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# NUTRITION AND IMMUNITY

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## Introduction

Since the acknowledgement and the acceptance of immunology as a branch of medicine at the end of the 19th centure, it has grown at a steadily increasing rate and has become diversified into special fields such as immunochemistry, immunogenetics, and immunopathology.

With the development of the health care systems, health care professionals realized that there was an urgent need to promote an improved sense of wellbeing and quality of life, and from this, preventive medicine emerged. Early work on immunology belonged to preventive medicine through the work of Edward Jenner, an English physician (1749–1823), who performed the first effective immunization against smallpox. Nonetheless the scientific approach was not applied to the study of immunologic phenomena until, almost a century later, Louis Pasteur (1822–1895) and his collaborators investigated the possibility of protecting against infection by vaccinations with attenuated strains of micro-organisms.

With the growing concern about foods which might contribute to major disease problems, investigators have been searching for the link between nutrition and immunology. Much of the initial work on nutritional modulation of immune responses originated in developing countries where both malnutrition and infection constitute a substantial problem, particularly among younger age groups; but the principal findings are applicable to other age groups and to other regions of the world. Today, many reviews and investigations have summarized the available information regarding nutrition and immunology.

This chapter will deal with the significant role of nutrition in immune function, and its role in promoting immunocompetence.

## The nature of immunity

As long as we live, we are continuously exposed to a large variety of infectious microbial agents – viruses, bacteria, rickettsia, fungi and parasites. For the

maintenance of homeostasis and health, our bodies are provided with a defence mechanism called the immune system.

The immune system constitutes a large part of our body compartments. Like the endocrine system, it exerts control within the body by virtue of circulating components capable of acting at sites far removed from their point of origin. A normally functioning immune system is an effective defence against foreign particles such as pathogenic microbial agents and against native cells that have undergone neoplastic transformation. Defective function of the immune system results in disease.

*Innate and adaptive immunity*

Functionally, the immune system has two divisions: the innate immune system and the adaptive immune system. Innate immunity acts as a first line of defence against infectious agents and most potential pathogens are halted before they establish overt infection. If these first defences are weakened, the adaptive immune system is activated and produces a specific reaction to each infectious agent which normally eradicates that agent. The adaptive immune system also remembers the infectious agent and can prevent it causing disease later (see Figure 1). For example, diseases such as measles and diphtheria produce life-long immunity following an infection[1].

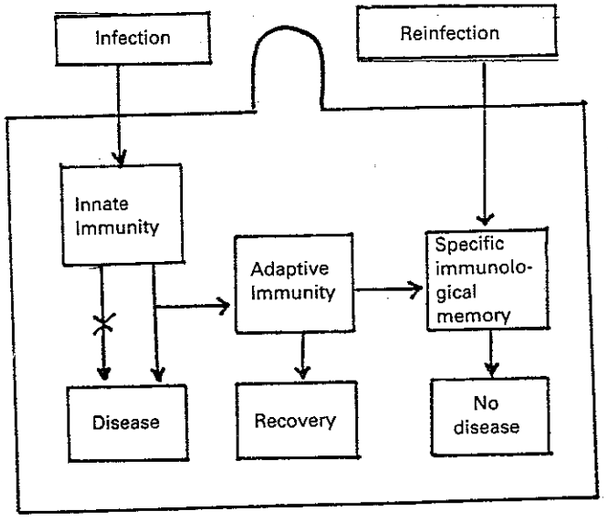


Figure 1. Simplified scheme of the innate and adaptive immunity. (Modified from Male D and Roitt I, 1989[1]).

**Immunity to infection**

Immunity and infection are inseparable. The scientific discipline of immunology was born of the study of how animals, by natural or artificial means, become immune to microbial infections and toxins. Since we live in a world filled with microorganisms; we are always in contact with bacteria, viruses, fungi, rickettsia, and a diversity of other parasitic or potentially parasitic life forms. Considering the continuous nature





of our encounters with micro-organisms, it can be imagined that our bodies receive persistent immunological stimulation.

Host defences against infection are at once local and systemic, non-specific and specific, humoral and cellular. It is difficult to identify any infectious agent that challenges single host defence mechanisms without affecting the other systems; hence the concept of multiple host defences is crucial to our understanding of susceptibility to infection.

*Immunity to viruses*

Viruses are a common cause of infections and may lead to many kinds of disease. Normally, the host recognizes viruses as foreign molecules and initiates an effective immune response which can prevent the entry of the virus into cells and its replication and spread. The initial phase of this antiviral response is recognition of viral components, particularly peptides, as foreign in the context of the major histocompatibility complex (MHC) antigens on the surface of the antigen-presenting cells. Once this recognition has occurred, a cascade of cellular and humoral responses to distinct viral determinants is established[2]. These antiviral humoral and cellular reactions complement each other. The ideal results of the interaction of the virus with the immune system is clearance of the virus, and host recovery and survival.

*Viral infection.* Viral infection starts with local invasion of an epithelial surface, and then after one or more viraemic phases, results in infection of the target organ, for example, the respiratory system or the nervous system[3]. Different viruses infect different cell types, and this is partly dependent on how the virus receptors are distributed on the cells. For example, the human immunodeficiency virus (HIV) primarily infects T helper cells because it attaches via CD4.

Since different immunological mechanisms are effective against different forms of antigen (for example, intracellular or extracellular), the relevance of any particular mechanism will depend on the way the viral antigens and the virion are encountered. The relevance to protection or immunopathology of the various effector systems of the immune response therefore depends on the phase of the infection and on the biology of the virus. For example, antibody is only capable of directly binding to extracellular viruses; antibody in association with complement (C1-C9) can cause lysis of cells carrying viral antigens, or directly damage enveloped viruses; the cell-mediated immune reaction (cytotoxic T cells, antibody-dependent cytotoxic cells) is potentially effective against intracellular viruses, which are recognized by the presence of viral antigens in the membrane of the infected cell.

*T cells and B cells.* To stimulate an adequate immune response, T cells must first recognize the antigen as foreign. T cells recognize antigens in the presence of MHC molecules expressed on the cell surface. It is well documented that many cytotoxic T lymphocytes (CTL) are $CD8^+$, and are dependent on MHC class I recognition for their cytotoxic activity; while T helper cells are $CD4^+$, MHC class II-restricted, and have a positive effect on B cell proliferation and differentiation.

*Major histocompatibility complex (MHC) molecules.* All T cell reactions are known to be MHC dependent. MHC molecules are cell surface proteins determining the

specificity of the cellular immune response. Antibody can bind to free virus, whereas T cell receptors recognize foreign antigens only when they are associated with an MHC molecule.

Viruses have the ability to induce the expression of MHC class I surface antigens, for example, neurotropic coronavirus infection[4] and chronic hepatitis B virus infection[5].

Class II MHC antigens are expressed on the surface of macrophages and B lymphocytes. They are responsible for antigen presentation on antigen-presenting cells. T helper cells recognize foreign peptides only in association with class II MHC molecules, for examples, in cytomegalovirus infection[6].

*Antiviral effects of antibody.* The antiviral effects of antibody are exerted via the following pathways[3]: (1) blockage of the critical sites of the virus surface; (2) collaboration with complement (in classic or alternative pathway) in neutralization, by coating the virus, or by lysing those with lipid membranes. Antibody is only capable of directly binding to extracellular viruses. IgG and IgM antibodies are limited in their actions to plasma and tissue fluids, whereas secretory IgA may protect epithelial surfaces and is therefore particularly important in protecting against viruses which lack a viraemic phase.

*Antiviral effects of cytokines.* 'Cytokine' is one term for a group of protein cell regulators, variously called lymphokines, monokines, interleukins (IL) and interferons (IFN), which are produced by a wide variety of cells in the body, play an important role in many physiological responses, are involved in the pathophysiology of a range of diseases, and have therapeutic potential[7]. Classically, interferons are secreted glycoproteins which can be divided into three general subgroups (IFNα, IFNβ, and IFNγ) depending on their sequence, physicochemical and biological activity, and their cellular origin. IFNα is secreted from leucocytes, IFNβ from fibroblasts and other non-immune cells, and IFNγ primarily from T lymphocytes and macrophages in response to stimuli from viruses and other antigens[8].

Recent published work suggests that interferons may have various antiviral activities. Their antiviral effects are exerted via several pathways which include the following:

(1) Increased expression of class I and class II MHC glycoproteins facilitating recognition of viral antigens by the immune system.
(2) Activation of cells with the ability to destroy virus-infected targets; these include natural killer (NK) cells and macrophages. IFNβ also stimulates B cells.
(3) Direct inhibition of viral replication.

Interferons can have an antiviral effects with or without inducing antibody production. For example, in vesicular stomatitis virus (VSV) infection, administration of IFNγ enhanced the production of virus-neutralizing antibodies[9]; in hepatitis A virus (HAV) infection, patients showed the induction of virus-specific T cells which were found to secrete human IFNγ and to be cytotoxic against HAV-infected fibroblasts[10].





In addition to interferon, another group of soluble cytokines is involved in antiviral immune responses. These are interleukin-1 (IL-1) which is produced by antigen-presenting cells, and IL-2 which is produced by T cells. IL-2 has a positive effect on the proliferation of T cells and previously stimulated B cells. It is also clear that another cytokine, tumour necrosis factor (TNF), plays an important role in immune regulation. Tumour recrosis factor consists of polypeptides synthesized primarily by macrophages, but also B cells activated by various inducers such as lipopolysaccharide, tubercle bacilli or viral infections. Tumour necrosis factor exerts several antiviral activities which are similar to those of IFNγ, but apparently work through a separate pathway. The induced antiviral effects of tumour necrosis factor towards several animal viruses occur either alone or in combination with other cytokines. For example, tumour necrosis factor is able to protect human WISH cells from the cytopathic effects of vesicular stomatitis virus by enhancing IFNβ production[11]; and human IFNγ and TNF exert a synergistic blockade on the replication of herpes simplex virus[12].

*Autoimmunity.* Viruses have long been supposed to induce an autoimmune response. Some of the resulting immune responses may be directed against self antigens. Several mechanisms have been proposed to explain virus-induced autoimmune response, these are[2]: (1) autoimmunization by antibody which is secreted by viral-infected B cells; (2) autoimmunization with tissue proteins released from virus-infected cells leading to autoantibodies or generation and expansion of self reactive T cell clones; and (3) molecular mimicry. For example, the retrovirus can initiate autoimmunity, which may lead to rheumatic and connective tissue disease; infection with Epstein-Barr virus can lead to infectious mononucleosis which has autoimmune potential; and coxsackie B virus infection is associated with auto-antibodies directed against cardiac myosin.

*Immunity to bacteria*

Interest in immunity to bacterial infections has a long history. Nowadays many bacteria infections are well controlled, in some cases as a result of immunological studies. However, several bacterial infections still cause major health problems because of their intimate relationship with the immune system, for example tuberculosis and leprosy.

*Non-specific barriers.* The body's defence against pathogenic bacteria consists of a variety of specific and non-specific mechanisms. The non-specific barrier to infection, before entry into the tissues, consists of intact skin, cilia on the epithelial surface of the trachea, the flushing mechanism of the urinary tract, pH changes in the stomach and vagina, and commensals occupying particular ecological niches and stopping pathogens from gaining access.

*The antibacterial effects of antibody and complement.* The sequence leading to an infectious disease caused by bacteria can be divided into the following steps: (1) attachment; (2) proliferation of organisms and avoidance of phagocytosis; (3) damage to the host; and (4) invasion or (5) toxin production.

Antibody has antibacterial effects that operate at different points[3]:

(1) Antibody to fimbriae, lipoteichoic acid and some capsules block attachment of the bacterium to the host cell membrane.
(2) Antibody can trigger complement-mediated damage to the gram-negative outer lipid bilayer.
(3) Antibody directly blocks bacterial surface proteins which pick up useful molecules from the environment and transport them across the cell membrane (eg for iron-chelating compounds).
(4) Antibody to M proteins and capsules opsonizes the bacteria via Fc and C3 receptors for phagocytosis.
(5) Immunorepellents – factors which interfere with normal phagocytosis and may be toxic for leucocytes – are neutralized.
(6) Neutralization of bacterial toxins occurs, eg tetanus and diphtheria toxins.
(7) Antibody will neutralize spreading factors such as enzymes, eg hyaluronidase.

Pathogens enter host cells either by invasion or by phagocytosis, which are both receptor-mediated endocytotic processes. Phagocytosis is accomplished by professional phagocytes and is assisted by opsonizing antibodies for which complementary receptors exist on the cell surface of professional phagocytes. These are Fc receptor for immunoglobulin and the C3bi fragment (CR3). However, certain bacteria exhibit antiphagocytic mechanisms, for example, inhibition of phagocytosis by streptococcal M-protein[13].

The level of the defence mechanisms in a bacterial infection is related to the nature of the organism and the disease caused. For example, in *Corynebacterium diphtheriae* and *Vibrio cholerae* infections, neutralizing antibody is probably sufficient for immunity, depending on toxin production; in Gram-negative infection, eg *Neisseria meningitidis*, antibody and the lytic pathway of complement will be needed to kill the organism; in Gram-positive infection, eg *Staphylococcus aureus*, opsonization by antibody and complement play a significant role in facilitating the killing of the organism by phagocytic cells.

*The role of T cells and interleukins in an antibacterial action.* T lymphocytes act as the potential mediators of protective immunity to intracellular bacteria. It is believed that acquired resistance to intracellular bacteria is a function of both CD4 and CD8 T cells, for example, participation of both CD4 and CD8 T cells in tuberculosis and listeriosis[13]. CD4 T cells recognize antigenic peptide in the context of MHC class II, while CD8 T cells respond to MHC class I antigenic peptide.

Toxins produced by certain bacteria can also stimulate the T cell response. Examples are enterotoxins produced by certain strains of *S. aureus* which cause food poisoning[14]; and toxic shock syndrome toxin (TSST) produced by another strain of *S. aureus*[15]. CD4 class II-restricted T cells and CD8 class I-restricted T cells, as well as some γ/δ T cells, were found to respond to these toxins provided that the accessory cells expressed class II molecules. These toxins are called 'superantigen', because they can stimulate T cells of different antigen specificity and genetic restriction. In contrast, broad T cell activation can contribute to pathogenicity. For example, toxic shock syndrome toxin causes the toxic shock syndrome by activating secretion of tumour necrosis factor, and polyclonal T cell stimulation may result in high levels of this interleukin.





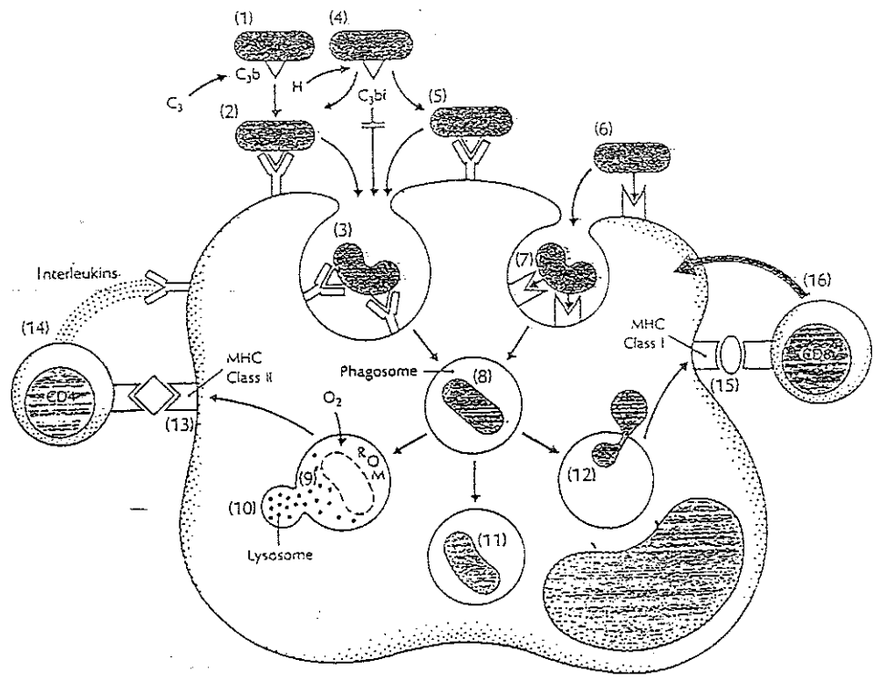


Figure 2. Simplified scheme of important events that can happen when a microbe meets a host cell: (1) Activation of the alternate complement pathway and binding of C3b. (2) Adherence of microbes via interaction of bound C3b with its receptor, CR1, on the surface of professional phagocytes. (3) C3b–CR1 interaction triggers phagocytosis. (4) Inactivation of bound C3b via binding of factor H by streptococcal M-proteins inhibits phagocytosis. (5) Direct binding to CR3 and other cell adhesion receptors. (6) Binding of a microbial protein, invasin, to a yet unknown ligand on the cell surface induces endocytosis. (7) Invasion of non-professional phagocytes occur via endocytosis. (8) After invasion and phagocytosis, microbes end up in a phagosome. (9) Activation of reactive oxygen metabolites. (10) Fusion with lysosomes results in killing of many microbes. (11) Microbial molecules which interfere with these events facilitate survival in the phagosome. (12) Evasion into the cytoplasm, eg by means of listeriolysin, also facilitates intracellular survival. (13) Stimulation of CD4 T cells by microbial products plus class II MHC molecules. (14) Macrophage activation by interleukins from CD4 T cells. (15) Association of products from intracellular pathogens with class I MHC molecules stimilates CD8 T cells. (16) Target cell lysis by CD8 T cells, ⇝, lysis; ⟶, leads to the next step, ⋯, activation. (From Kaufamann, E., 1989[13]).

Another cytokine, IFNγ, has recently been shown to activate tuberculostatic capacity in murine macrophages *in vitro*[16]. It also seems to be active *in vivo*, for example, against *L. monocytogenes*[17]. In the human, it is possible that monocyte activation of mycobacterial growth inhibition is accomplished by IFNγ indirectly via 1,25-dihydroxyvitamin D3[18,19]. The simplified scheme of interaction between a microbe and a host cell is seen in Figure 2.

*Autoimmunity*. Certain strains of streptococci, for example group A streptococci, can produce M-proteins, which are considered to be antiphagocytic factors, and hence are of major relevance to virulence. M-proteins, however, do not only contain protective epitopes but also contain epitopes which cross-react with human tissue, and antibodies against these have been implicated in the pathogenesis of the post-streptococcal autoimmune diseases, rheumatic cardiac disease and glomerulonephritis; in addition, cytolytic T cells may be involved.

Heat-shock proteins, products of certain bacteria (eg *M. tuberculosis* and *M. leprae*)[20,21], provide a possible link between infection, protection and autoimmunity. Heat shock proteins are induced by a variety of stress conditions including not only heat, but also attack by reactive oxygen metabolites, anaerobic metabolism, or deprivation of nutrients, essential ions and metabolites[22]. These molecules could then be subjected to intracellular processing and could be presented in the context of MHC molecules on the surface of infected cells. Increased titres of antibodies to autologous heat-shock proteins have been found in several autoimmune diseases, for example, systemic lupus erythematosus[23].

*Immunity to fungi*

Immunity to fungal infections is thought to be similar to that involved in resistance to bacterial infections. Cell-mediated immunity is predominant in resistance to fungal infections since patients develop a delayed-type hypersensitivity reaction to fungal antigens, and the occurrence of chronic infections is associated with a lack of these reactions. Nevertheless, in protection against systemic fungal infections, granulocyte function, cytokine production by natural killer and other cells, the complement system, and possibly humoral immunity may be more important.

*Natural cellular defences*. The three host cell types that are important in attacking the fungi are the neutrophils, the moncytes/macrophages, and the natural killer cells[24]. For example, *C. neoformans* activates and binds C3bi and this opsonization is essential for phagocytosis of encapsulated cryptococcal isolates by neutrophils and monocytes/macrophages[25]; the human blood monocyte β-glucan receptors which bind *C. albicans blastoconidia* may influence subsequent phagocytic response[26]; and natural killer cells can inflict damage directly on cryptococcal cells[27] and indirectly on *C. albicans*[28]. Natural effector cellular defences may be intensified by cytokine. For example, human neutrophil activity against *Torulopsis glabrata* and *C. albicans* can be augmented by pretreatment of the neutrophils with tumour necrosis factor[29]; IL-3, granulocyte/macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF) can also potentiate the anticandidal activity of macrophages[30].

*The antifungal actions of T cells*. Cell-mediated immunity is a crucial host resistance mechanism against systemic mycotic infections. Many studies have been performed to investigate the T cell responses against fungi. In human subjects who had recovered from cryptococcosis, cryptococcal antigen-reactive T cells would proliferate in response to a soluble culture filtrate antigen[31].

IFNγ would also amplify the immune protective mechanism; for example, *H.*





*capsulatum*-reactive T cells produce IFNγ which in turn activates macrophages to restrict the intracellular growth of the *H. capsulatum* yeast cells[32].

*Immunity to protozoa*

Recent progress in molecular biology has enabled the development of vaccines against some of the most debilitating parasitic disease. For example, in malaria a number of genes encoding the potential vaccines have been cloned, expressed and characterized. It is generally realized that this contemporary development cannot be separated from the understanding of the basic rules governing the effector mechanisms in these diseases.

*Effector mechanisms*. Various kinds of effector cells such as macrophages, neutrophils, eosinophils, and even platelets help defend the host against invasion by parasites and act to control the multiplication and spread of parasites already in residence. The antiparasitic activities of these cells are enhanced by interaction with cytokines released by other types of cell in response to infection.

No single immunological effector mechanism acts in isolation; but in general terms, humoral antibody is expected to be effective in neutralizing and destroying pathogens which have life-cycles involving recirculation in the blood or the lymph; in contrast, pathogens which are predominantly intracellular (particularly inside the cells of the macrophage lineage) should be more susceptible to cell-mediated immunity, involving the secretion of lymphokines by specific T cells and the activation of phagocytic cells or killer cells. For example, in leishmaniasis, cell-mediated immunity rather than specific antibody plays the major role in the hosts's resistance against both the cutaneous and the visceral forms of the disease.

*The antiparasitic effects of T cells*. The relative importance of CD4 versus CD8 T cells in anti-protozoal immunity has long been controversial. In malaria, both CD4[33] and CD8[34] T cells are crucial for host protection. The former are important at the blood stage of infection and antibody synthesis, whereas the latter are essential at the sporozoite stage. In murine visceral leishmaniasis, depletion of either CD4 or CD8 T cells inhibits protective immune responses, suggesting that both cell types are required for effective immunity[35].

Recently, studies are emerging on the important role of CD4 T cell subsets in protozoal immunity[36]. CD4 T cell clones can be separated into two subsets depending on the lymphokines they produce following stimulation[37]. One subset, designated T helper ($T_H$)1, produces IL-2 and IFNγ, while the other subset, designated $T_H2$, produced IL-4 and IL-5. Several other lymphokines, such as IL-3 and GM-CSF, appear to be produced by both cell subsets, although in some cases in different quantities. $T_H1$ and $T_H2$ have different functions. For example, in cutaneous leishmaniasis $T_H1$ mediates resistance while $T_H2$ mediates susceptibility[38].

*The antiparasitic effects of antibody*. The mechanisms by which specific antibody controls parasitic infections are as follows[39]:

(1) Antibody can act directly on protozoa to damage them, either by itself or by interacting with the complement system.

(2) Antibody can neutralize a parasite directly by blocking its attachment to a new host cell.
(3) Antibody can enhance phagocytosis mediated by Fc receptors on macrophages.
(4) Antibody is also involved in antibody-dependent cytotoxicity, for example, in infections caused by *T. cruzi*.

*The role of cytokines in protozoal immunity*. It is well documented that IFNγ has a protective role in malaria[40], Chagas' disease[41] and toxoplasmosis[42]. The protection shown by IFNδ is probably through the activation of macrophages which form a hostile environment to the intracellular parasites.

Tumour necrosis factor, which is produced by macrophages, also has protective effects against parasitic infections. For example it can suppress *P.chabaudi adami* infection in CBA mice[43], while treatment of macrophages with recombinant tumour necrosis factor plus lipopolysaccharide results in a significant reduction in the number of intracellular organisms in experimental *T. cruzi* infection compared with mock-treated macrophages[44].

It has now been shown that recombinant GM-CSF (rGM-CSF), which shares no sequence homology with IFNδ, is also a potent activator of cultured human monocyte-derived macrophages and induces the intracellular kiling of *Leishmania donovani*[45] and *T. cruzi*[46] *in vitro*, although it was less potent and less effective than IFNγ in this system.

*Immune suppression*. Chronic parasitic infection may also lead to immune suppression. For example, mice infected with *T. cruzi* generally develop abnormal immune suppression which has been variously attributed to suppressive macrophages, suppressor T cells, deficiency in IL-2 production or suppressor substance[47]; and the induction by IFNδ of MHC class II expression by *L. donovani*-infected macrophages was markedly suppressed[48]. It was proposed that the failure of infected cells to express MHC antigen in response to IFNδ is mediated at the level of MHC class II mRNA induction[49].

*Immunity to Helminths*

In common with all other branches of infectious disease, studies of immunity to helminths have been revolutionized by the application of molecular biology, molecular genetics and molecular immunology. Parasitic worms that infect man include trematodes, for example schistosomes, some cestodes (tapeworms), some nematodes such as *Trichinella spiralis*, hookworms, ascaris and the filarial worms. Tapeworms and hookworms inhabit the gut, while adult schistosomes live in the blood vessels.

*Immune response to helminths*. Increased immunoglobulin E (IgE) levels and blood and tissue eosinophilia are characteristic of the immunology of helminth infection[50]; both responses are under T lymphocyte control. Two lymphokines, designated IL-4 and IL-5 are responsible for IgE production[51] and eosinophilopoiesis respectively. It can be concluded that the increase in IgE and the eosinophilia in worm infestations like schistosomiasis and ascariasis are T-cell-dependent.

There have been several publications on the T cell responses of individuals with parasitic infestations compared with those of individuals who, despite living in the





same endemic area, have no infestations (and are therefore presumably immune)[52]. For example, Nutman *et al.*[53] found that symptomatic individuals infected with lymphatic filariasis had defective T cell responses (in terms of IL-2 and IFNδ production) when their cells were exposed to parasite antigen. Ward *et al.*[54] likewise showed that non-infected subjects in an onchocerca-exposed population exhibited higher IL-2 production when cells were pulsed with parasite antigen than did infected subjects.

Since many parasitic worms pass through complicated life cycles involving migration through various parts of the host's body and development of different stages in different organs before they reach the site where they finally mature and spend the rest of their lives, different kinds of cell and antibody may act at different stages in the life cycle[39]. For example, eosinophils are more effective in killing the newborn larvae of *T. spiralis* than other cells, macrophages are more effective against the microfilariae, and in each case antibody mediating the reaction is stage-specific.

It is also well established that complement plays an essential role in immunity to parasitic worms through its interaction with specific antibody via the classical pathway. Several parasites, including adult worms, infective larvae of *T. spiralis* and schistosomules of *S. mansoni*, activate the alternative pathway directly.

*Immune suppression*. Parasitic worms can cause disruption of lymphoid cells or tissue directly. For example, newborn larvae of *T. spiralis* release a soluble lymphocytotoxic factor; and schistosomes can cleave a peptide from IgG that inhibits many cellular immune response. *S. japonicum* infections are associated with profound disturbances in host immune responsiveness and Yamashita *et al.*[55] have described the mechanisms of disturbed T lymphocyte function in mice in terms of alteration in the IL cascade reaction. Although production of IL-1 remained essentially normal, responsiveness to IL-1 decreased during infection, and both the production and the responsiveness to IL-2 declined dramatically within a few weeks of infection.

**Malnutrition and immunodeficiency**

Simply defined, malnutrition means poor nutrition, but in the broader sense, malnutrition may take many forms, including excesses as well as deficiencies of body nutrients. Both deficits and excesses may be generalized, involving multiple nutrients, or they may be limited to one, or only a few, of the many nutrients the body needs to maintain normal health and body composition.

Generalized malnutrition is a common cause of acquired, correctable immune system dysfunction. Infectious diseases are extremely prevalent in children with either the marasmus or kwashiorkor forms of generalized malnutrition.

Among the immunological changes noted, cell-mediated immune response is most consistently and profoundly affected by undernutrition. All of the lymphoid organs are atrophied and depleted of lymphocytes. The extent of these morphological changes may equal that seen in primary cellular deficiencies. Reduction in tonsil size is a useful bedside indicator of malnutrition. The proportion and absolute number of T cells recognized by their ability to form rosettes with sheep red blood cells are decreased and correlate with reduction in lymphocyte transformation response. The 'null' cells are increased[56]. The immunological changes associated with various degrees of protein-energy malnutrition are summarized in figures 3,4 and 5, and table 1.

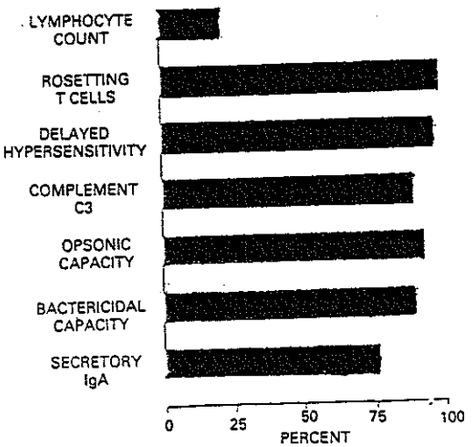


Figure 3. Immunological changes associated with severe protein-energy malnutrition (weight-for-height less than 60 percent). The percentage incidence of dysfunction of the major parameters of immune response is shown. (From Chandra RK, 1981.[56])

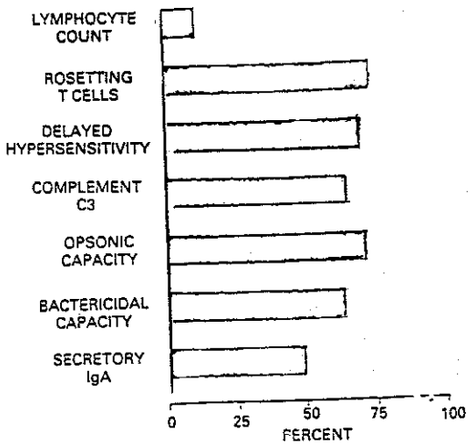


Figure 4. Immunological changes seen in moderate protein-energy malnutrition (weight-for-height 60 to 70 percent). (From Chandra RK, 1981.[56])

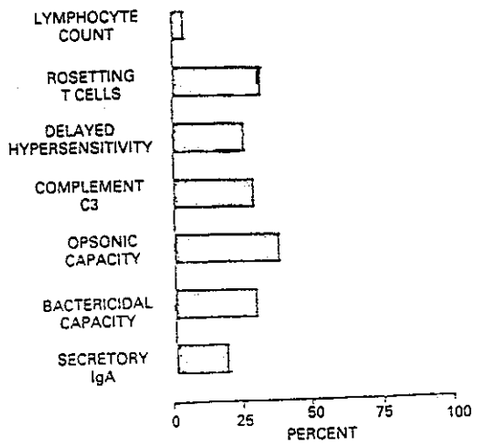


Figure 5. Immunological alterations observed in marginal protein-energy malnutrition (weight-for-height >70 to 80 percent). (From Chandra RK, 1981[56].)

The effects of malnutrition on infection may be synergistic, antagonistic, or show no apparent interaction. In synergistic interactions, infections are made worse by malnutrition, whereas antagonistic interactions occur when an infection is milder than would be expected in a malnourished host. Although most bacterial infections become more severe with malnutrition, nutrient deficiencies have attenuated some viral infections. The generalized weakening of host defensive mechanisms, including those of the immune system, can explain synergistic interactions. Antagonism occurs because host cells and invading micro-organisms compete for available nutrients and





Table 1. Summary of the effects of protein-calorie malnutrition on immune function.

| | Human | Animal |
|---|---|---|
| Lymphoid anatomy | | |
| Thymus | ↓ | ↓ |
| Spleen | ↓ | ↓ |
| Lymph nodes | ↓ | ↓ |
| Other lymphoid tissue | ↓ | ↓ |
| Total circulating lymphocytes | ↓ | ↓ |
| Humoral immunity | | |
| Circulating B lymphocytes | ↓ or N | |
| Serum Ig levels | ↑ or N | ↓ |
| Serum antibody response to antigen | ↓ | ↓ |
| Secretory IgA | ↓ | |
| Splenic laque forming cell response | | ↓ |
| Cellular immunity | | |
| Circulating T lymphocytes | ↓ | |
| Delayed cutaneous hypersensitivity | ↓ | ↓ |
| Allograft rejection | | N or ↑ or ↓ |
| Tumour cytotoxicity | | ↑ |
| Immunity to intracellular-organism | ↓ | |
| Lymphocyte proliferation | | |
| (a) Concanavalin A | ↓ or N | |
| (b) PHA | ↓ or N | N or ↑ or ↓ |
| (c) PWM | ↓ or N | |
| Lymphokine productioin | ↓ | |
| Phagocytic function | | |
| Monocyte chemotaxis | ↓ | ↓ |
| PMN chemotaxis | N | ↑ |
| PMN phagocytosis | N | |
| RES function | | ↑ or ↓ |
| Interacellular killing | ↓ or N | N |
| Complement | ↓ | ↓ |

PHA = phytohaemagglitinin; PMN = Polymorphonuclear leucocyte; RES = reticuloendothelial system; N = normal; ↓ = depressed; ↑ = increased.
(From Dowd PS, Heatley, RV, 1984, ref. 83).

because the host-immune reaction that normally produces disease symptoms is suppressed. Viruses, for example, must use metabolic processes of the host cell to multiply, and nutritionally deprived cells may not contain the nutrients needed for viral proliferation. Parasites such as malaria may also be less able to multiply when the patient is malnourished. Tuberculosis may be acutely exacerbated by feeding starving people; the body's inflammatory reaction to the tubercle bacillus, which is suppressed by starvation, may fluorish after feeding and cause symptoms, particularly if the patient has not received antituberculosis drugs.

In this context, it is also worthwhile distinguishing between the acquired immunodeficiency resulting from starvation and that arising in acute illness or injury. Malnutrition due to starvation produces different effects on metabolism and body composition from those due to illness or injury, and this difference profoundly affects susceptibility to infection. During uncomplicated starvation, extensive metabolic changes serve to conserve body protein stores. Metabolic rate is reduced, nitrogen is conserved, and the use of body fat as a source of energy is increased. Because protein is conserved, immune system competence and resistance to infection persist until starvation is greatly advanced.

In contrast, the extreme body wasting (cachexia) caused by acute illness or injury is associated with rapid protein breakdown and a concomitant weakening of resistance mechanisms. Metabolic rate and loss of body nitrogen increase, and large quantities of gluconeogenic amino acids are metabolized to produced glucose, branched chain amino acids are oxidized in muscle cells to produce energy, and the metabolic destruction of tryptophan and phenylalanine is accelerated. Such diversions of free amino acids reduce their availability for the synthesis of new proteins. The adequacy of immune functions and other host defence mechanisms ultimately depends on the ability of body cells to synthesize a variety of new proteins. But protein synthesis is impaired when the supply of free amino acids is inadequate or when an imbalance exists among the essential free amino acids. Thus, when overwhelming disease or trauma causes severe generalized malnutrition, the resulting deficits of body protein and free amino acids can be linked directly to a depression in host resistance. In short, the metabolic consequences of fever and loss of appetite lead to poor nutritional status, deficits in immune system competence, and an increased susceptibility to infectious disease within a relatively short time.

## High risk groups of malnutrition acquired immunodeficiency

*In infancy and childhood*

Malnutrition is the most prevalent nutritional disorder of children, and represents a major public health problem in developing countries. In the so-called developed countries, protein-energy malnutrition (PEM) can still happen in certain groups of children, for example those living in institutions.

Infants with protein-energy malnutrition are prone to develop serious, often life-threatening, infectious disease, particularly diarrhoeal disease. Early studies indicated that the immunocompetence of infants with protein-energy malnutrition was compromised significantly[57]. Among the changes documented are impaired delayed cutaneous hypersensitivity; decreased levels of haemolytic complement and C3; low lymphocyte response to phytohemagglutinin; and decreased secondary antibody response to antigens. These conditions can lead to increased morbidity and mortality in infants and children, and thereby magnify the demand for medical services.

*In adolescence*

'Adolescence' is characterized by a marked increase in growth rate, which is often referred to as the 'adolescent growth spurt'. This phenomenon is accompanied by marked changes in body size, and also in energy requirements to provide for growth and for the metabolism of the additional tissue.





As well as having increased energy requirements, adolescents are prone to the misuse of tobacco, alcohol and drugs which can elicit nutritional deficiencies, as can the common affliction of acne (see section on 'age-orientated preventive nutrition in adolescence'). Undernutrition in individuals, irrespective of their age, will depress the immune function. Some health problems in adolescents involving immunocompetence will be discussed here.

*Overweight and obesity*. Early studies reported an increased incidence of respiratory infections and postoperative sepsis in the obese, often resulting in more prolonged hospital treatment. For example, Holley *et al.*[58] reported that obese patients are more prone to suffer from postoperative wound complications than non-obese patients. Infection is a frequent primary or contributing cause of death in the obese.

Obese persons may manifest micronutrient deficiencies, particularly zinc and iron, and this condition may influence immunocompetence[59]. Hyperlipidaemia is a frequent complication of obesity, and high lipid levels may affect immune responses. Serum containing high levels of cholesterol and low-density lipoproteins can inhibit *in vitro* lymphocyte transformation responses to mitogens and phagocytosis by polymorphonuclear leucocytes.

There is much evidence of a relationship between weight reduction in obese people and enhancement of immune response. A study conducted by McMurray *et al.* in 1990[60] concluded that long term energy restriction in obese patients is associated with significant effects on *in vitro* lymphocyte stimulation and on normal neutrophil function. Improvement of immune function has also been observed in 22 morbidly obese patients after gastric bypass and weight loss[61].

*Alcoholism*

Early studies showed that alcoholics had a greatly increased liability to infections, particularly pneumonias, and a greater mortality rate when infected. Many investigators have noted subsequently that there is an increased incidence of various bacterial infections in alcoholics. Numerous factors are responsible for the decreased resistance of alcoholics to infections. Although the immune system may be suppressed in alcoholic liver damage or malnutrition, excessive alcohol alone may damage the immune system[62]. Heavy intakes of alcohol may cause the following disturbances:

(1) Alteration in the production and turnover rates of lymphocytes in the thymus or spleen, or both, with a resultant shift in the relative concentrations of the lymphocyte subpopulations (B cells and T cells).
(2) Significant reduction of the circulating T lymphocyte counts[63].
(3) Reduction of β-endorphins in the brain with concomitant depression of killer cell activity.
(4) Inhibition of cell-mediated immunity which is manifested by impaired delayed type hypersensitivity; this may contribute to the high prevalence of tuberculosis among alcoholic subjects[64].
(5) Suppression of antiviral immunity[65].

Many studies have also shown that alcohol may contribute to granulocytopenia

(probably the result of a combination of diminished marrow white cell reserves and increased utilization of granulocytes at the site of infection); impairment of granulocyte adherence and mobilization; depression of neutrophil chemotaxis *in vitro*; and transient decrease in the *in vitro* bactericidal activity of serum against certain organisms.

Other factors favouring infections in alcoholics are folate deficiency, protein-energy malnutrition, liver damage, pulmonary dysfunction, depression of the cough reflex, and impairment of reflex closure of the glottis.

*In elderly people*

Elderly people represent a growing proportion of the world's population, and they will present a major challenge to health-care policy makers and providers in the future. In 1980 there were 370 million persons worldwide aged 60 years and over, representing 8.5% of the world's total population. Their numbers are projected to reach one billion by the year 2020. This increased survival of populations to later life is more evident in developing regions. By the year 2020, 72% of the elderly population are expected to live in developing countries[66]. Table 2 characterizes the population projection in the developed and developing countries in the year 2000. Aging is accompanied by a variety of physiological, psychological, economic and social changes[67] that may compromise nutritional status[68-70], and by illness, problems with drug-nutrient interaction, and lack of precise information regarding nutrient requirements[71].

Table 2. World population projection.

| Year | Total population (millions) | Population 65+ years | Percentage 65+ years |
|---|---|---|---|
| Developing countries | | | |
| 1980 | 3284 | 129 | 3.9 |
| 2000 | 4297 | 229 | 4.7 |
| Developed countries | | | |
| 1980 | 1131 | 129 | 11.4 |
| 2000 | 1272 | 167 | 13.2 |

(Source: Age and sex composition by population by country, 1960–2000. New York, United Nations, 1979).

PHYSIOLOGICAL CHANGES

The following physiological changes occur with aging:

- The sense of smell, and possible of taste, decreases with age. These changes may result in decreased appetite as well as impaired utilization of nutrients and limitation of function.
- Dental problems, common in old age, decrease the ability to chew certain foods.





- Physical disabilities in the elderly, such as diminution of vision, may make eating less pleasant.
- Decreased physical activity also may predispose elderly people to the development of osteoporosis.
- Changes such as osteoarthritis can affect mobility and decrease an older person's ability to purchase and prepare food.
- Malabsorption may occur. This can be caused by a decrease or absence of gastric acid secretion and by interactions with medications commonly prescribed for older persons. Haboubi *et al.*[72] reported that malnutrition in the elderly could be caused by occult malabsorption due to small bowel bacterial growth.
- There is a decline in lean body mass[73], which is considered to be the source of glutamine synthesis[74].

PSYCHOLOGICAL CHANGES

The most common psychological factor affecting nutrition is depression, and is most often related to chronic diseaes and to poverty, which are common among older persons.

ECONOMIC AND SOCIAL CHANGES

Elderly people are prone to low income which results from retirement from the workforce, the effects of inflation on fixed incomes, death of a wage-earning spouse, or failing health. For the institutionalized elderly, although institutional food is likely to meet minimum standards for nutrient content, factors such as lack of choice or limited day-to-day variety may increase the risk of inadequate consumption. Loneliness and social isolation in the elderly can also lead to inadequate nutrient intake[75].

Given the declining nutritional intake, elderly people are at high risk of severe malnutrition, both of macro- and of micronutrients, which then impairs their well-being[76], and subsequently causes increased morbidity and mortality[77]. Considerable evidence documents an age-related decline in immune competence[78]. Similar defects have been observed in protein-energy malnutrition and zinc deficiency[79,80], and there is evidence that both may exist in the aged ill and perhaps even in healthy aged individuals[81].

Protein-energy malnutrition in individuals of any age alters the proportion of T cell types, depresses T cell function, impairs delayed hypersensitivity reactions, and impairs thymic factor activity. Such changes are strongly associated with increased susceptibility to infectious disease[56,82,83], for example, nosocomial infections with respiratory tract viruses[84,85]; and moreover, can reduce the efficacy of vaccination in the elderly, for example, influenza vaccination[86,87].

If nutritional deficiencies are related to impaired immune function in older people, correcting the deficiencies should improve it[88]. Among older people, dietary supplements have been associated with improved antibody responses to viral vaccines[89], and several studies have reported improved immune function as a result of zinc supplementation[81,90,91].

**Nutrition and AIDS** (See next chapter 'HIV infection, AIDS and nutrition'.)

Throughout the world there are growing numbers of cases of the acquired

immunodeficiency syndrome (AIDS). In the United States alone it is estimated that more than 1.5 million people are infected with the human immunodeficiency virus (HIV)[92], and globally, it is estimated that several times that number are infected.

Despite its recognition as a major world health problem, the management of the patients with AIDS is still far from satisfactory. Recent advances in AIDS research, including vaccine development, drug treatment, and the management of complications, have given hope for the future. Through the use of the newer drug therapies and improved medical management, persons with AIDS are surviving longer.

Attention is currently also focused on the potential role of nutritional management in AIDS, as malnutrition represents a frequent problem in persons infected with HIV. It has been proposed that the timing of death in these patients may be more strongly related to the degree of body cell mass depletion than to any specific underlying infection.

*Body composition studies*

Protein-energy malnutrition is common in AIDS sufferers. The cause is multifactorial and includes conditions that lead to diminished food intake, alteration in intermediary metabolism, and nutrient malabsorption[93]. Weight loss is a prominent feature of AIDS. For example, Dworkin *et al.*[94] reported that 96% of 22 patients referred for gastrointestinal complaints lost a mean of 34 19lb; somatic protein (mid-arm muscle circumference) and visceral protein (serum albumin, retinol-binding protein, and iron-binding capacity) were also reduced in HIV-infected persons. Since 1987, HIV seropositivity with wasting (weight loss of >10% over two months) has been classified as AIDS by the Centers for Disease Control.

*Pathophysiological mechanisms of PEM in AIDS*

The pathophysiological mechanisms of PEM in AIDS include:

(1) Inadequate food intake caused by mechanical difficulties with eating, for example, problems with chewing or swallowing due to diseases localized to the oral cavity, pharynx, or oesophagus; or loss of appetite (anorexia) which may be a side effect of various medications or a direct effect of increased release of cytokines, such as TNF, IL-1, interferon, and others.
(2) Changes in intermediary metabolism, for example, elevated fasting hypertriglyceridaemia in patients with AIDS results from decreased lipoprotein lipase activity, increased fatty acid synthesis and esterification, and increased lipoprotein synthesis in the liver.
(3) Malabsorption caused by intestinal dysfunction. For example, diarrhoeal illness occurs in more than 50% of people with AIDS[95]. Many studies have also documented xylose and fat malabsorption in HIV-infected persons, even in the absence of diarrhoea[96,97].

It can be concluded that deficiencies of both micronutrients and macronutrients can affect persons with AIDS. As micronutrients are involved in immune function, their deficiency may compound the clinical immune deficiency, rendering them more susceptible to infection or exacerbating the severity of existing infections.





*Nutritional support for patients with AIDS*

Given that severe malnutrition is likely to complicate AIDS, nutrition support may contribute to an improved quality of life in these patients, although the actual impact of malnutrition and its treatment upon the ultimate clinical course of the diseases is still poorly understood. The primary goals set by the Task Force on Nutrition Support in AIDS[98] for good nutritional management are to preserve lean body mass, provide adequate levels of all nutrients, and minimize symptoms of malabsorption. The approach to the nutritional management of patients with AIDS should consider the following three stages: HIV seropositive but asymptomatic, underweight but stable, and actively wasting[93]. Special considerations must be given to growing infants and children and pregnant or lactating women.

Nutritional conselling represents one of the major components of the management of the individual who is HIV seropositive but remain asymptomatic. Nutritional counselling should include an understanding of the value of a good diet to protect against exacerbation of nutritional complications. The ultimate goal must be to avoid the development of protein-energy malnutrition.

The patient who is underweight but stable must also undergo nutritional assessment. This consists of: diet history (past and present); calculation of nutrient intake: anthropometric measurements such as weight, height, skinfold thickness, and mid-arm circumference (to measure somatic protein stores); laboratory tests for anaemia (blood count), and serum albumin; functional measurements of muscle power (eg hand grip strength); and measurement of short-term visceral protein deficits (serum retinol-binding protein and prealbumin) when protein-energy malnutrition is suspected. Further specific tests can be introduced for suspected nutrient malabsorption.

The same approach is also applicable for the patients with active wasting; however, a greater sense of urgency is required. For example, prompt treatment of infectious complications; and total parenteral nutrition for cases where nutritional requirements cannot be met using the gastrointestinal tract.

**Implications to preventive nutrition**

As preventive nutrition represents a great potential strength of clinical nutrition, every efforts should be made to reduce the prevalence of acquired immunodeficiency caused by malnutrition. The goal is the reduction of infection rate, which acts as an index of immunodeficiency, among high risk groups.

The spectrum of acquired immunodeficiency due to malnutrition has changed substantially along with the development of clinical nutrition, and now ranges from the long established problem of immunodeficiency caused by protein-energy malnutrition to the contemporary issue of obesity-induced immunodeficiency.

The scope of prevention should involve primary prevention, which will promote the well-being of the community; secondary prevention, which may delay the onset of disease until a later stage, or reduce the effects of acquired immunodeficiency; and, even if both primary and secondary prevention are out of reach, tertiary prevention will still be applicable.

*Primary prevention*

Nutritional education in the community represent the most important part of primary prevention. Its aims should be as follows:

(1) To maintain energy balance to prevent overweight and obesity.
(2) To reduce the consumption of fat.
(3) To encourage breast-feeding.
(4) To increase fibre and fruit consumption.
(5) To reduce alcohol consumption.
(6) To provide informatin on appropriate food handling and storage methods to prevent outbreaks of food-borne disease[99,100].
(7) To ensure that food service personnel receive adequate training in sanitary food handling and storage procedures.
(8) To encourage the development of new products that are free of substances likely to induced allergic symptoms in susceptible individuals[99].
(9) To encourage nutrition education in supermarkets, which are considered as potential sites for public health nutrition[101].
(10) To provide adequate formal nutrition training for physicians, who constitute the major source of nutrition information for persons over 65 years of age[102].

*Secondary prevention*

The aim of secondary prevention is to halt further deterioration resulting from malnutrition-induced acquired immunodeficiency. Primary health care is involved in secondary prevention. The measures that should be undertaken in secondary prevention include the following: (1) a good diet history; (2) calculation of nutritional intake; (3) identification of high risk groups and provision of corrective nutrition where possible; (4) treatment of intercurrent infection as quickly and as effectively as possible to minimize depletion of body nutrients[99,100]; (5) regular assessment of nutritional status in persons with infective illnesses, with appropriate nutritional support measures whenever necessary[99,100].

## Future direction

It is obvious that nutrition plays a crucial role in promoting immune function. As immunization represents an appropriate method of preventing various infectious diseases by enhancing cellular or humoral immune responses, future studies should be directed towards investigating the potential benefit of improved nutrition in promoting immunization-induced immune responses. On the other hand, since immunization itself can induce some functional alterations in the body, it may also be important to examine the effects of immunization on nutritional state, both in health individuals and in high risk groups.

## Conclusion

Nutrition plays a significant role in modulating immunocompetence. Almost all nutrient deficiencies can result in impaired immune function, and intakes of certain nutrients in excess of recommended levels have been shown to enhance immune responses compared to those observed with 'adequate' levels of the nutrient. Conversely, both acute and chronic inflammatory conditions, as well as infectious and neoplastic diseases, result in metabolic changes in the host that can adversely affect nutritional status.

As immunization has proved to be an effective way of preventing various infectious diseases, future studies should be directed towards investigating the





benefits of nutritional support on immunization-induced cellular and humoral immune responses, and *vice versa*.

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# 3

# HIV INFECTION, AIDS AND NUTRITION

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## Introduction

The diseases developing in people with human immunodeficiency virus (HIV) infection have attracted great attention because of their rarity, severity and the need to find and evalulate new treatments. Nevertheless, knowledge about the role of nutrition in the development of symptoms in people infected with HIV and its evolution to the acquired immunodeficiency syndrome (AIDS) is gaining importance. In this short chapter I shall summarize current knowledge about nutritional intervention in the primary care setting.

## Wasting and malnutrition

The loss of body weight is the most common indicator of the evolution of HIV infection in the absence of the frank development of AIDS-associated diseases[1]. In fact, the association of protein-energy malnutrition (PEM) and HIV infection has led some authors to view malnutrition as a co-factor of HIV in the development of AIDS rather than a consequence of the infection itself[2-7]. The characteristics of the immune deficiency present during HIV infection are shared by PEM and some diseases associated with AIDS are also present in severe malnutrition[8].

The traditional division in three categories of the causes of malnutrition; decreased dietary intake, intestinal malabsorption and inappropriate metabolism, provides a useful analytical framework. People with HIV infection frequently present a decrease in food intake. In some, anorexia represents one of the symptoms of the difficult psycho-social adjustment to the knowledge of being infected with HIV. In others, avoidance of foods decreases the pain associated with chewing and swallowing in the presence of oropharyngeal and oesophageal diseases. Consideration must also be given to anorexia and nausea associated with many of the medications used to prevent and control complications of the immune deficiency. For example, both zidovudine and pentamidine may cause nausea as a side-effect[9]. Anorexia is also noted to be present during malabsorption and systemic infections[10].

The malabsorption present in some persons infected with HIV may be the result of a primary enteropathy caused by HIV or the result of gastrointestinal infections secondary to the immune deficiency[11,12]. If AIDS enteropathy has just recently

received recognition, intestinal infections are well documented. The most common enteric pathogen seen in persons with AIDS is *Cryptosporidium sp.* Although not a specific pathogen of immune-compromised persons, it also infects immuno-competent persons causing a self-limiting diarrhoea, cryptosporidiosis is a frequent cause of increased nutrient losses from the intestine[12]. The frequent watery stools evidently cause great disturbances and are difficult to control due to limited therapeutic options. A more recently identified parasite *Microsporidium sp.*, shares this absence of a specific treatment. Another parasite, *Isospora belli*, causes profuse diarrhoea but responds to pharmacological therapy[13]. Other enteric pathogens causing diarrhoea and malabsorption include Cytomegalovirus, *Salmonella* and *Shigella sp.* and *Mycobacterium avium intracellulare*[12]. So, enteric infections contribute to the malnutrition of HIV infection by dramatically increasing nutrient loss through exudative and secretory diarrhoea, by malabsorption of nutrients because of villous atrophy and by blood loss in specific infections.

Alterations of metabolism has been shown during HIV infection. However, the changes are not stereotyped. A gradual loss of body weight due to a hypermetabolic state compatible with cachexia can be observed[14]. But a starvation-like response with a decrease in the metabolic rate has also been reported[15]. A mainstay of therapy in chronic illnesses remains: malnutrition should be prevented to decrease the risk of opportunistic diseases and their concurrent alterations of metabolism, and treatment of intercurrent diseases should be aggressive to stop wasting. Treatment of CMV infection with ganciclovir for example, was shown to reverse the body-mass depletion associated with this opportunistic infection[16].

**Nutritional intervention**

The management of nutritional needs of persons infected with HIV ranges from the basic nutritional evaluation and education, to the intensive care of parenteral nutrition. The aim of nutritional intervention is however the same throughout this spectrum, namely the prevention and control of body weight loss. In fact, it has been shown that time of death of persons with AIDS is related to body-cell-mass depletion[17]. Thus, increased survival and preservation of quality of life with proper nutritional intervention is a realistic goal.

An initial intervention with asymptomatic persons infected with HIV will cover general advice pertaining to a balanced diet and the prevention of body weight loss and nutrient deficiencies[18]. The importance of getting early dietary advice when changes related to either the evolution of the disease, the start of prophylactic therapies or the development of opportunistic infections appear, has to be stressed at the beginning of counselling. Cutting down the delay between the apparition of symptoms and the prescription of the proper nutritional intervention will contribute to the preservation of body mass.

Nutritional intervention during the course of HIV infection is a dynamic process requiring the detection of potential and actual deficiencies and impending protein-energy malnutrition. Moreover, it requires the astute manipulation of diet content and form, and frequently, of the mode of feeding. The management of decreased intake secondary to upper gastro-intestinal tract disease, being it infectious, neoplastic, or iatrogenic, is basically the same as the interventions developed for head and neck cancer patients. Depending on the symptoms present, the choice of





food may either decrease pain or inflammation, decrease mechanical difficulties or prevent the aggravation of nausea and vomiting[12,19]. But a decreased intake, as we have seen previously, is not the only factor associated with the development of malnutrition during HIV infection. Malabsorption and diarrhoea concur in the deterioration of the nutritional status of persons with HIV infection.

The choice of nutritional intervention can be based on the extent of intestinal damage rather than the cause the diarrhoea and malabsorption[19]. The most severe form is total small bowel disease, a condition requiring hospitalisation and parenteral nutrition. A less severe form is partial small bowel disease, where the malabsorption is mostly the result of ileal dysfunction. A generalized colitis causing important diarrhoea and rapid wasting is a third category. A mild form of enteropathy that causes an increase in the frequency of bowel movements, without however being associated with significant weight loss or malabsorption, is also described[19]. For each of these categories, specific nutritional recommendations are made in regard to the delivery mode of nutrients. Generally, the diets and formulas are low in fat, low in lactose and low in fibre. However, bulking agents are indicated for nonspecific enteropathy.

There will be rare cases where parenteral nutrition may be indicated. And then, only for short-term nutritional support where intestinal function is expected to return[19,20]. An improvement in nutritional status and quality of life is however ascribed to prolonged parenteral nutrition regimens[21,22]. A safer course than parenteral nutrition, specially in the context of the care of an immuno-compromised patient, is the use of enteral nutrition through nasogastric tubes or gastrostomies[8,19,23]. It should be noted that enteral feeding at home, in some cases only at night, provides both an intensive and manageable intervention for patients with severe upper gastro-intestinal disease but preserved intestinal function.

For all its potential in correcting or stopping body-mass depletion, intensive nutritional support may not yield results until opportunistic infections are treated[11]. And in some cases the severity of the illness will preclude any improvement in spite of aggressive treatment and nutritional support[22]. It is of note however, that anti-retroviral therapy with zidovudine and dideoxynosine has been associated with weight gain in some patients[24]. Thus, a combined approach using both treatment of opportunistic infections and HIV infection, may permit a positive response to nutritional support.

**Nutrient supplementation**

The impact of nutrient status on the competence of the immune system has been a relatively recent preoccupation[8]. Interest in that association has rapidly increased with the recognition of similarities between the changes in immune function present in severe malnutrition and AIDS[6]. However, specific studies of nutrient levels in HIV infection and immuno-competence are still rare. It is not surprising then to note the practical absence of clinical trials of nutrient supplementation in HIV infection. The current line of thought is thus that prevention of deficiencies is the aim of any supplementation and that using specific nutrients as therapeutic agents for the immune deficiency of HIV infection is not supported by any studies[9].

There are however, numerous alternative therapies offered to persons with HIV infection and most of them pertain to some radical modifidation of the habitual diet

or to the addition of a substance[25,26]. In the context of HIV infection, the claims of the proponents of these therapies fall into receptive ears. Persons with HIV infection using these remedies do not believe they are curative but they think some good may be obtained through their use[27].

**Food safety**

The immuno-compromised person presents a *de facto* higher risk of developing diseases from agents not usually considered pathogenic[8]. During the counselling of persons with HIV infection, care must be given to the descriptions of methods permitting the control of food-borne disease. A general statement would be that a person with HIV infection should avoid raw food of animal origin and prevent cross-contamination of foods during preparation[28,29].

**Nutrition and children with HIV infection**

The causes of malnutrition in adults with HIV infection; inadequate food intake, malabsorption and modified metabolism, are expressed in children through the failure to thrive syndrome. Correction of inadequate intake through modification of diet and feeding routes can prevent malnutrition and even provide catch-up growth[30,31]. The management of children with HIV infection is not however straightforward. Dietary counselling will be given to the parents, and frequently resources are extended to their limit. Their capacity to cope with the increasing complexity of caring for a child with HIV infection will have to be taken into account during the intervention. Of note is the important aspect of delayed neurological and behavioural development associated with both the HIV infection and the prolonged and frequent hospital stays[9]. The common situation of a family where parent and child are infected with HIV, in an austere socio-economic environment, creates a situation where nutritional support outside the hospital may be very difficult to implement.

**Psychological and social factors in nutritional intervention**

In asymptomatic persons with HIV infection, the receptivity to nutritional counselling might be quite good. However, one must be aware that trying out unproven remedies and unbalanced diets is a common behaviour in those having to cope with an unforgiving disease. The attitude must be one of tolerance of the person's choices. Trying to convince without judging will be more effective in preventing extremes in dietary behaviours. Nutritional counselling may yield more positive results if the family (in its broadest sense) is involved in the early stages of the intervention. The interaction around food is one of the most valued social activity in any culture, and preventing misunderstandings helps to preserve this precious contribution in any persons' life.

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