosis among Negroes. *Milbank Mem Fund Q* 1950; 28:127–159.
251. Asfora J. Vitamin C in high doses in the treatment of the common cold. *Int J Vitam Nutr Res* 1977; (suppl 16):219–234.
252. Schultz MP. Studies of ascorbic acid and rheumatic fever. II. *J Clin Invest* 1936; 15:385–391.
253. Getz HR, Long ER, Henderson HJ. A study of the relation of nutrition to the development of tuberculosis. *Am Rev Tuberc* 1951; 64:381–393.
254. Melnick SL, Alvarez JO, Navia JM, et al. A case-control study of plasma ascorbate and acute necrotizing ulcerative gingivitis. *J Dent Res* 1988; 67:855–860.
255. Lund CC, Crandon JH. Human experimental scurvy and the relation of vitamin C deficiency to postoperative pneumonia and to wound healing. *JAMA* 1941; 116:663–668.
256. Kaiser AD, Slavin B. The incidence of hemolytic streptococci in the tonsils of children as related to the vitamin C content of tonsils and blood. *J Pediatr* 1938; 13:322–333.
257. Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 1978; 299:690–694.
258. Bumbalo TS, Jetter WW. Vitamin C in tuberculosis. *J Pediatr* 1938; 13:334–340.
259. Banerjee S, Sen PB, Guha BC. Urinary excretion of combined ascorbic acid in pulmonary tuberculosis. *Nature* 1940; 145:706–707.
260. Pijoan M, Sedlacek B. Ascorbic acid in tuberculous Navajo indians. *Am Rev Tuberc* 1943; 48:342–346.
261. Bumbalo TS. Urinary output of vitamin C of normal and of sick children. *Am J Dis Child* 1938; 55:1212–1220.
262. Getz HR, Koerner TA. Vitamin nutrition in tuberculosis. *Am Rev Tuberc* 1943; 47:274–283.
263. Heise FH, Martin GJ. Ascorbic acid metabolism in tuberculosis. *Proc Soc Exp Biol Med* 1936; 34:642–644.
264. Martin GJ, Heise FH. Vitamin C nutrition in pulmonary tuberculosis. *Am J Dig Dis Nutr* 1937; 4:368–374.
265. Jetter WW, Bumbalo TS. The urinary output of vitamin C in active tuberculosis in children. *Am J Med Sci* 1938; 195:362–366.
266. Chang CE, Lan TH. Vitamin C in tuberculosis. *Am Rev Tuberc* 1940; 41:494–506.
267. Abbasy MA, Hill NG, Harris LJ. Vitamin C and juvenile rheumatism, with some observations on the vitamin C reserves in surgical tuberculosis. *Lancet* 1936; 2:1413–1417.

268. Abbasy MA, Harris LJ, Ellman P. Vitamin C and infection. Excretion of vitamin C in pulmonary tuberculosis and in rheumatoid arthritis. *Lancet* 1937; 2:181–183.
269. Getz HR, Koerner TA. Vitamin A and ascorbic acid in pulmonary tuberculosis. *Am J Med Sci* 1941; 202:831–847.
270. Sweany HC, Clancy CL, Radford MH, Hunter V. The body economy of vitamin C in health and disease. *JAMA* 1941; 116:469–474.
271. Chakrabarti B, Banerjee S. Dehydroascorbic acid level in blood of patients suffering from various infectious diseases. *Proc Soc Exp Biol Med* 1955; 88:581–583.
272. Awotedu AA, Sofowora EO, Ette SI. Ascorbic acid deficiency in pulmonary tuberculosis. *East Afr Med J* 1984; 61:283–287.
273. Harde E, Rothstein IA, Ratish HD. Urinary excretion of vitamin C in pneumonia. *Proc Soc Exp Biol Med* 1935; 32:1088–1090.
274. Bullowa JGM, Rothstein IA, Ratisch HD, Harde E. Cevitamic acid excretion in pneumonias and some other pathological conditions. *Proc Soc Exp Biol Med* 1936; 34:1–7.
275. Rinehart JF, Greenberg LD, Christie AU. Reduced ascorbic acid content of blood plasma in rheumatic fever. *Proc Soc Exp Biol Med* 1936; 35:350–353.
276. Faulkner JM, Taylor FHL. Vitamin C and infection. *Ann Intern Med* 1937; 10:1867–1873.
277. Rinehart JF, Greenberg LD, Olney M, Choy F. Metabolism of vitamin C in rheumatic fever. *Arch Intern Med* 1938; 61:552–561.
278. Abt AF, Hardy LM, Farmer CJ, Maaske JD. Relation of vitamin C to scarlet fever, rheumatic infections and diphtheria in children. *Am J Dis Child* 1942; 64:426–442.
279. Banerjee S, Belavady B. Dehydroascorbic acid level of blood in health and in typhoid fever. *Lancet* 1953; 2:912–913.
280. Abbasy MA, Harris LJ, Hill NG. Vitamin C and infection: excretion of vitamin C in osteomyelitis. *Lancet* 1937; 2:177–180.
281. Sayed SM, Roy RB, Acharya PT. Leucocyte ascorbic acid and wound infection. *J Indian Med Assoc* 1975; 64:120–123.
282. Sinha SN, Gupta SC, Bajaj AK, et al. A study of blood ascorbic acid in leprosy. *Int J Lepr* 1984; 52:159–162.
283. Abbasy MA, Harris LJ, Ray SN, Marrack JR. Diagnosis of vitamin C subnutrition by urine analysis. *Lancet* 1935; 2:1399–1405.
284. Wilson CWM. Vitamin C metabolism and the common cold. *Eur J Clin Pharmacol* 1974; 7:421–428.
285. Davies JEW, Hughes RE, Jones E, et al. Metabolism of ascorbic acid in subjects infected with common cold viruses. *Biochem Med* 1979; 21:78–85.
286. Terezhalmay GT, Botomley WK, Pelleu GB. The use of water-soluble bioflavonoid-ascorbic acid complex in the treatment of recurrent herpes labialis. *Oral Surg* 1978; 45:56–62.
- 286a. Hunt C, Chakravorty NK, Annan G, et al. The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections. *Int J Vitam Nutr Res* 1994; 64:212–219.
287. Ganguly R, Waldman RH. Effect of orange juice on attenuated rubella virus infection. *Indian J Med Res* 1977; 66:359–363.
288. Ganguly R, Khakoo R, Spencer JC, Waldman RH. Immunoenhancing agents in prevention and treatment of influenza and other viral respiratory infections. *Dev Biol Stand* 1977; 39:363–372.
289. Heise FH, Martin GJ, Schwartz S. Vitamin C and blood sedimentation. *Br J Tuberc* 1937; 31:23–31.
290. Radford M, DeSavitsch E, Sweany HC. Blood changes following continuous daily administration of vitamin C and orange juice to tuberculous patients. *Am Rev Tuberc* 1937; 35:784–793.
291. Kaplan A, Zonnis ME. Vitamin C in pulmonary tuberculosis. *Am Rev Tuberc* 1940; 42:667–673.

292. Bogen E, Hawkins L, Bennett ES. Vitamin C treatment of mucous membrane tuberculosis. *Am Rev Tuberc* 1941; 44:596–603.
293. Babbar IJ. Therapeutic effect of ascorbic acid in tuberculosis. *Indian Med Gaz* 1948; 83: 409–410.
294. Baur H, Staub H. Therapy of hepatitis with ascorbic acid infusions. *Schweiz Med Wochenschr* 1954; 84:595–597.
295. Kirchmair H, Kirsch B. Treatment of epidemic hepatitis in children with high doses of ascorbic acid. *Med Monatschrift* 1957; 11:353–357.
296. Kirchmair H. Epidemic hepatitis in children and its treatment with high doses of ascorbic acid. *Dtsch Gesundheitsw* 1957; 12:1525–1536.
297. Baetgen D. Results of the treatment of epidemic hepatitis in children with high doses of ascorbic acid in the years 1957–1958. *Med Monatschrift* 1961; 15:30–36.
298. Baur H. Poliomyelitis therapy with ascorbic acid. *Helv Med Acta* 1952; 19:470–474.
299. Tang AM, Graham NMH, Kirby AJ, et al. Dietary micronutrient intake and risk of progression to AIDS in HIV-1-infected homosexual men. *Am J Epidemiol* 1993; 138:937–951.
300. National Research Council. Recommended Dietary Allowances. 10th ed. Washington, DC: National Academy Press, 1989.
301. Luberoff BJ. Symptomectomy with vitamin C: a chat with Robert Cathcart. *Chemtech* 1978; 8:76–86.
302. Cathcart RF. Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy. *Med Hypotheses* 1981; 7:1359–1376.
303. Klenner FR. Virus pneumonia and its treatment with vitamin C. *South Med Surg* 1948; 110: 36–38, 46.
304. Klenner FR. Massive doses of vitamin C and the virus diseases. *South Med Surg* 1951; 113: 101–107.
305. Klenner FR. Observations on the dose and administration of ascorbic acid when employed beyond the range of a vitamin in human pathology. *J Appl Nutr* 1971; 23:61–88.
306. Dalton WL. Massive doses of vitamin C in the treatment of viral diseases. *J Indiana State Med Assoc* 1962; 55:1151–1154.
307. Gotzsche AL. Pernasal vitamin C and the common cold (letter). *Lancet* 1989; 2:1039.
308. Rivers JM. Safety of high-level vitamin C ingestion. *Ann NY Acad Sci* 1987; 498:445–454.
309. Bendich A, Langseth L. The health effects of vitamin C supplementation: a review. *J Am Coll Nutr* 1995; 14:124–136.

Vitamin **C** in Health and Disease

edited by

Lester Packer

*University of California
Berkeley, California*

Jürgen Fuchs

*Johann Wolfgang Goethe University
Frankfurt, Germany*



MARCEL DEKKER, INC.

NEW YORK • BASEL • HONG KONG

Library of Congress Cataloging-in-Publication Data

Vitamin C in health and disease / edited by Lester Packer, Jürgen Fuchs.

p. cm.— (Antioxidants in health and disease ; 5)

Includes index.

ISBN 0-8247-9313-7 (hardcover : alk. paper)

1. Vitamin C—Health aspects. I. Packer, Lester. II. Fuchs, Jürgen. III. Series.

[DNLM: 1. Ascorbic Acid—physiology. 2. Ascorbic Acid—therapeutic use. 3. Ascorbic Acid—chemistry. W1 AN884 v.5 1997 / QU 210 V8363 1997]

615'.328—dc21

DNLM/DLC

for Library of Congress

97-7703
CIP

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the address below.

This book is printed on acid-free paper.

Copyright © 1997 by Marcel Dekker, Inc. All Rights Reserved.

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA