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ORIGINAL COMMUNICATION

Nutrition and the immune system from birth to old age

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For millennia, food has been at the center of social events, in times of joy and in times of sorrow. Protein-energy malnutrition is associated with a significant impairment of cell-mediated immunity, phagocyte function, complement system, secretory immunoglobulin A antibody concentrations, and cytokine production. Deficiency of single nutrients also results in altered immune response: this is observed even when the deficiency state is relatively mild. Of the micronutrients, zinc, selenium, iron, copper, vitamins A, C, E and B_6, and folic acid have important influences on immune responses. Overnutrition and obesity also reduce immunity. Low-birth-weight infants have a prolonged impairment of cell-mediated immunity that can be partly restored by providing extra amounts of dietary zinc. In the elderly, impaired immunity can be enhanced by modest amounts of a combination of micronutrients. These findings have considerable practical and public health significance.
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Introduction

Food has been at the center of all cultures, in times of joy and in times of sorrow. Today we realize the crucial importance of dietary intake and nutritional status in regulation of host defenses and risk of both acute and chronic disease. Epidemiological observations have confirmed that infection and malnutrition aggravate each other. However, nutrition does not influence all infections equally (Scrimshaw *et al*, 1968; Chandra, 1990, 1996; Keusch *et al*, 1983;). For some infections (eg pneumonia, bacterial and viral diarrhea, measles, tuberculosis), there is overwhelming evidence that the clinical course and final outcome are affected adversely by nutritional deficiency. For others (eg viral encephalitis, tetanus), the effect of nutritional status is minimal. For still others (eg influenza virus, human immunodeficiency virus), nutrition exerts a moderate influence.

It is now established that nutritional deficiency is commonly associated with impaired immune responses, particularly cell-mediated immunity, phagocyte function, cytokine production, secretory antibody response, antibody affinity and the complement system (Chandra & Newberne, 1977; Gershwin *et al*, 1984; Bendich & Chandra, 1990; Chandra, 1992b). In fact, malnutrition is the commonest cause of immunodeficiency worldwide. In this selective review, the interactions between nutrition, immunity and infection have been highlighted for two age groups — low-birth-weight infants and older individuals at mid-life and beyond.

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Low-birth-weight infants

The prevalence of low birth weight (LBW), defined as weight less than 2500 g, varies from a low of 7% in some industrialized countries to as much as 40% in some poor countries of Africa. LBW results in reduced immune responses and, in those who are small for gestationcal age (SGA), impaired immunocompetence may persist for many years. LBW is associated with a higher morbidity and mortality. Whereas the overall proportion of infants who died or were handicapped was similar in average for gestational age (AGA) and SGA groups, the former are at higher risk of death in the immediate postnatal period while the latter are at higher risk of morbidity in the first year of life. Infection is one of the recognized causes of increased illness in SGA infants. In our experience, upper and lower respiratory tract infections are three times more frequent in SGA infants than in AGA infants (Table 1). It appears that the morbidity pattern in

Table 1 Immunological findings in small-for-gestational-age low-birth-weight infants

Immunological dysfunction	*Group I*	*Group II*
Illness days/100 child days (mean)	6	17*
Impaired cell-mediated immunity	16	14*
Decreased IgG	4	4
Decreased IgG2 level	5	7*
Reduced opsonic activity	7	9*

Forty-one infants were divided into two groups: those who were relatively asymptomatic (group I, $n=25$) and those often ill with infection (group II, $n=16$). Data are shown as the number of infants with the abnormality, except for illness days, which are shown as mean.
*Significantly different from group 1.

the SGA group has a bimodal distribution, about two-thirds showing a near-normal rate of illness, comparable to that of healthy full-term infants, whereas one-third have an increased illness rate, almost three times that of the full-term infants. 'Stunted' SGA infants have a higher neonatal mortality, lower neonatal morbidity but a lower post neonatal morbidity compared with 'wasted' SGA infants.

Immune responses

SGA infants show atrophy of the thymus and prolonged impairment of cell-mediated immunity. These general findings have been seen in infants as well as in laboratory animals. In animal models of intrauterine nutritional deficiency, protein-energy malnutrition as well as deprivation selected nutrients results in reduced immune responses in the offspring (Chandra, 1975b). In LBW infants, the number of T lymphocytes is reduced and their response to mitogens is decreased. Delayed cutaneous hypersensitivity to a variety of microbial recall antigens as well as to strong chemical sensitizer 2, 4 dinitrochlorobenzene, is impaired (Chandra, 1975c, 2001; Moscatelli *et al*, 1976). Serum thymic factor activity is reduced in SGA infants tested at one month of age or later (Chandra, 1992b). In contrast to AGA LBW infants, who recover immunologically by about 2–3 months of age, SGA infants continue to exhibit impaired cell-mediated immune responses for several months or even years (Chandra 1990, 1991). This is particularly true for those infants whose weight-for-height is less than 80% of standard. The prolonged immunosuppression in some SGA infants correlates with clinical experience of infectious illness (Table 2) and thus may have considerable biological significance.

Phagocyte function is deranged in LBW infants. There is a slight reduction in the ingestion of particulate matter and a significant reduction both of metabolic activity and in bactericidal capacity (Chandra, 1975c). IgG from the mother acquired through placental transfer is the principal immunoglobulin in cord blood. The half-life of IgG is 21 days and thus all infants show physiological hypoimmunoglobulinaemia between 3 and 5 months of age. This is pronounced and prolonged in LBW infants (Chandra, 1975a), because their level of IgG at birth is significantly lower than that of full-term infants. There is a progressive rise in IgG concentration with gestational age and birth weight, especially in infants below 2500 g.

Table 2 Risk of respiratory infections in SGA infants expressed as odds ratio with reference to full-term healthy infants. Follow-up until age 3 y

Upper respiratory tract infection	2.3 (1.4–3.0)
Lower respiratory tract infection	2.9 (1.7–3.4)

All four subclasses of IgG are detected in fetal sera as early as 16 weeks of gestation, the bulk consisting of IgG1. In SGA LBW infants the cord blood levels of IgG1 are reduced much more than in those of the other subclasses. Thus the infant:-maternal ratio is significantly low for IgG1 but not for IgG2. The number of immunoglobulin-producing cells and the amount of immunoglobulin secreted is decreased in SGA infants who are symptomatic, that is, those who have recurrent infections. In the second year of life, SGA infants show a marked reduction in IgG2 levels and often show infections with organisms that have a polysaccharide capsule.

Besides a careful attention to the amount and type of macronutrients, it may be useful to examine the benefit derived from extra amounts of selected micronutrients. There are some anecdotal observations that link additional dose of vitamins A and E and of iron and zinc to enhanced immunity. Recent intervention studies indicate a significant benefit of zinc supplements for enhancing immunity and reducing the incidence of infection in both preterm AGA and SGA infants (Chandra, 2001, 2002a, b; Ashworth, 2002).

Nutrition and immunity at midlife and beyond

The progressive increase in the proportion and absolute number of individuals beyond 50 y of age has led to heightened attention to their physiological needs. Older subjects tend to have a higher incidence of infection and each episode lasts longer than in younger individuals. For these reasons, several attempts have been made to study the immune system at various ages and to examine ways by which immunity can be enhanced by diet and nutritional supplements (Chandra, 1990; 1996; Bendich, 2001).

It is recognized that, in many older subjects, the immune system is not very capable of providing defense against microorganisms, malignant cells and other 'foreign' agents. Ageing is associated with a reduction in many immune responses in most, but not all elderly individuals. Changes in immunity associated with ageing include decreased delayed hypersensitivity, reduced interleukin-2 production, decreased lymphocyte response to mitogens and antigens, low rate of seroconversion, and decreased antibody titer after vaccination. Immune dysfunction as assessed by the prevalence of autoantibodies also increases in the elderly. However, in some elderly persons, the immune system remains as vigorous as it was when they were young. The number of pluripotent cells with the ability to colonize peripheral

lymphoid sites and to mature into competent cells decreases with age. The ability of stem cells to undergo clonal proliferation decreases and the generation of B-cells and homing of precursor cells into the thymus is reduced. This restraint on stem cell kinetics and reserves may be critical to elicit an effective response to stress, such as infection. Elderly patients with sepsis often fail to mount leukocytosis, although the expected shift to the left of immature polymorphonuclear leukocytes does occur.

In the elderly, delayed-hypersensitivity cutaneous responses to ubiquitous recall antigens derived from bacterial and fungal products, as well as to 2, 4-dinitrochlorobenzene, are reduced in frequency and in size. Lymphopenia and anergy have important prognostic significance in old age. The number of circulating T-lymphocytes is slightly decreased. The number of CD8 + cells is variously reported as normal, decreased, or increased.

Functional alterations associated with these changes in the number of cells include decreased lymphocyte proliferation in response to mitogens and antigens, reduced production of macrophage migration inhibition factor and of interleukin 2, impaired mixed lymphocyte reaction, and decreased natural killer cell activity. There is also a sharp decline in thymulin activity. There is a reduction in serum IgA. Generally, primary antibody response is decreased but antibody titer after booster immunization is often comparable in the young and the elderly. There is, however, a delay in reaching the peak antibody response in the elderly.

For many antigens, antibody production by B-cells requires helper factors generated by T-cells. Antibody responses to such antigens are decreased in old age and the affinity of the antibody may be reduced. There are no data on sIgA antibody responses of old individuals. Polymorphonuclear leukocytes obtained from the elderly have reduced migration ability, both random and chemotactic. The uptake of microorganisms is slightly reduced and has been attributed to a more rigid cell membrane. There is partial reduction in the magnitude of the metabolic burst associated with phagocytosis, and lysis of candida is impaired.

Nutrition is a critical determinant of health. For a variety of reasons, older individuals tend to have a high prevalence of nutrient deficiencies. Based on surveys conducted in India, Europe, USA and Canada, it has been estimated that as many as 35% of persons who are 50 y of age or above have a demonstrable deficiency of one or more vitamins and trace-elements. Composite results of such surveys are shown in Table 3. In most instances, it is not possible to diagnose the nutritional deficiency by clinical history and examination. Nevertheless, such subclinical deficiency may well have significant physiological effects such as those on the immune system and cognitive function. The clinical outcome of impaired immunity is an increased incidence of common infections affecting the upper and lower respiratory, urinary and genital tracts. The consequences of impaired cognition are loss of short-term memory, reduced ability for abstract tasks and shorter attention span.

Table 3 Prevalence of nutrient deficiencies in apparently healthy elderly

Nutrient	*Prevalence (%)*
Vitamin A	8
Beta-carotene	11
Vitamin B_1	3
Vitamin B_2	4
Vitamin B_6	7
Folic acid	8
Vitamin B_{12}	11
Vitamin C	16
Vitamin D	12
Vitamin E	10
Iron	14
Zinc	19
Selenium	7
Copper	3
Iodine	3

It is recognized that nutrient intake should not only prevent the classic deficiency diseases, but also could reduce illness and improve health. The type of nutrients and the quantity required to achieve such a beneficial effect varies with the index being studied and whether more than one nutrient is being healthful cannot be provided by a reasonable quantity and variety of natural foods. Thus, nutrient supplements may be important for health promotion and prevention of certain chronic diseases. This view goes against the prevailing dogma in nutritional science that a balanced diet is sufficient to achieve all nutritional requirements.

Many studies address this issue (Meydani *et al*, 1995, 1997; Penn *et al*, 1991; Bogden *et al*, 1990; Talbott *et al*, 1987; Chandra, 1992a, 1997, 2002a,b). Single nutrients have been shown to have important effects on laboratory and health indicators of the elderly. Vitamin B_6, zinc and low-dose vitamin E improved immune response in older subjects. However, high doses of vitamin E were associated with impaired immune responses (Chandra, 1997). There was decreased bactericidal activity of polymorphonuclear leukocytes among subjects given 1600 mg of vitamin E for one week. There was a reduction in hexose monophosphate shunt activity and hydrogen peroxide release, the latter being the principal reduction product of oxygen involved in bacterial killing. Others have found decreased bactericidal activity, decreased acid phosphatase release, and reduced response to phytohaemagglutinin in adults given 300 mg of vitamin E daily for 3 weeks. An epidemiologic study did not find a significant association between mortality in the elderly and vitamin E intake.

Because deficiencies of more than one micronutrient have been detected in the elderly and since there are interesting interactions among micronutrients, several studies have examined the effect of combinations of vitamins and trace elements on immune responses and incidence of infection (Chandra, 1997). Delayed hypersensitivity increased in those with high retinol levels and occurrence of infection was

reduced in those with high levels of tocopherol. The daily consumption of a multivitamin–mineral supplement for one was associated with enhanced delayed hypersensitivity and lymphocyte response to mitogens, but these effects were reduced by ingestion of an additional 15 mg of zinc and reduced further by 100 mg of zinc each day (Bodgen *et al*, 1990) Elderly hospitalized patients given a supplement of vitamins A, C, and E for 4 weeks showed a high number of CD4+ and CD8+ T-cells and increased lymphocyte proliferative response to mitogen compared with the placebo group (Penn *et al*, 1991). In our study, the administration of a low-dose multimicronutrient supplement with increased amounts of vitamin C, vitamin E and beta-carotene was associated with an increase in the number of T-cell subsets, enhanced lymphocyte response to mitogen, increased interleukin-2 production, greater natural killer cell activity, and increased response to influenza virus vaccine compared with the group given placebo (Chandra, 1992a). In addition, supplemented subjects experienced fewer days of infection than individuals in the placebo group.

Practical applications

Recent observations on nutrition-immunity interactions has opened up exciting possibilities for nutritional intervention for both primary and secondary prevention of infection in high-risk groups. Nutritional deficiencies are seen often in hospitalized patients. These individuals are susceptible to develop life-threatening opportunistic infections. Recent animal work has highlighted the value of nutrient-enriched diets in improving immune responses and survival following challenge with organisms such as *Listeria*, and limited clinical studies have confirmed these observations. Similarly, a large proportion of the elderly have reduced dietary intakes and low blood levels of various nutrients. They are also prone to respiratory infection. Several investigations have shown a correlation between nutritional status and incidence of infection in old age. The results of a few recent intervention trials indicate that modest supplements of micronutrients improve immune responses and more significantly, reduce the incidence of respiratory infection and antibiotic usage. In addition, post-vaccination immune responses are higher in subjects given nutritional supplements than in untreated controls.

Much new work on HIV shows that nutritional support reduces the mother-to-infant transmission of the virus and decreases the incidence of complicating infections. These are a few examples of the profound clinical and public health implications of this topic.

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