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Nutrition and the immune system

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Historical accounts, recent epidemiological observations and clinical findings have strengthened the concept that both nutritional deficiencies and nutritional excesses impair immune responses and alter susceptibility to infection and other diseases (Chandra, 1992*a*,*b*). This applies equally to humans (Chandra, 1992*c*) and animals (Burkholder & Swecker, 1990). Four general concepts are reviewed in the present paper. First, protein–energy malnutrition (PEM) and deficiencies of single nutrients impinge on immune responses. Second, nutrition is an important determinant of immunity at the two ends of the age spectrum, namely in young infants and in the elderly. Third, obesity and excessive intake of nutrients alter immunocompetence. Finally, these interactions of nutrition and immunity have several practical applications for clinical medicine and public health.

The topic has been discussed extensively in monographs and review articles (Chandra & Newberne, 1977; Beisel, 1982; Cunningham-Rundles, 1982; Watson, 1984; Gershwin *et al.* 1985; Chandra, 1988, 1990, 1991, 1992*b*; Bendich & Chandra, 1990; Bendich *et al.* 1990), which contain citations to individual papers and specific studies.

THE IMMUNE SYSTEM

The immune system protects the host from microbial invasion and is essential for survival. Individuals born with severe deficits in immunity and animals in whom the immune system has been deliberately destroyed, live for a very short time. Any discussion of host defences must be prefaced by emphasizing the complexities and heterogeneity of immunocompetent cells, their subpopulations and products such as interleukins and interferons, and other inducer and/or regulator systems, e.g. complement, involved in immune responses. There are two principal sections of the immune system: innate and adaptive. Innate immunity does not require previous exposure and experience, and includes the complement system, phagocyte, lysozyme, physical barriers of skin and mucous membranes. On the other hand, adaptive immunity comes into play because of previous contact and memory; it consists of antibodies of five different immunoglobulin isotypes and cell-mediated immunity that depends on various thymus-

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processed (T) lymphocyte subsets and their products, the lymphokines. These two tiers of the immune system are not isolated. In biology, various components of defence interact with one another, both enhancing and inhibiting others. A good example is the interaction between T- and B-lymphocytes in achieving the final goal of antibody production. Antigen-presenting cells (e.g. macrophage) facilitate the introduction of antigen to both T- and B-cells. T-helper cells enhance the ability of B-cells to change to antibody-producing plasma cells. A practical corollary of this is the number and variety of pathogenetic mechanisms that may underlie the syndrome of common varied immunodeficiency in which there is a moderate reduction in serum IgG concentration. This may be the result of a reduced number of B-cells, reduced synthesis or secretion of IgG, a decrease in the number or function of T-helper lymphocytes or an increase in the number and function of T-suppressor lymphocytes, inactivation of IgG by autoantibody, and other mechanisms.

IMMUNE RESPONSES IN NUTRITIONAL DEFICIENCIES

Lymphoid tissues have a high rate of cell proliferation and there is a rapid turnover of proteins. These features make the immune system extremely vulnerable to the damaging effects of nutritional deficiencies, as seen also in the gastrointestinal tract. Lymphocytes, polymorphonuclear leucocytes and macrophages are known to depend for their function on metabolic pathways that employ various nutrients as critical cofactors.

The most consistent effects of nutritional deprivation are on cell-mediated immunity, lymphocyte subsets, complement system, phagocyte function, secretory antibody response and antibody affinity (Fig. 1). These observations are briefly reviewed.

Delayed cutaneous hypersensitivity responses both to recall and new antigens are markedly depressed. There is a significant positive correlation between the size of skin response and visceral protein synthesis as judged by serum albumin concentration. It is not uncommon to have complete anergy to a battery of different antigens. These changes are observed in moderate deficiencies as well. Findings in patients with kwashiorkor were more striking compared with those in marasmus. One plausible reason for reduced cell-mediated immunity in PEM is the reduction in mature fully differentiated T-lymphocytes that can be recognized by the classical technique of rosette-formation or by the newer method of fluorescent labelling with monoclonal antibodies. The reduction in serum thymic factor activity observed in PEM may underlie the impaired maturation of T-lymphocytes. There is an increase in the amount of deoxynucleotidyl transferase activity in leukocytes, a feature of immaturity. The number of helper CD4+ cells is decreased markedly, often to values less than 50% of controls. The change in number of CD8+ suppressor T-cells is less marked. Thus, the helper:suppressor ratio is significantly decreased. Lymphocyte proliferation and synthesis of DNA are reduced, especially when autologous patient plasma is used in cell cultures. This may be the result of inhibitory factors as well as deficiency of essential nutrients lacking in patient's plasma. Serum antibody responses are generally intact in PEM, particularly when antigens in adjuvant are administered or in the case of those materials that do not evoke T-cell response. Rarely, the antibody response to organisms such as *Salmonella typhi* may be decreased. Before impaired antibody response can be attributed to nutritional deficiency, one must carefully rule out infection as a confounding factor. However, antibody affinity is decreased in patients who are malnourished. This may provide an

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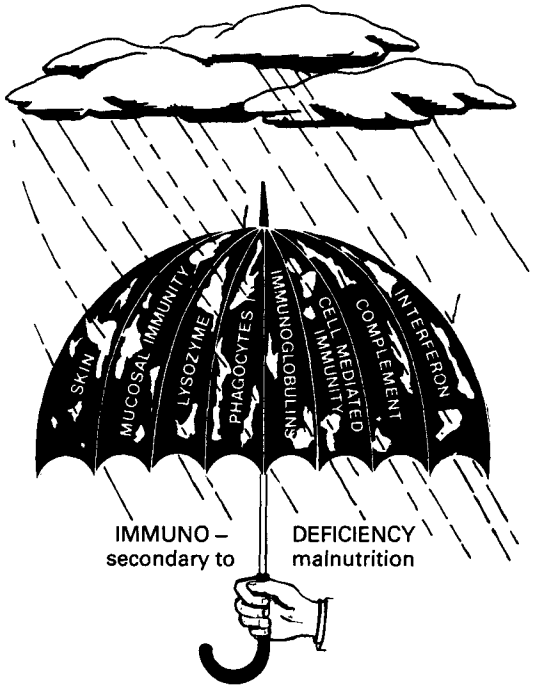

Fig. 1. A simple view of the immune system as a protective umbrella, consisting of physical barriers (skin, mucous membranes), non-specific mechanisms (complement, lysozyme, phagocytes) and antigen-specific processes (antibodies and cell-mediated immunity). In nutritional deficiencies, most of the host defence mechanisms are breached, allowing microbes to invade and produce clinical infection that is more severe and prolonged. Reproduced with permission from ARTS Biomedical Publishers.

explanation for a higher frequency of antigen–antibody complexes found in such patients. As opposed to serum antibody responses, secretory IgA antibody levels after deliberate immunization with viral vaccines are decreased; there is a selective reduction in secretory IgA levels. This may have several clinical implications, including an increased frequency of septicaemia in undernourished children.

Phagocyte function is affected in PEM. Complement is an essential opsonin and the levels and activity of most complement components are decreased. The best documented is a reduction in complement C3, factor B, and total haemolytic activity. Although the ingestion of particles by phagocyte is intact, subsequent metabolic activation and destruction of bacteria is reduced.

There is much recent interest in the role of cytokines in promoting and amplifying immune responses. A number of distinct substances have been identified and their physiological roles studied. These are polypeptide compounds with a wide range of molecular weight. Included in the human lymphokines are interleukin-1, interleukin-2 (IL-2), interleukin-3, colony-stimulating factors, interleukin-4, B-cell differentiating factor, interferons (α, β, γ) and tumour necrosis factor. Changes in the production and function of various lymphokines and monokines in PEM have been reviewed recently (Chandra, 1990). Briefly, macrophage migration inhibition factor has been found to be

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decreased, whereas there is little change in leukocyte migration inhibition factor. γ-Interferon production is decreased. Interleukin-1 production and functional activity on target cells is depressed. IL-2 production may be subnormal and there are alterations in IL-2 receptor binding.

INDIVIDUAL NUTRIENTS AND IMMUNE RESPONSES

The effects of changes in dietary intake of micronutrients (Gross & Newberne, 1980; Chandra & Dayton, 1982; Bendich & Chandra, 1990), toxic heavy metals (Chowdhury & Chandra, 1987) and lipids (Chandra & Deganus-Amorin, 1992; Erickson *et al.* 1992; Venkatraman & Fernandes, 1992) on immune functions have been reviewed extensively. Isolated deficiencies of nutrients are rare with the exception of Fe, vitamin A and Zn. However, they frequently complicate PEM and many systemic diseases. Five general concepts have been advanced (Chandra, 1991): (1) alterations in immune responses occur early in the course of reduction in micronutrient intake; (2) the extent of immunological impairment depends on the type of nutrient involved, its interactions with other essential nutrients, severity of deficiency, presence of concomitant infection, and age of the subject; (3) immunological abnormalities predict outcome, particularly the risk of infection and mortality; (4) in the case of many micronutrients, excessive intake is associated with impaired immune responses; (5) tests of immunocompetence are useful in titration of physiological needs and in assessment of safe lower and upper limits of intake of micronutrients.

Vitamin A deficiency results in a slight reduction in the weight of the thymus, decreased lymphocyte proliferation in response to mitogens, antigen-specific antibody production and T-lymphocyte proliferation *in vitro*, and increased bacterial adherence to respiratory epithelial cells. Carotenoids have important immunoregulatory functions involving T- and B-lymphocytes, natural killer cells and macrophages. Zn deficiency, both acquired and inherited, is associated with lymphoid atrophy, decreased cutaneous delayed hypersensitivity responses and homograft rejection, phagocyte dysfunction, and lower thymulin activity. Does dietary Fe intake influence immunity and risk of infection? On the one hand, free Fe is necessary for bacterial growth: removal of Fe with the help of lactoferrin or other chelating agents reduces bacterial multiplication, particularly in the presence of specific antibody. On the other hand, Fe is needed by natural killer cells, neutrophils and lymphocytes for optimal function. Thus, bactericidal capacity is reduced in Fe deficiency (Fig. 2). This may be due to the deficiency of Fe-dependent myeloperoxidase and cytochrome enzymes. The molecular explanation for impaired lymphocyte function in Fe deficiency may lie in part in the deficiency of ribonucleotidyl reductase that is needed for cell proliferation. For no other trace element is the discussion of deficiency and risk of infection so biased and controversial as is true of Fe. The concept of 'Fe nutritional immunity' emphasizing the effect of Fe deprivation in limiting the multiplication of bacteria is an attractive hypothesis with considerable *in vitro* evidence but clinical findings do not support the suggestion that Fe deficiency protects against infection or that correction of Fe deficiency, particularly if it is achieved gradually by oral Fe therapy, increases the incidence or severity of infectious disease in man.

There is much evidence to indicate that dietary lipids have an immunoregulatory role. The postulated pathogenetic mechanisms include modulation of eicosanoid synthesis, changes in cell membrane, altered number and density of receptors, changes in the

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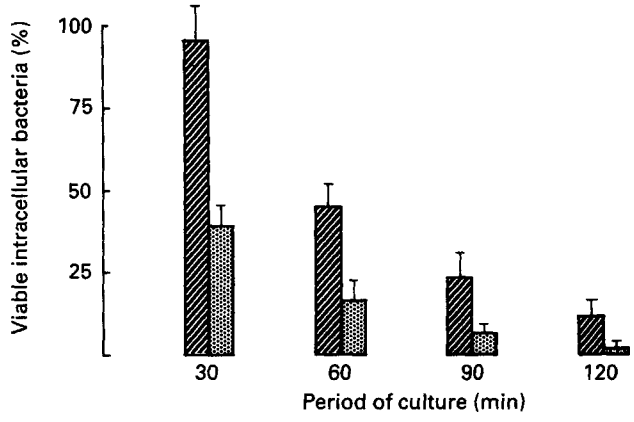

Fig. 2. Bactericidal capacity of neutrophils in iron deficiency. The number of surviving intracellular bacteria is increased in Fe deficiency (▨) compared with that in Fe-replete controls (▩). This is seen throughout the 120 min of cell-bacteria culture. (From Chandra, 1992*c*.)

number and function of selected subsets of cells, and altered production and action of cytokines. Essential fatty acid deficiency reduces a variety of immune responses. On the other hand, excessive intake of most lipids impairs cell-mediated immunity and phagocyte function to a variable extent. The extent of dysfunction depends on the amount and type of lipid, age of the animal, nature of challenge, and other variables.

NUTRITION AND IMMUNOCOMPETENCE IN INFANCY AND OLD AGE

Newborn infants have suboptimal immune responses and are susceptible to infection. When growth retardation and nutritional deficiency complicate the picture, as in low-birth-weight infants, impairment of immunocompetence is more marked and longer-lasting. The most consistent effects are on cell-mediated immunity. In preterm infants, Zn supplements facilitate recovery of the immune system (Chandra, 1991). In animal models, PEM and deprivation of single nutrients result in reduced immune responses in the offspring (Fig. 3; Chandra, 1975; Beach *et al.* 1982).

Recent studies on nutrition and immunity in the elderly have provided four main conclusions (Chandra, 1989): (1) immunological decline is not an inevitable part of aging; thus, many elderly subjects maintain vigorous immune responses at a level that is comparable to that seen in younger subjects; (2) nutritional deficiencies are quite common in this age-group; approximately 35% of the elderly show evidence of PEM or selected nutrient deficiencies; (3) the correction of nutritional deficiencies does improve immune responses even in old age; (4) appropriate nutritional counselling and dietary therapy, sometimes with medicinal supplements, results in reduced respiratory illness. These findings have considerable practical importance.

OBESITY AND EXCESSIVE INTAKE OF NUTRIENTS

Obese adolescents and adults show a higher risk of infection, including post-operative sepsis, than lean controls, and there is a slight impairment of delayed cutaneous

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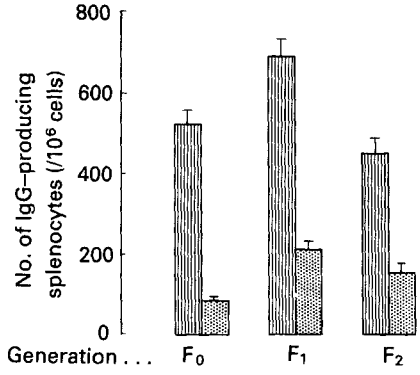

Fig. 3. Intergenerational effects of nutritional deficiency. IgG-antibody-producing spleen cells were estimated in mice subjected to partial starvation (65% of energy intake compared with controls). The offspring were given *ad lib.* access to food. The F1 and F2 generation offspring of starved female dams mated with healthy well-nourished males showed a significant reduction in antibody response. F0 and F1 animals were tested at age 9 weeks and F2 at age 6 weeks. (▨), Starved rats; (▥), control rats. (Data from Chandra, 1975.)

hypersensitivity responses, decreased lymphocyte response to mitogens, and reduced bactericidal capacity of neutrophils. Some of the immunological abnormalities may be due to associated deficiencies of selected micronutrients such as Fe and Zn that are encountered more frequently in the obese compared with lean controls. In genetically obese animals, such as the *ob/ob* mouse, natural killer cell activity is decreased. The generation of cytotoxic T-lymphocytes following stimulation *in vivo* is decreased but is normal if sensitization is carried out *in vitro*. This suggests that the microenvironment of the obese animal, including hyperlipidaemia, hyperglycaemia and altered levels of insulin, glucagon, cortisol and adrenocorticotrophic hormones, may partly be responsible for impaired cellular responses.

A slight excess intake of certain nutrients may be associated with enhanced immune responses. These include β-carotene, vitamin A, vitamin E, Zn and Se. Increased amounts of arginine and glutamine are reported to enhance immune responses, particularly in the face of stress such as burns, trauma or sepsis. At the same time, it must be emphasized that all nutrients given in quantities beyond a certain threshold will reduce immune responses. This has been shown for Zn, Se, vitamin A and vitamin E. Fe overload may promote bacterial septicaemia and increase the frequency of symptomatic malaria in endemic areas. The mechanisms of these immunotoxic effects are not clear, but in the case of Zn overdose, alterations in serum and cell-bound low-density lipoproteins, reduced levels of other nutrients, changes in membrane structure and receptor expression, are some possibilities (Chandra, 1984).

PRACTICAL APPLICATIONS

The interactions of nutrition and immunity have considerable applied significance. First, changes in immune responses occur early in the course of nutritional deficiency. Thus, we can employ immunocompetence as a sensitive functional indicator of nutritional status (Sarchielli & Chandra, 1991). Second, anergy and other immunological changes

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correlate with poor outcome both in medical and surgical patients in terms of complications, duration of hospital stay and mortality (Chandra, 1983). This is particularly useful when impaired immunity is considered in association with hypoalbuminaemia. In field surveys, impaired cell-mediated immunity and reduced levels of complement components precede and predict the occurrence of infection (Chandra, 1991). Third, opportunistic infections occur more frequently among those patients with cancer and those with the acquired human immunodeficiency syndrome (AIDS) who are also malnourished. The incidence of complicating infections can be reduced if appropriate preventative and therapeutic nutritional management is carried out in such patients. Fourth, response to immunization is modulated by the nutritional status of the host and protective efficacy of vaccines may be suboptimal in the undernourished individual. Fifth, immune responses can be used to define safe upper and lower limits of nutrient intake (Chandra, 1991). Finally, both nutritional deficiencies and excesses impair immunity and increase the risk of infectious disease and other disorders. Thus, moderation is a good dictum in biology and medicine, and it applies equally to nutritional immunology.

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