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# *Vitamin C and Infectious Diseases*

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## 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 ($\geq$ 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]<br>−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]<br>−3 | 0.012 | 8.85 |
| | Total: | 1343 | Median | −26 | $\chi^2$ (16 df) = 68.9 | |
| | | | Mean | −31 | combined $p(1 - t)$ = | |
| | | | Weighted mean | −15 | 0.00000001 | |

[a]Studies 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).

[b]The outcome is the duration of cold symptoms except when otherwise indicated.

[c]The number of subjects; the number of episodes is not given in the report.

[d]Days of morbidity for sore throats.

[e]Induced rhinovirus infection.

[f]Severity of symptoms.

[g]Severity of symptoms at the fourth day after challenge.

[h]$p$ Value for comparing the sickness days between the groups.

[i]At the onset of a cold episode an additional 3 g/day was given for 3–5 days.

[j]Days 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; $p(1\text{-}t) = 0.00003$), 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 | | | |
|---|---|---|---|---|---|---|---|
| | | | | Vitamin C | Placebo | RR | 90% CI |
| 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 |

[a]Studies 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 Chediak-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. o-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. coll* (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] | $p$ $(1 - t)$ | 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 |

[a]Type 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.

[c]Vitamin 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.

[d]The 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

| Ref. | Plasma vitamin C limit (μmol/L) | Cases/total Vitamin C levels High | Low | OR | (90% CI)[a] | $p^a$ (1 − t) | Subjects/notes |
|---|---|---|---|---|---|---|---|
| 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<br>1.00[c] | (0.06, 0.33)[b] | <0.001<br>— | 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 |

[a]For calculation of OR, 90% CI, and $p$ value, see Table 5. OR, odds ratio; CI, confidence interval.
[b]Unadjusted OR from logistic regression analysis calculated in the reference.
[c]OR 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

| | Cases/total Vitamin C levels | | | | |
|---|---|---|---|---|---|
| Ref. | High | Low | OR (90% CI)[a] | $p^a$ $(1 - t)$ | Subjects/notes |
| Intervention study: supplementation: 1 g/day | | | | | |
| 38 | 6/57 | 13/57 | 0.40 (0.16, 0.97) | 0.043 | Children |
| Observational study: limit: 49 μmol/L (8.6 mg/L) in blood | | | | | |
| 256 | 4/32 | 30/64 | 0.16 (0.06, 0.42) | <0.001 | From table 1 in Ref. 256. Children referred to tonsillectomy |

[a]For 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 G 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 Terezhalmy 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 admnistered 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, Terezhalmy 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 Terezhalmy'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. Terezhalmy 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 | 759 ± 907 (SD) | 0.25 | SGOT (unit) |
| | | | | | 33% (2) | 62% (5) | 0.17 | PCTG with chronic liver disease |
| | | | | | 7.6 ± 2.0 | 6.9 ± 2.1 (SD) | 0.27 | 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) | 65% (65) | 0.010 | PCTG feeling better |
| | | | | | 49% (49) | 33% (33) | 0.012 | 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% | 25% | — | PCTG feeling better |
| | | | | | 72% | 25% | — | PCTG with increase in hemoglobin |

[a]Type of control: C, placebo not used; F, vitamin C added to food; P, placebo-controlled; DB, double-blind.

[b]For dichotomous data the mid-*p* value was calculated (cf. Table 5) and for continuous variables the *t*-test was used.

[c]PCTG, 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.

[d]Terezhalmy et al. also gave their patients bioflavonoids (0.6–1 g/day).

[e]Vitamin C was given as orange juice.

[f]Vitamin C was administered for 2 weeks after the blood transfusion, i.e., it was terminated before the occurrence of the episodes.

[g]The 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.

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# Vitamin C in Health and Disease


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