

## **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. D-Isoascorbic acid also caused suppression of replication (180), suggesting a mechanism based on a non-specific antioxidant effect. It is not clear whether the effect is physiologically relevant. In one study vitamin C did not affect the Replication of selected respiratory viruses in cell culture (185).

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

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

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