Vitamin E and infectious diseases in the aged

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The incidence of infectious diseases, particularly respiratory diseases, increases with age. Age-associated decline in immune function contributes to the increased susceptibility of the aged to infections. Vitamin E supplementation has been shown to improve some aspects of immune function in aged animals and human subjects. The protective effect of vitamin E against viral or bacterial infections in experimentally-challenged young animals has been reported. We investigated the effects of supplementation with vitamin E and other antioxidants on resistance to influenza infection in young and old animals. While vitamin E-supplemented young mice showed only a modest reduction in lung viral titre, vitamin E-supplemented old mice exhibited a highly significant ($P < 0.05$) reduction in viral lung titre. In subsequent studies, we focused on the mechanism of vitamin E-induced reduction of influenza viral titre. The results of these studies as well as those reported by other investigators on the relationship between vitamin E and infectious diseases will be reviewed.

Vitamin E: Infectious Disease: Ageing: Influenza: Immune function

Infectious diseases in the aged

The incidence of infectious diseases, particularly respiratory diseases, increases with age and is associated with higher morbidity and mortality rates than in the young. Infectious diseases are common in the elderly, many of whom require hospitalization, contributing greatly to the medical costs associated with the care of the elderly. Among infectious diseases, respiratory tract infections are the leading cause of mortality in the USA (Ruben \textit{et al.}, 1995; Pinner \textit{et al.}, 1996). From 1979 to 1994 the overall death rates for pneumonia and influenza (P&I) increased by 59% (from 20·0 to 31·8 deaths per 100 000 population), which reflects the increase in the proportion of individuals in the older age-group and the higher death rates due to P&I in this age-group. In 1992, individuals aged 65 years and older accounted for 89% of all P&I deaths. From 1979 to 1992, P&I death rates among those aged 65 years and older increased by 44% (from 145·6 to 209·1 deaths per 100 000 population). Based on predicted shifts in the age distribution of the US population, total incidence of respiratory infectious diseases and health care cost associated with them will substantially increase (Centers for Disease Control and Prevention, 1995).

Among respiratory viruses, influenza viruses are the most challenging when development of more effective preventive strategies is considered; they change antigenic character (antigenic drift and antigenic shift) at irregular intervals and predispose the host to bacterial superinfections (Leigh \textit{et al.}, 1991). The clinical expression of infection with influenza virus is variable and is partially influenced by the nature of the infecting virus, but to a greater extent is modulated by the age, physiological state and immunological experience of the host. The risk of serious and fatal disease is higher in the very young, the elderly, or in patients with certain well-defined pre-existing conditions such as cardiovascular disease, broncho-pulmonary disease and diabetes. These conditions predispose an individual not only to the risk of acquiring influenza virus infection, but also to the risk of suffering severe disease once infection is established (Kilbourne, 1987). Barker & Mullooly (1980) reported that the risk of hospitalization due to influenza increased three to four times in patients age 65 years and older with pre-existing conditions such as cardiovascular, pulmonary and renal diseases, and diabetes compared with those without such pre-existing conditions. Thus, older individuals, who are more likely to have coexistent chronic diseases, are most susceptible to the lethal effects of influenza (Cesario & Yousefi, 1992).

Abbreviations: CTL, cytotoxic T lymphocyte; IFN, interferon; IL, interleukin; NK, natural killer; PG, prostaglandin; P&I, pneumonia and influenza; Th, T-helper.

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Effects of influenza infection on the host

The influenza viruses are responsible for a wide spectrum of clinical symptoms, including fever, headache, myalgia, malaise, anorexia and cough, and may also cause upper or lower respiratory tract infections indistinguishable from those due to other viruses. Clinical symptoms vary widely in severity and often are accompanied by a variety of complications. Secondary bacterial infection is the most common life-threatening complication of influenza infection. *Staphylococcus aureus*, *Staphylococcus pneumoniae* and *Haemophilus influenzae* are the most common pathogens following influenza infection and may result in local immunosuppression. The increased susceptibility to secondary bacterial invasion following influenza infection is attributed to decreased mucociliary clearance by the airways, enhanced bacterial adherence to influenza-infected cells, immunosuppression caused by virus infection, and decreased bacterial clearance by phagocytes (Rouse & Horohov, 1986; Wyde et al. 1989; Leigh et al. 1991). On the other hand, *S. aureus* has been shown to secrete a protease capable of activating haemagglutinin by proteolytic cleavage in vitro. Thus, co-infecting micro-organisms such as *S. aureus* can lead to extensive spread of infection in the lung by increasing viral replication before the host defence system becomes effective (Tashiro et al. 1987).

An excessive production of reactive oxygen species and a decreased antioxidant status have been shown to occur with influenza infection, human immunodeficiency virus infection and septic shock (Hennet et al. 1992; Greenspan & Aruoma, 1995; Goode et al. 1995). Neutrophils and macrophages are known to produce superoxide free radicals (O•−) and H2O2, which are needed for defence against ingested or invading microbes. However, these reactive oxygen species could increase viral infections through activation of proteases (Hennet et al. 1992), and augment the tissue damage seen in the lungs after influenza virus infection by oxidizing cellular lipids, proteins and nucleic acids (Maeda et al. 1987). The O•−-generating capacity of alveolar phagocytic cells has been shown to increase about 8-fold following influenza infection. The activity of xanthine oxidase (EC 1.1.3.22), which is responsible for the generation of oxygen free radicals, was shown to be elevated in serum and lung tissues of mice infected with the influenza virus (Maeda & Akaike, 1991). We have also observed increased production of H2O2 by lung cells stimulated with zymosan in young and old C57BL mice following influenza infection (Fig. 1). Hennet et al. (1992) reported that influenza infection in mice resulted in a decrease in total concentrations of the antioxidants GSH, vitamins C and E from the lungs, especially in the early stages of the infection. This decrease may be due to decreased production of antioxidants. A decrease in the concentration of these antioxidants may reduce the ability of tissues to protect against oxidative stress and may result in local immunosuppression.

Immunological factors involved in the control of influenza virus

Natural killer (NK) cells, production of interferon (IFN)-α, β or γ, cytotoxic T lymphocyte (CTL), CD4+ T-cells, and B-cells are all thought to be involved in the control of influenza virus. NK cells are among the first lines of defence against infectious agents, since they can be activated without previous sensitization. NK activity in the lung was two to three times higher in the mice infected with influenza virus compared with the non-infected mice (Stein-Streilen et al. 1983). Stein-Streilen & Guffee (1986) have shown that administration of anti-asialo GM1, which blocks NK activity in mice and hamsters, markedly increases mortality from influenza infections in both species.

IFN are the major contributors to the first line of anti-viral defence, and their production precedes the fall in viral titres (Sweet & Smith, 1980). IFN-α and β (type I), produced by any cell, induce an anti-viral state in cells by stimulating the transcription of several genes coding for proteins such as oligo-2′,5′-adenylate synthetase, dsRNA-dependent protein kinase (protein kinase P1/eIF2), and the Mx proteins. The oligo-2′,5′-adenylate synthetase converts ATP to oligo-2′,5′-adenylate (2′,5′-linked oligomers of adenosine with 5′ terminal triphosphate residues) and oligo-2′,5′-adenylate binds to and activates the RNase L which degrades single-stranded viral and cellular RNA (De Maeyer & De Maeyer-Guignard, 1994). Protein kinase P1/eIF2 limits viral spread by blocking viral protein synthesis (Samuel, 1991). Murine Mx1 protein which has a distinct nuclear targeting signal can specifically inhibit the replication of influenza virus at the transcriptional level. Meanwhile, human MxA protein is located in the cytoplasm of the cell and inhibits the replication of influenza virus at post-transcriptional and translational levels (Pavlovic et al. 1992). On the other hand, IFN-α (type II) produced by T-cells and NK cells not only exerts direct anti-viral influences but also regulates several aspects of immune response, including stimulation of macrophages and NK cell activity, upregulation of expression of major histo-compatibility complex molecules, and control of immunoglobulin class switching (Boeham et al. 1997).
Cytotoxic T-cells play an important role in recovery from influenza virus infection. McMichael et al. (1983) found that subjects with higher peripheral-blood CTL activity cleared viruses more effectively than those with lower CTL activity. An important characteristic of CTL in host defence against influenza is the ability to cross-react with different influenza A subtypes. This characteristic is responsible for heterotypic immunity; i.e. the host is still partially protected when periodic antigenic shifts in the influenza virus surface proteins occur (Bender et al. 1994). Although class I major histocompatibility complex-restricted CD8+ CTL may be the main mediators of influenza virus clearance in normal mice, an alternative mechanism such as virus-specific class II major histocompatibility complex-restricted CD4+ T-cells can terminate the infection. CD4+ T-cells can mediate virus clearance by promoting influenza-specific B-cell response, acting directly on class II major histocompatibility complex+ target cells in the virus-infected lung, secreting cytokines, or providing help for other potential effectors such as the γ and δ T-cells (Doherty et al. 1997).

B-cells also make a significant contribution to recovery from influenza virus infection. Antibodies can fight the infection by inhibiting the maturation and release of progeny virus from infected host cells, and by preventing released virus from propagating to other epithelial cells (Gerhard et al. 1997). However, experiments in mice lacking functional CD8+ CTL (Bender et al. 1991), mice with a disruption in the IFN-γ gene (Graham et al. 1993), mice depleted of IFN-γ by in vivo neutralization (Sarawar et al. 1994; Baumgarth & Kelso, 1996), or B-cell-deficient mice (Topham et al. 1996) have failed to prove their essential role in eliminating influenza virus, although some delay in clearance of virus was observed. These results indicate the presence of multiple mechanisms for the control of influenza infection.

**Ageing and immune function**

Ageing is a complex process affecting a wide variety of functions, including the function of the immune system (Tada, 1992). Among immune cells, T-cells are considered to be the most vulnerable to the deleterious effects of ageing (Bloom, 1994). Effros & Walford (1983) demonstrated that the peak CTL response was delayed in old mice compared with young mice following in vivo inoculation with influenza. The magnitude of CTL activity among old mice at peak response was 30% lower than that of the young mice. Several factors, including decreased thymic output and interleukin (IL)-2 production, decline in the number of T-cells that can express IL-2 receptors, an age-related shift towards T-cells expressing memory phenotype, and age-related changes in signal transduction mechanisms in T-cells, seem to contribute to the decline in CTL activity with ageing (Miller, 1990; Bloom, 1994; Lesourd & Meaume 1994). Since CTL is required for the control of virus infection by lysing infected cells, decreased CTL activity with ageing contributes to delayed viral clearance in the elderly.

There are marked age-dependent changes in the production of cytokines. There seems to be a dysregulation in the T-helper (Th)1–Th2 system, with a shift towards Th2 responses in the aged. An age-associated decrease in IL-2 production is well documented (Nagel et al. 1988). A majority of the reports (Abb et al. 1984; Frasca et al. 1997; Mbawuike et al. 1997) indicate a decrease in IFN-γ production with ageing, although both an increase (Engwerda et al. 1996) and no change (Fagiolo et al. 1993; Sindermann et al. 1993) in its production have also been reported.

Several studies have shown that the antibody response to vaccination decreases with ageing (Cook et al. 1987; Burns et al. 1993). Several factors contribute to decreased antibody production, including changes in T-cell function (Cook et al. 1987) and production by macrophages of suppressive factors (Delfraissy et al. 1982; Beharka et al. 1997).

**Vitamin E and immune function**

Supplementation with vitamin E has been shown to enhance cell-mediated and humoral immune responses in both animal and human models (Meydani et al. 1986, 1990). Meydani et al. (1990, 1997) showed that supplementation with vitamin E significantly increased antibody titre to hepatitis B and tetanus vaccine, and also increased the delayed-type hypersensitivity skin response, IL-2 production, and the mitogenic response to an optimal dose of concanavalin A, and decreased prostaglandin (PG) E2 synthesis by peripheral-blood mononuclear cells in elderly human subjects.

The immunostimulatory effect of vitamin E seems to be mediated by either reducing PGE2 synthesis and/or by decreasing free radical formation. Vitamin E supplementation has been shown to have effects on some of the immunological factors involved in the control of influenza infection, including NK cells, Th1 cytokine (IL-2 and IFN-γ) production, and production of suppressive factors (e.g. PGE2) which regulate CTL activity. Wang et al. (1994) showed that retrovirus-infected C57BL/6 mice, vitamin E supplementation restored the virus-induced decrease in production of IL-2 and IFN-γ by splenocytes, and prevented virus-induced suppression of NK activity. We have also shown that vitamin E supplementation prevents the sheep erythrocyte-induced suppression of NK activity (Meydani et al. 1988). Decreased PGE2 synthesis observed with vitamin E supplementation may be one of the mechanisms through which vitamin E exerts its effect on NK activity, since PGE2 has been shown to inhibit NK and CTL activity (Parhar & Lala, 1988).

**Vitamin E and resistance against infection**

*Animal studies*

The immunostimulatory effect of vitamin E has been shown to be associated with resistance to infections. Animal studies which have investigated the effects of vitamin E on infectious diseases are summarized in Table 1. The dose and duration of the supplementation, infectious organisms involved, and route of administration vary greatly. However, with few exceptions most of the studies reported a
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<td>Mice, C57BL/6 (n 6)</td>
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<tr>
<td>Pigs (n 6)</td>
<td>NA</td>
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<tr>
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<td>0·74 g/cow per d, duration NA</td>
<td>Natural occurrence of clinical mastitis due to Streptococci, coliform, Staphylococci, Clostridium bovis</td>
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<td>Chicks, broiler (n 12–14)</td>
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<tr>
<td>Chicks, broiler (n 10)</td>
<td>1 d</td>
<td>300 mg/kg diet for 6 weeks, starting 3 weeks before first infection</td>
<td>E. coli, post-thoracic air sac</td>
<td>Lower mortality</td>
<td>Tengerdy &amp; Nockels (1975)</td>
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<tr>
<td>Chicks, Leghorn (n 22)</td>
<td>1 d</td>
<td>300 mg/kg diet for 4 weeks before infection</td>
<td>E. coli by IV injection</td>
<td>Lower mortality</td>
<td>Likoff et al. (1981)</td>
</tr>
<tr>
<td>Pigs (n 10)</td>
<td>6–8 weeks</td>
<td>100 000 mg/t diet</td>
<td></td>
<td>for 10 weeks, starting 2 weeks before infection</td>
<td>E. coli by IM injection</td>
</tr>
</tbody>
</table>

IP, intraperitoneal; IV, intravenous; IM, intramuscular; NA, not available; bw, body weight; IL, interleukin; IFN, interferon; Ab, antibody.

* Values indicate no. of animals per group.
† DL-α-tocopheryl acetate was used unless otherwise indicated.
‡ All-rac-α-tocopheryl acetate.
§ Vitamin E injectable (aqueous); Animal Health Research, Hoffman La Roche Inc.
|| Vitamin E; Thompson-Hayward, Minneapolis, MN, USA.
nutritional status in influenza virus-infected mice. A highly significant difference post hoc test: day 2 $P < 0.01$, days 5 and 7 $P < 0.05$.

We chose the murine influenza virus model for studying the effect of vitamin E on viral infection for several reasons. As mentioned previously, influenza virus is a continuing threat to human subjects, especially the elderly, and causes oxidative stress to the host. Although influenza virus is not a natural pathogen in mice, it can be adapted to mice to induce pathological and clinical outcomes similar to those seen in human subjects (Peterhans, 1994). In addition, the divergence in T- and B-cell specificities for the virus reported in human subjects occurs in mice (Effros & Walford, 1987). In our study (Hayek et al., 1997), old mice had a significantly higher viral titre ($P < 0.05$) than young mice on days 2 and 7 after infection. Old mice fed on a diet high in vitamin E (500 mg DL-$\alpha$-tocopheryl acetate/kg) had significantly lower lung viral titres than old mice fed on a diet containing an adequate level of vitamin E (30 mg DL-$\alpha$-tocopheryl acetate/kg) following influenza virus infection (Fig. 2). This effect of vitamin E supplementation on lung viral titre in old mice was observed as early as 2 d after infection, and continued on days 5 and 7 post infection. However, vitamin E-supplemented young mice had a significantly lower viral titre ($P < 0.05$) than the control group on day 5 post infection only.

The effect of vitamin E does not appear to be mediated through enhancing the activity of CTL, since there was no effect of vitamin E supplementation on primary pulmonary CTL activity measured against influenza-infected MC57G cells, influenza B-infected LB27 cells (control), and influenza-infected LB27 cells. However, the lack of an observed vitamin E effect on CTL may be due to the fact that CTL activity was measured in an enriched T-cell population depleted of macrophages. Macrophages are the main source of PGE$_2$, a compound that has been shown to inhibit CTL activity. Vitamin E has been shown to decrease PGE$_2$ production by macrophages (Wu et al., 1998). Thus, in vivo, the effect of vitamin E might be mediated through enhancement of CTL activity. This is not likely, however, as the effect of vitamin E was observed as early as 2 d after infection, while the potent influenza-specific CD8+ CTL activity can be found in the lung only after 7 d of infection (Doherty, 1995)."
viral titre compared with those fed on the control diet (30 mg/kg; log_{10} viral titre 2.6 v 4.0 respectively, P = 0.017) and did not show the influenza-induced weight loss after infection (Han et al. 1997). Other antioxidants did not have a significant effect on viral titre or weight loss. These results suggest that mechanisms other than antioxidant protection might be involved in the vitamin E effect.

To investigate the mechanism of the effect of vitamin E on lowering influenza viral titre, especially the role of cytokines, we (Han et al. 1998) studied the effect of vitamin E on splenocyte cytokine production in young and old C57BL mice infected with influenza virus after feeding diets containing 30 or 500 mg DL-α-tocopheryl acetate/kg for 8 weeks. Old mice fed on vitamin E-supplemented diet had higher IL-2 and IFN-γ production and lower viral titres compared with old mice fed on the control diet following influenza infection. In addition, a significant inverse correlation (r = −0.721, P < 0.05) was observed between IFN-γ levels and viral titres, indicating that mice with higher IFN-γ production have a lower viral titre. These results suggest that vitamin E supplementation in old mice changes the age-associated dysregulation of Th1–Th2 balance which may be involved in the resistance to influenza infection. Further studies are needed to confirm the involvement of Th1 cytokines in vitamin E-induced protection against influenza infection.

**Human studies**

Only a limited number of studies have investigated the effect of vitamin E supplementation on resistance to infection in human subjects. Harman & Miller (1986) supplemented 103 patients in a chronic care facility with 200 or 400 mg DL-α-tocopheryl acetate daily for 6 months, and determined the serum antibody titres to influenza virus vaccine and the number of cases of pulmonary, urinary tract, and other infections. There was no effect of vitamin E on the serum titres or the incidence of infectious disease. Unfortunately, because data on the subjects’ health status, medication use and other relevant variables were not reported, it is hard to determine the importance of confounding factors. Chavance et al. (1989) reported that vitamin E status was negatively related to the number of infections during the past 3 years in 208 healthy individuals aged 60–82 years. As with other retrospective studies, it is difficult to prove a causal relationship between vitamin E status and incidence of infection from these data. In particular, it is possible that the high incidence of infection among subjects with low vitamin E status reflects decreased vitamin E levels due to frequent past infection. Chandra (1992) gave ninety-six healthy elderly individuals a multi-nutrient supplement (vitamin A, β-carotene, thiamin, riboflavin, niacin, vitamin B₆, folate, vitamin B₁₂, vitamin C, vitamin D, vitamin E, Fe, Zn, Cu, Se, I, Ca and Mg) for 12 months. The supplemented group had higher antibody response to influenza vaccine and less infection-related illness than the placebo group. Since the intervention was a multi-nutrient supplement it is impossible to attribute the effect to a particular nutrient. However, vitamin E was the only nutrient provided at 440 % of the recommended dietary allowance; other nutrients were provided at 30–200 % of the recommended dietary allowance. Girodon et al. (1996) conducted a double-blind placebo-controlled study in which eighty-one elderly subjects in a geriatric centre were supplemented with trace elements (Zn 20 mg and Se 100 mg), vitamins (vitamin C 120 mg, β-carotene 6 mg, and α-tocopherol 15 mg), or a combination of trace element and vitamins, for 2 years. Subjects who received trace elements alone or with the vitamin mixture had significantly fewer infectious events. The lack of a protective effect of the vitamin mixture could be due to low levels of vitamins. For example, the vitamin E concentration in the supplement was far less than that reported to have an immunostimulatory effect (Meydani et al. 1997) or that in the multivitamin mixture used by Chandra (1992). We are currently conducting a randomized double-blind placebo-controlled study to determine the effect of 1 year of supplementation with vitamin E on the incidence of respiratory infection in elderly nursing-home residents.

**Conclusions**

Despite the development of antibiotics and vaccines, infectious diseases are a continuing threat to human subjects, especially the elderly. Immunostimulatory effects of vitamin E supplementation have been well documented in both animal and human studies. Several animal studies have shown increased resistance to bacterial and viral infection following vitamin E supplementation. However, there are no controlled studies which have investigated the effect of vitamin E on infectious diseases in human subjects. Carefully-designed clinical intervention
trials are needed to determine the clinical significance of any immunostimulatory effect of vitamin E in human subjects.

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