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## Vitamin C and the common cold

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The effect of vitamin C on the common cold has been the subject of several studies. These studies do not support a considerable decrease in the incidence of the common cold with supplemental vitamin C. However, vitamin C has consistently decreased the duration of cold episodes and the severity of symptoms. The benefits that have been observed in different studies show a large variation and, therefore, the clinical significance may not be clearly inferred from them. The biochemical explanation for the benefits may be based on the antioxidant property of vitamin C. In an infection, phagocytic leucocytes become activated and they produce oxidizing compounds which are released from the cell. By reacting with these oxidants, vitamin C may decrease the inflammatory effects caused by them. Scurvy, which is caused by a deficiency in vitamin C, is mostly attributed to the decreased synthesis of collagen. However, vitamin C also participates in several other reactions, such as the destruction of oxidizing substances. The common cold studies indicate that the amounts of vitamin C which safely protect from scurvy may still be too low to provide an efficient rate for other reactions, possibly antioxidant in nature, in infected people.

**Ascorbic acid: Infection: Neutrophils: Superoxide: Hypochlorite**

Twenty years ago Linus Pauling (1970a) wrote the book *Vitamin C and the Common Cold* in which he claimed that vitamin C is beneficial against the common cold. Pauling (1970a) based his opinion on several earlier studies. For example, Cowan *et al.* (1942) reported 30 % fewer days of sickness in a group taking supplemental vitamin C (0.2 g/d) compared with a control group, and Ritzel (1961) observed about half the number of sickness days in the vitamin C group (1 g/d) compared with controls. Pauling (1971a) made a statistical analysis of four double-blind studies which were the only investigations available that had used a regular intake of at least 0.1 g/d. He found a very low probability ( $P = 0.00002$ ) that all the decreases in the total morbidity observed in the vitamin C groups would have occurred by chance. The studies also indicated that the vitamin would decrease the incidence of the common cold, although the combined significance was lower ( $P = 0.001$ ). Of these four studies, the one carried out by Ritzel (1961, 1976) used the largest dose (1 g/d) and found the greatest benefit. This led Pauling (1970a, 1971a, b) to conclude that such amounts would considerably decrease the incidence of, and morbidity due to, the common cold. However, the studies Pauling referred to had some shortcomings (Dykes & Meier, 1975), and so far not many nutritionists and physicians have been convinced of the usefulness of vitamin C in the prevention or treatment of the common cold.

Pauling's (1970a) book provoked disagreement and irritation because he wrote it for laymen, even though the opinions expressed in it were not generally accepted in medicine. He was considered to have abused the respect due to a double Nobel prize winner. However, one result of Pauling's (1970a) book was that several controlled trials were performed to clarify the possible role of vitamin C in the common cold. Table 1 lists the studies carried out since 1970 in which at least 1 g vitamin C/d was regularly given to

subjects. Thus, they tested the validity of Pauling's (1970*a*, 1971*a*, *b*) conclusions. So far, over one hundred articles have dealt with the role of vitamin C in the common cold (Pauling, 1970*a*; Briggs 1984; Truswell, 1986; Kleijnen *et al.* 1989).

#### *Effect on incidence*

According to the studies listed in Table 1, vitamin C has no significant prophylactic effect against the common cold when the incidence is considered. Several studies have shown a small decrease in the number of episodes of the common cold in the vitamin C group; however, other studies have found a small increase in the incidence. A statistically significant decrease in the incidence has been observed in only two rather minor studies (Charleston & Clegg, 1972; Sabiston & Radomski, 1974).

Another variable reflecting the prophylactic effect that has been measured in a few studies is the percentage of subjects free of illness. Anderson *et al.* (1972) found that 26% of the vitamin C group, but only 18% of the control group, remained free of illness ( $P < 0.05$ ). Coulehan *et al.* (1974) made a similar observation which was also statistically significant. Furthermore, a statistically significant negative correlation has been reported between the daily vitamin C intake and the incidence of common cold symptoms in a group of 527 subjects (Cheraskin *et al.* 1973). Whether all the small decreases in the incidence are due to a minor biological effect or due to statistical artifacts cannot be answered on the basis of available studies.

#### *Decrease in morbidity*

There has been a consistent decrease in the duration of the common cold episodes, or amelioration of the symptoms in all studies (Table 1). In this respect Pauling's (1970*a*, 1971*a*, *b*) claims have been corroborated. All the studies have been double-blind, except that by Charleston & Clegg (1972). Not all the results are statistically significant, yet all of them point consistently in the same direction. None of the studies shows an increase in morbidity, which would be expected if the results were mainly due to chance. The probability that none of the eighteen studies would find an increase in the duration of the episode purely by chance is  $1:2^{18}$  ( $P = 0.000004$ ).

The benefits which have been observed in the studies differ substantially. This is not surprising, since several factors may affect the efficacy of vitamin C. The studies have used different types of subjects, and they have been performed in different geographical regions. There are several types of viruses which may cause the common cold (Sperber & Hayden, 1988), and the criteria for the disease have not been consistently defined.

One possible cause of the differences is the background intake of vitamin C, which is not usually determined. This factor can be observed clearly in the study by Miller *et al.* (1977). Before the study the subjects excreted, on average, 300 mg vitamin C/d in their urine. The level of intake must have been even larger, since not all is absorbed from the intestine, and only part is excreted in urine. Thus, the background intake in these subjects has been much greater than the recommended dietary allowance, (RDA; 60 mg/d; National Research Council, 1989). If one intends to study whether amounts larger than the RDA have a beneficial effect on the common cold, then the background intake should be quite close to the recommendation, in contrast to the study by Miller *et al.* (1977). Anderson *et al.* (1972, 1975) found that supplemental vitamin C is more beneficial to those who have a low daily intake of fruit juice, which points out the importance of the background intake. The level of background intake may be a source of error in other studies besides that of Miller *et al.* (1977), but unfortunately it was usually not determined and, thus, the validity of the control groups cannot be evaluated in this respect. Assuming that the background intake has been larger than the RDA in most cases, this factor would tend to decrease the observed effect.

Table 1. Vitamin C and the common cold: common cold studies carried out since 1970, in which subjects have regularly received at least 1 g of vitamin C/d

Reference	No. of subjects	Duration of study (months)	Dose (g/d)	Incidence (colds/person)		Effect on incidence (%)	Average duration of episodes (d)		Effect on duration or symptoms (%)	Statistical significance (duration or symptoms): P
				Vitamin C	Placebo		Vitamin C	Placebo		
Anderson <i>et al.</i> 1972, 1973	818	3	1+3 <sup>a</sup>	1.38	1.48	-7	3.96	4.18 <sup>b</sup>	-5	< 0.05
Charleston & Clegg, 1972 Elliott, 1973 Schwartz <i>et al.</i> 1973 Anderson <i>et al.</i> 1974	90	4	1	0.94	1.86	-49	1.04	1.32 <sup>c</sup>	-21	< 0.01
	70	3	2	—	—	±0	0.88	1.31 <sup>d</sup>	-33	< 0.02
	21	1 <sup>f</sup>	3	1	1	0	3.5	4.2	-17	< 0.02
	868	3	1	1.51	1.53	0	—	—	-72 <sup>e</sup>	< 0.01
Coulehan <i>et al.</i> 1974	{ 382 259	3	1	1.51	1.53	0	5.04	5.40 <sup>h</sup>	-7	< 0.01 <sup>i</sup>
		3	1	0.10	0.12	-17	4.87	5.40 <sup>h</sup>	-10	< 0.05 <sup>i</sup>
		3	2	0.12	0.13	-8	4.95	5.65	-12	< 0.05 <sup>i</sup>
Sabiston & Ramdomski, 1974	112	1	1	0.11	0.25	-56	4.44	6.29	-29	< 0.05 <sup>i</sup>
Clegg & Macdonald, 1975	211	4	1	1.01	1.04	-3	4.2	5.6 <sup>j</sup>	-25	< 0.05
		4	1 <sup>1</sup>	0.69	1.04	-33	0.8	2.4 <sup>k</sup>	-67	< 0.05
Karlowski <i>et al.</i> 1975 Coulehan <i>et al.</i> 1976 Elwood <i>et al.</i> 1976 Miller <i>et al.</i> 1977	90	9	3	1.27	1.36	-7 <sup>m</sup>	7.2	7.6	-5	< 0.05
	868	4	1	0.23	0.23	0	7.0	7.6	-8	< 0.05
	688	3	1	1.85	1.98	-7	6.7	7.1	-5	< 0.05
	24	5	1	4.8	3.8	+26	5.5	5.8	-5	< 0.05
		5	1	4.8	3.8	+26	5.97	6.38	-6	< 0.05
Ludvigsson <i>et al.</i> 1977	{ 158 615	2	1	0.78	0.71	+10	7.7	8.3 <sup>b</sup>	-7	< 0.01
		3	1	1.39	1.28	+9	0.8	1.0 <sup>n</sup>	-20	< 0.01
Pitt & Costrini, 1979	674	2	2	1.81	1.80	0	22.5	27.3 <sup>o</sup>	-18	< 0.01
		3	1	1.30	1.61	-19	8.90	14.53 <sup>b</sup>	-39	< 0.01
Carr <i>et al.</i> 1981	{ 88 <sup>p</sup> 102 <sup>q</sup>	3	1	1.30	1.61	-19	2.68	3.87 <sup>d</sup>	-31	< 0.05
		3	1	1.30	1.61	-19	9.54	10.14 <sup>b</sup>	-6	< 0.05
Bancalari <i>et al.</i> 1984 Briggs, 1984 Mink <i>et al.</i> 1988	62 528 16	3	2	1.19	1.53	-22	2.77	3.22 <sup>d</sup>	-14	< 0.05
		3-6	1	0.47	0.46	0	11.2	11.5 <sup>b</sup>	-3	< 0.05
		1 <sup>r</sup>	2	0.50	0.87	-42	1.87	1.97 <sup>o</sup>	-5	< 0.05

<sup>a</sup> At the onset of a cold episode an additional 3 g/d was given for 3 d. <sup>b</sup> Symptoms present. <sup>c</sup> Confined to house. <sup>d</sup> Days off work or absence from school. <sup>e</sup> Days of morbidity for sore throats. <sup>f</sup> Induced rhinovirus infection. <sup>g</sup> Symptoms were less severe in subjects receiving vitamin C; the difference was most significant at the fourth day of infection. <sup>h</sup> Test groups are compared with one of two placebo groups that better matched the test groups with respect to the data of previous cold episodes. <sup>i</sup> Significance for total morbidity. <sup>j</sup> Nasal symptoms. <sup>k</sup> Constitutional symptoms; such as headache, general malaise, chills and fever. <sup>l</sup> 1 g of D-ascorbic acid per day. <sup>m</sup> Data for incidence is based on 190 subjects. <sup>n</sup> Days in bed. <sup>o</sup> Severity of symptoms; for unit, see the reference. <sup>p</sup> Twins living apart. <sup>q</sup> Twins living together.

Some of the studies have used twins as subjects (Miller *et al.* 1977; Carr *et al.* 1981) which may cause protocol problems, since playful boys particularly may change the tablets that they are expected to ingest regularly. In these two studies no protocol was used to eliminate the possibility of tablet interchange by children living in the same home. In the study of Miller *et al.* (1977) the vitamin C content in the urine of boys, but not of girls, receiving a placebo increased greatly. Obviously, the girls obeyed the rules better than the boys, who probably swapped tablets. In the case of the girls, vitamin C decreased the duration and severity of colds by a statistically significant amount ( $P < 0.05$ ). Furthermore, in the study of Carr *et al.* (1981), vitamin C appeared ineffective in twins living together, while it was more effective than the placebo for twins living apart (Table 1).

According to some studies, vitamin C seems to have a greater effect on the subjective feeling of severity, but a smaller effect on the objective symptoms of the common cold (Anderson *et al.* 1972, 1975; Sabiston & Radomski, 1974; Ludvigsson *et al.* 1977; Pitt & Costrini, 1979). Thus, the episode is only somewhat shorter but the severity is significantly decreased by the vitamin. This observation has several implications. First, the absence from school or from work is of greater practical importance than the presence of a runny nose. Thus, the clinical significance of vitamin C may be greater than one may conclude by strict pathology (e.g. the effect on nasal symptoms). Second, some of the studies which have found only a minor effect from the vitamin have recorded only the objective symptoms and not variables which are connected to the subjective feeling of the severity (Clegg & Macdonald, 1975; Elwood *et al.* 1976). Third, the smaller effect on the objective symptoms may suggest that the major effect of vitamin C in these studies is not a stimulation of the immunological system. Instead, the major effect of the vitamin may be due to the suppression of harmful host responses which are triggered by the viral infection, and the prevention of the decrease in the vitamin level which regularly occurs during the cold episode (see p. 10). Both these mechanisms may cause a greater effect on the subjective feeling of the severity, and a smaller effect on the natural progress of the viral infection.

One of the critical factors in the studies has been the maintenance of the double-blind protocol. Karlowski *et al.* (1975) found in a questionnaire that several subjects had guessed correctly whether they were receiving the placebo or the vitamin and, therefore, the authors concluded that the protocol was partially broken. In their study, the placebo tablets were made of lactose and, thus, they could be distinguished from ascorbic acid tablets by taste. However, in several other studies the placebo and the vitamin tablets were indistinguishable (e.g. Anderson *et al.* 1972; Elliott, 1973; Coulehan *et al.* 1974; Ludvigsson *et al.* 1977; Pitt & Costrini, 1979; Carr *et al.* 1981). Another reason for the breaking of the code may be the benefit shown by the vitamin. For example, Asfora (1977) initiated a double-blind study to determine whether 6 g vitamin C/d was beneficial when given at the onset of the cold episode. The benefits were so obvious that the physician could recognize the subjects receiving the vitamin by their clinical progress. Therefore, the double-blind study was terminated, and a less-well-controlled study was performed (see p. 7). Vitamin C also decreased the morbidity and mortality due to parainfluenza infection in an animal study, where the risk of the placebo effect is smaller (Murphy *et al.* 1974).

The design of the studies and the quality of the reports show some variation. One of two studies showing the greatest benefits was reported concisely (Elliott, 1973), while the other gave insufficient details and was not published in a regular scientific forum (Sabiston & Radomski, 1974). On the other hand, a high background intake of the vitamin, or observing only the nasal and throat symptoms, may provide an explanation for some of the smallest benefits that have been reported. The study by Anderson *et al.* (1972) was intended to show definitely that Pauling (1970a) was wrong, and while it appears to be the most carefully planned and extensively analysed, its observed benefits were not the lowest nor the

highest reported. Thus, the consideration of the quality of the studies does not seem to make a clear statement in the quantitative variation of the results. For the technical details and for the complete set of results of the eighteen studies, the reader is referred to the original publications.

#### *Therapeutic studies*

The studies listed in Table 1 used regular vitamin intake, but in some other cases the therapeutic effect of vitamin C has been examined. In such cases the vitamin was administered only after the onset of the common cold episode. Asfora (1977) gave the same subjects either vitamin C (6 g/d for 5 d) or other medications (e.g. aspirin) during different episodes, but not in a double-blind fashion. Vitamin C decreased the average duration of common cold episodes from 6.9 to 3.6 d (–48 %,  $P < 0.01$ ). If the vitamin supplementation was initiated later than 24 h after the start of the cold episode, the benefit was much smaller.

Anderson *et al.* (1974) tested the therapeutic effect of 4 and 8 g doses given only on the first day of sickness. When eight classes of symptoms were followed to determine the duration of cold episodes, the larger dose was consistently more effective than the smaller in shortening the duration. In another double-blind study Anderson *et al.* (1975) used 1.5 g vitamin C for the first day of the cold episode, and 1 g/d for the next 4 d. The vitamin-receiving group had a significant ( $P < 0.05$ ) decrease in terms of days confined indoors (–25%), days feeling ‘feverish’ (–29%) and days feeling ‘cold and shivery’ (–27%). Several other symptoms were also decreased, but not to a degree of statistical significance.

Karlowski *et al.* (1975) gave 3 g vitamin C/d for 5 d from the start of the episode: the control group had an average episode duration of 7.1 d, while the vitamin-receiving group had a duration of 6.5 d (–8 %). The shortest duration (5.9 d; –17%) was in a group which was regularly given 3 g/d, and an extra 3 g/d when they caught a cold (total 6 g/d). In this study a prophylactic group (3 g/d) was also included. This fourth group had an average episode duration of 6.7 d (–5%). Thus, the benefit in this double-blind study was consistently greater with larger levels of vitamin intake. A pair-wise comparison did not show a statistical significance for any pair of groups. However, no statistical analysis was made to determine the probability that such a consistent pattern of results for four groups would appear randomly.

Elwood *et al.* (1977) and Tyrrell *et al.* (1977) also studied the therapeutic effect of vitamin C by double-blind studies: these studies showed no clear benefit. Elwood *et al.* (1977) found a decrease in the duration of ‘simple’ colds (nasal symptoms) in men (–30%,  $P < 0.01$ ), but an increase in women (+22%), and no clear effect on ‘chest’ colds (cough or other chest symptoms). An odd observation by Tyrrell *et al.* (1977) was that men treated with the vitamin had a significant reduction in reoccurring colds affecting the same subject. However, in both these studies the period of vitamin supplementation was much shorter than the average duration of the cold episodes. These studies used 3–4 g vitamin C/d for only 3 d (total 10 g), while the average duration of the cold was 5 and 8 d for ‘simple’ and ‘complex’ colds respectively (Elwood *et al.* 1977), and 8 d (Tyrrell *et al.* 1977). Accordingly, in these two studies the test period was shorter than that in the studies of Anderson *et al.* (1975), Karlowski *et al.* (1975) and Asfora (1977), which may partially explain the differences in the results. Also, due to the protocol, the vitamin supplementation in all studies in Table 1 covered the entire cold episode.

The therapeutic trials have not been extensive enough to allow clear conclusions, yet they indicate that a regular ingestion of vitamin C is not needed to gain benefit from the vitamin for the relief of common cold symptoms. The results of Anderson *et al.* (1974) and Karlowski *et al.* (1975) suggest that the therapeutic effect may be dose-dependent. To obtain a better quantitative estimation for the best amounts, and for the significance of

vitamin C in the amelioration of the common cold symptoms, it is quite clear that more therapeutic investigations with better experimental design are required.

#### *Secondary infections*

The common cold and certain other viral infections are sometimes accompanied by secondary bacterial infections (Abramson & Mills, 1988). Some of the vitamin C-related common cold studies have measured the incidence of secondary infections. Asfora (1977) reported a much lower incidence of bacterial complications when patients were treated with vitamin C. Coulehan *et al.* (1976) found thirteen subjects in the control group that were  $\beta$ -haemolytic streptococcus positive, while in the vitamin C group only six were positive ( $P < 0.1$ ). Pitt & Costrini (1979) found seven cases of pneumonia in the control group, but only a single case in the vitamin C group ( $P < 0.04$ ). However, this small amount of information does not allow any definite conclusions to be drawn.

#### *What are the upper limits for 'physiological' amounts?*

The vitamin C doses that have been used in the common cold studies are markedly larger than the RDA of 60 mg/d. In contrast to humans and guinea-pigs, most other mammals synthesize vitamin C by themselves in amounts which correspond to 1–10 g/d when extrapolated to the human size (Levine, 1986). Of course, one may not conclude that such amounts are certainly the best for humans, yet one should not maintain the rigid opinion that the doses used in the common cold studies are strictly pharmacological. According to Pauling (1970*b*) and Eaton & Konner (1985), the typical diet of our ancestors may have contained 0.4–2 g vitamin C/d and, therefore, such levels are not very high for human physiology, even though the optimal amount is an open question. Moreover, the rate of synthesis in animals is not constant, but increases due to various stress factors. Vitamin C synthesis in the rat may increase tenfold in response to some drugs (Conney *et al.* 1961); also, a low ambient temperature increases the rate of synthesis (Dugal, 1961). Accordingly, the best levels for humans may depend on several factors, with the optimal level for a person infected by a virus possibly being larger than for people in good health.

Vitamin C is quite safe even in large amounts and, despite some warnings, large doses do not result in calcium-oxalate stones, impaired vitamin B<sub>12</sub> status or iron overload (Rivers, 1987). One common side-effect of large doses of vitamin C is diarrhoea and other stomach problems which, in healthy people, are caused by 4–10 g/d. The stomach problems are apparently caused because a large portion of the dose is not absorbed from the intestine. Viral infections such as the common cold and some other diseases affect the metabolism of vitamin C. People with a common cold may ingest over 30 g vitamin C/d without getting diarrhoea (Luberoff, 1978; Cathcart, 1981). According to Cathcart (1981), such very large doses are beneficial in treating viral diseases, and the best amount seems to be one slightly smaller than the dose which causes stomach problems. Large amounts of vitamin C have also been used by others in the treatment of the common cold and other infectious diseases (Klenner, 1951, 1971; Dalton, 1962; Regnier, 1968; Stone, 1972). These doses have usually been larger than those used in the controlled experiments. This invites the speculation that an even larger effect might have been observed in the therapeutic trials if larger doses of the vitamin had been used.

#### *Biochemical model*

At the biochemical level, the effect of vitamin C on the common cold may be explained to a large degree by the protection it may provide against the oxidizing agents that are produced by neutrophilic leucocytes. Neutrophils are phagocytic cells which participate in the destruction of viruses and bacteria (Lehrer *et al.* 1988; Hurst & Barrette, 1989; Weiss, 1989; Anderson & Theron, 1990). Viruses and bacteria are engulfed into an intracellular

vacuole, the phagosome, where they are digested. For this purpose, several proteases (e.g. elastase (EC 3.4.21.37)) are released into the phagosome from intracellular granules. In addition, there is also an enzyme-mediated 'respiratory burst', which results in the production of a set of reactive oxygen-derived compounds. Contact with a foreign particle causes the activation of membrane bound NADPH-oxidase, which produces superoxide in the phagosome. Superoxide dismutates to oxygen and hydrogen peroxide: the hydrogen peroxide formed is used as a substrate for the myeloperoxidase (EC 1.11.1.7)-catalysed reaction, which converts chloride to hypochlorite. Hypochlorite is an extremely effective oxidant which reacts with amines, sulphhydryl groups, aromatics and unsaturated carbon bonds among others; it is the common household bleaching reagent.

The strongly reactive substances released by the neutrophils are intended to participate in the destruction of viruses and bacteria within the phagosomes, but they also have several harmful effects on the body. To some degree, they escape from the cell and cause damage to sensitive biochemical compounds in the extracellular space and in the cell membranes. One of the critical targets appears to be the  $\alpha_1$ -proteinase inhibitor, which is rapidly inactivated by hypochlorite. The  $\alpha_1$ -proteinase inhibitor is present in plasma where it reacts rapidly with elastase, and thereby protects the extracellular space from the escaped protease. Inactivation of the inhibitor allows the released elastase to remain active. Thus, among other damaging reactions, the reactive oxidants may indirectly cause the activation of proteolysis. The oxygen radicals and the proteases have been implicated in several kinds of neutrophil-mediated non-infectious inflammatory diseases (Jackson & Cochrane, 1988; Weiss, 1989; Ward & Varani, 1990). Studies with model systems have suggested that various oxidant scavengers can prevent neutrophil-induced injury (Jackson & Cochrane, 1988; Anderson & Theron, 1990). In a test system, physiological concentrations of vitamin C provided concentration-dependent protection for the  $\alpha_1$ -proteinase inhibitor against hypochlorite (Theron & Anderson, 1985; Halliwell *et al.* 1987). Also, in a model system of lung inflammation, vitamin C inhibited the influx of neutrophils to the lungs, and thereby it may protect the lungs from neutrophil-mediated injury (Nowak *et al.* 1989).

It has been shown that the respiratory burst of neutrophils causes efficient oxidation of extracellular vitamin C (Hemilä *et al.* 1984; Anderson & Lukey, 1987; Frei *et al.* 1988; Thomas *et al.* 1988). Intracellular vitamin C is also partially oxidized (Stankova *et al.* 1975; Winterbourn & Wissers, 1983). Vitamin C is apparently the most efficient antioxidant in human plasma (Frei *et al.* 1988, 1989; Halliwell & Gutteridge, 1990) and, therefore, the concentration of the vitamin may be a significant factor in counteracting the escaped oxidants.

Common cold episodes are usually caused by rhinovirus infections (Sperber & Hayden, 1988). The pathogenesis of rhinovirus infections is not well understood. However, according to Turner *et al.* (1982) and Hendley (1983), the viral infection *per se* does not seem to be the main reason for the symptoms since there is only slight damage to the nasal epithelium. Instead, the host responses have been suggested to play a crucial role in the pathogenesis. In support of this model, a rhinovirus infection does not produce detectable damage or cytopathic effects on a monolayer culture of nasal epithelial cells (Winther *et al.* 1990). Neutrophils appear in the nasal mucosa early in the course of infection, even before the appearance of symptoms, which suggests a role for them in the pathogenesis (Winther *et al.* 1984*a, b*). Furthermore, upon infection with rhinoviruses, human embryonic lung fibroblast cultures start to produce a chemo-attractant for the neutrophils (Turner, 1988), and there is a strong correlation between the severity of symptoms and the number of neutrophils in the nasal lavages (Naclerio *et al.* 1988). The respiratory syncytial virus (RSV) is another of the several viruses which cause the common cold. A RSV-antibody complex has been shown to activate the respiratory burst of neutrophils and the resulting oxidants have been suggested to play a role in the pathogenesis of the RSV infection (Faden *et al.*



1983). Thus, neutrophils and their activation may have a crucial role in the pathogenesis of the common cold.

Consistently, a common cold episode significantly decreases the vitamin C concentration in leucocytes (Hume & Weyers, 1973; Wilson, 1975), and may also decrease it in plasma (Schwartz *et al.* 1973). The decrease within the leucocytes is quite small if subjects are given 6 g vitamin C/d during the cold episode (Hume & Weyers, 1973). In addition, the excretion of vitamin C in the urine is markedly decreased during a cold episode (Schwartz *et al.* 1973; Davies *et al.* 1979). These changes indicate that vitamin C is utilized during the common cold infection, and a possible reason may be the activation of neutrophils.

No clinical trials have been made to determine the role of oxygen radicals in the common cold. However, the harmful effects of superoxide production in an influenza A infection have been shown in mice. The infection increases superoxide production by phagocytic leucocytes several-fold. Furthermore, the activity of xanthine oxidase (*EC* 1.1.3.22), a superoxide-producing enzyme, is increased in serum and in the lungs. The mortality due to influenza infection is decreased if mice are injected with superoxide dismutase (*EC* 1.15.1.1) which causes the breakdown of superoxide (Oda *et al.* 1989). However, this does not show that superoxide *per se* is necessarily the most harmful compound. The role of superoxide could be indirect as, for example, it enhances the production of hypochlorite (Kettle & Winterbourn, 1990). Accordingly, the oxygen radicals appear to play a role in respiratory virus infections *in vivo*, although one must be cautious when extrapolating from data for mice influenza to the human common cold. Vitamin C reacts efficiently with superoxide and hypochlorite, and in sufficiently high concentrations it may provide protection similar to superoxide dismutase.

The reaction of vitamin C with the released oxidants has two implications. First, vitamin C may decrease the oxidation of sensitive compounds in the plasma and in the cell membranes by reacting rapidly with the generated oxidants. Second, vitamin C participates in many reactions in the body, and a reduced concentration due to its oxidation may cause a decrease in the reaction rates of several other vitamin C-dependent reactions.

Previously, the possible role of neutrophil activation in the common cold was only briefly suggested (Faden *et al.* 1983; Hemilä *et al.* 1984). However, there generally has been an increasing suspicion that the oxygen radicals, generated by neutrophils and by several other mechanisms, may play a significant role in many diseases such as; immune complex caused diseases, the toxicity of certain drugs, atherosclerosis, cancer, and a long list of others (Cross *et al.* 1987; Jackson & Cochrane, 1988; Cohen, 1989; Halliwell, 1989; Heffner & Repine, 1989).

The reaction of vitamin C with released oxidants is a reasonable model to explain the benefits observed in the common cold studies, yet there are also other reactions whereby vitamin C could be connected to the common cold.

#### *Other effects of vitamin C*

There is much information to suggest a role for vitamin C in the physiology of neutrophils. Within neutrophils the concentration of vitamin C is approximately fifty times that found in plasma (Washko *et al.* 1989). This high concentration may protect intracellular regions from oxidants that leak into the cytoplasm.

Neutrophil chemotaxis *in vitro* is significantly stimulated by 2–5 mM-vitamin C (Goetzl *et al.* 1974; Boxer *et al.* 1979). Although this concentration is markedly higher than the level in plasma (0.01–0.15 mM), a physiological significance is supported by an increase in neutrophil chemotaxis when normal subjects are supplemented with 2–3 g vitamin C/d (Anderson *et al.* 1980). Furthermore, leucocytes from scorbutic guinea-pigs exhibit significantly reduced migration compared with normal cells (Ganguly *et al.* 1976; Goldschmidt *et al.* 1988).

Vitamin C may affect the bactericidal capacity of neutrophils. Neutrophils from scorbutic guinea-pigs have decreased phagocytic activity according to several studies (Nungester & Ames, 1948; Mills, 1949; Merchant, 1950; Chatterjee *et al.* 1975a). Monocytes incubated with different concentrations of the vitamin (0–1 mM) show a clear correlation between the extracellular vitamin C concentration and the efficiency of phagocytosis (Thomas & Holt, 1978). Also, a decrease in the bactericidal activity of leucocytes from scorbutic guinea-pigs has been described in two reports (Shilotri, 1977; Goldschmidt *et al.* 1988), but not in another (Stankova *et al.* 1975). Furthermore, corticosteroids cause defects in neutrophil functions, but vitamin C supplementation (2 g/d) restores the respiratory burst in the neutrophils of patients treated with corticosteroids (Chretien & Garagusi, 1973).

The effect of vitamin C on phagocytosis and chemotactic response appears to be due to the modulation of tubulin tyrosination by an antioxidant effect. Tubulin is the subunit of microtubules which play a central role in the contractile machinery that causes cellular movements such as phagocytosis and locomotion. Microtubule organization seems to depend on the redox state of the cell (Nath & Gallin, 1983, 1987).

The oxidants produced by neutrophils cause auto-oxidation of the cells themselves, which results in the inhibition of phagocytosis, chemotaxis and respiratory burst (Baehner *et al.* 1977; Tsan, 1980; Stendahl *et al.* 1984). This auto-oxidation has been attributed to hydrogen peroxide and hypochlorite. The decrease in phagocytosis due to auto-oxidation was not observed in neutrophils isolated from subjects supplemented with vitamin E, a lipid-soluble antioxidant. However, vitamin E decreased the bactericidal activity at the same time (Baehner *et al.* 1977). Also, auto-oxidative inhibition of the respiratory burst components by hypochlorite may be decreased by vitamin C (Anderson & Lukey, 1987). Still, auto-oxidation is not the only means whereby a viral infection may impair the functions of neutrophils; neutrophil deactivation by influenza viruses appears to have other mechanisms as well (Hartshorn & Tauber, 1988).

Although several studies suggest that vitamin C is important in the function of neutrophils, many of them are neither extensive nor detailed enough to allow a clear and consistent picture to emerge. The role of vitamin C in the function of neutrophils does not appear to be an obvious explanation for the effects the vitamin has on common cold symptoms. However, the decrease in the vitamin level caused by the cold episode may render the neutrophils more susceptible to auto-oxidative damage. Defects in phagocytosis, chemotaxis or the respiratory burst of the neutrophils would tend to make the host more sensitive to secondary infections. Such a mechanism could explain the decrease in secondary infections reported in some studies when supplemental vitamin C was administered (see p. 8).

The common cold is sometimes treated with antihistamines (Sperber & Hayden, 1988). Vitamin C appears to react non-enzymically with histamine (Chatterjee *et al.* 1975b, c; Subramanian, 1978), and a significant negative correlation has been reported between the levels of vitamin C and histamine in human plasma (Clemetson, 1980). Common cold infection may cause a transient increase in bronchial responsiveness to inhaled histamine, and vitamin C has been found to inhibit this effect (Bucca *et al.* 1989). Histamine has been suggested to play a role in the increased airway hyperactivity of asthma patients in rhinovirus infection (Lemanske *et al.* 1989). RSV infection in children is sometimes accompanied by wheezing, and histamine levels are often increased in the patients with wheezing (Welliver *et al.* 1981). However, there is no increase in the levels of histamine in the nasal lavages of normal subjects infected with rhinovirus (Naclerio *et al.* 1988). Accordingly, histamine breakdown by vitamin C might have some role in certain cases, but obviously it is not the main mechanism for the decrease in common cold symptoms.

Several *in vitro* studies have shown inactivation of bacteria and viruses by vitamin C

(Drath & Karnovsky, 1974; Samuni *et al.* 1983). The inactivation is caused by a metal ion-catalysed reaction which uses vitamin C as a pro-oxidant. The level of metal ions able to catalyse the reaction is very low in the body, and in normal physiological conditions vitamin C is an antioxidant and not a pro-oxidant (Halliwell & Gutteridge, 1990). Thus, the inactivation reaction does not seem to occur freely in plasma, yet there is the possibility of a site-specific reaction. For example copper ions bound to specific sites of DNA may catalyse strand breakage by a vitamin C-dependent reaction (Wang & Ness, 1989).

### Conclusions

Vitamin C has consistently ameliorated the symptoms of the common cold in several controlled studies, and this observation is not unexpected on biochemical grounds. However, the optimal doses and the real significance of vitamin C cannot be inferred from the studies performed. What practical conclusions should be drawn? Because of potential side-effects and its quite moderate direct effects, vitamin C has been suggested to be useless clinically for the common cold (Chalmers, 1975; Dykes & Meier, 1975; Coulehan, 1979). However, several of the potential risks have appeared to be unfounded (Rivers, 1987), and there is some information to suggest that the benefit may be greater with higher doses.

The common cold studies also have more general implications. The goals of nutritional recommendations are to prevent overt deficiencies; for example the recommended dose of vitamin C has been chosen only for the prevention of scurvy (Hemilä, 1984, 1986; Levine, 1986; Pauling, 1986; Ginter, 1989). At the biochemical level, scurvy has been considered to be mostly due to decreased collagen synthesis. However, vitamin C is a significant factor in the function of several enzymes; e.g. it participates in the transformation of cholesterol to bile acids, and in the metabolism of carnitine (Levine, 1986; Ginter, 1989). Also, vitamin C participates in the transformation of dopamine to norepinephrine, and in several other reactions of both nervous and endocrine systems (Levine and Morita, 1985; Diliberto *et al.* 1987; Glembotski, 1987). Furthermore, vitamin C has several non-enzymic functions, e.g. it reacts with nitrite (Tannenbaum & Wishnok, 1987), with several oxidizing agents, and probably with histamine. The nutritional recommendations are not based on studies determining the best amounts for these other reactions. The RDA (60 mg/d) may be too low to provide good protection against oxidizing reagents, and 150 mg/d has been suggested as a better dose with respect to the reaction with the oxidants (Frei *et al.* 1989). The recommended levels are intended to be adequate to meet the 'nutrient needs' of healthy persons, yet the concept of exact 'nutrient need' appears to lack a sound biochemical basis (Hemilä, 1991).

Common cold studies show that the level of vitamin C intake is of importance even in the absence of an overt deficiency. Furthermore, in several disease conditions such as the common cold, the level of intake derived from a normal or a balanced diet may be insufficient for optimal body function.

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