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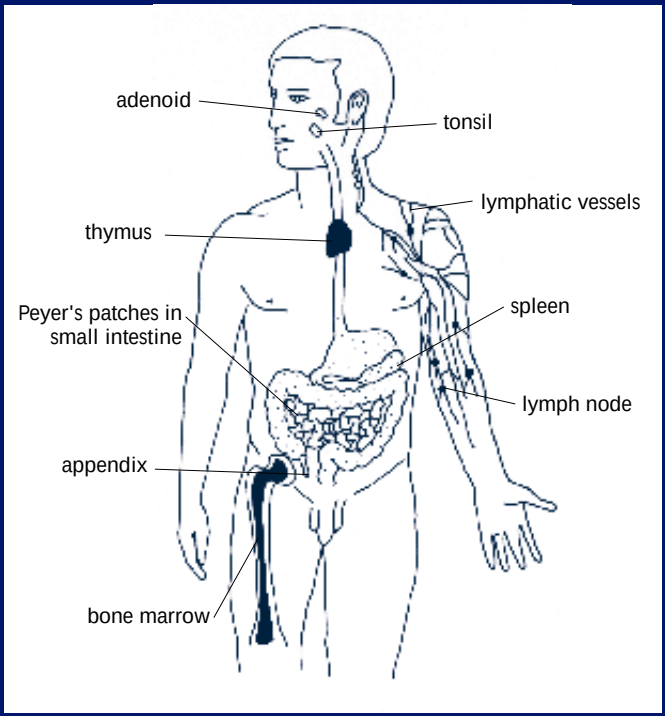

NUTRITION AND IMMUNITY IN MAN

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FOREWORD

The immune system guards against invasion by foreign microorganisms and molecules. In this way it protects us from fatal illnesses and communicable diseases. The immune system stays in a delicate balance between destruction of foreign cells and avoidance of self-destruction. Its proper functioning is fundamental for survival.

During the last twenty years our understanding of the complex nature of the immune system and its many interactions with nutrition and the host has greatly increased. AIDS viruses can attack and destroy immune cells leading to HIV disease. Immune cells may become overactive turning their defence against cells of the host such as in autoimmune diseases. Emerging research suggests that dietary intervention with macro- and micronutrients can modulate immune function and in some cases reduce the risk of disease.

In 1993 ILSI Europe took the initiative to constitute the task force *"Immunity in Man"* for studying the many interactions of nutrition and immunity. It was felt that a comprehensive review of this fast evolving topic would be needed. The first objective of the task force was to identify scientists in the field of nutritional immunology and to compile data on the role of macro- and micronutrients in immunity.

In 1994 the preparatory work of the task force merged with activities of ILSI North America for joint organization of a Conference on *"Nutrition and Immunity"*. The conference was held in Atlanta in May 1997. Scientists from several disciplines presented their data and reviewed the current status of nutritional immunology with particular reference on gut immunology, effects of pre- and probiotics and the roles of vitamins, carotenoids, trace elements and essential fatty acids in modulating immune functions in health and disease.

The present monograph has been prepared based on the science presented at the Atlanta conference. Its aim is to introduce readers into the complex subject of immunology and the many facets of nutritional immunology. The first chapter provides a basic overview on immune cells, cytokines and host defence. In the second chapter dietary factors that alter or modulate the immune response are discussed. Special consideration is given to vitamins, carotenoids, zinc and selenium. A further chapter discusses the specific role of probiotics in gut immunology. The implication of immune cells and cytokines in the pathology of various diseases such as viral infections, asthma, cancer and heart disease is the subject of the last chapter.

We are confident that the monograph will help readers to gain a concise overview and will help to increase our understanding of this fast evolving field of vital interest.

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CONTENTS

INTRODUCTION

It has been known since the time of Hippocrates that poorly nourished people are more susceptible to infectious diseases. Associations between famine and epidemics of infectious disease have been noted throughout history.

Under-nutrition impairs the immune system, suppressing immune functions that are fundamental to protect the host efficiently from bacterial and viral infections. In addition, under-nutrition may potentiate the effects of both viral and bacterial infections. For example, some viruses cause only mild illness in well nourished children but can be fatal in those with malnutrition.

Scientists have understood since the 1960s that the immune system plays a critical role in the relationship between malnutrition and infection. This inter-relationship applies not only to nutritionally deprived children in developing countries but also to people of all ages throughout the world. Those especially susceptible include the elderly, individuals with eating disorders, alcoholics and patients with debilitating diseases, all of whom may suffer from nutrition-related impairments in immune function. Adverse effects on immune function may even be present in some instances of "over-nutrition" (such as obesity or excessive intakes of total fat or certain types of fatty acids), as well as in micronutrient deficiencies and nutritional imbalances.

Another major focus of current research is the possibility of stimulating the immune system of healthy people by nutritional means in the hope of improving health. For example, some scientists are investigating the possibility that supplementation with certain nutrients, such as vitamin E, at levels above the Recommended Dietary Allowances (RDA) may improve immune function in vulnerable segments of the population, such as the elderly. In addition, diseases like allergy and asthma have their roots in disorders of the immune system, but it is also becoming apparent that the immune system is involved in cardiovascular disease and cancer. The course of all these diseases may be altered by dietary intervention.

THE FUNCTIONING OF THE IMMUNE SYSTEM

The human body has an intricate system of defence mechanisms which protects it against potentially harmful foreign agents. This complex system of molecules, cells and tissues is widely dispersed throughout the body (Figure 1). The body has various non-specific defence mechanisms like skin and mucous secretions. However, the defences under consideration in this monograph are those belonging to the immune system.

Specific immune mechanisms

At the heart of the immune system is a sophisticated specific system of defences with three extraordinary capabilities:

- the ability to distinguish the body's own components from those of foreign invaders (often referred to as the ability to distinguish "self" from "non-self")
- the ability to recognize and respond, in specific ways, to an essentially unlimited number of different molecules
- the unique capacity to respond with an accelerated and enhanced response on re-exposure to a previously encountered foreign agent (that is, the system has "memory").

The recognition of self is accomplished by means of an elaborate system of specific molecules present on the surfaces of all cells in the body. In normal circumstances the cells of the immune system do not attack those cells which carry these distinctive marker molecules which denote self. However, any encounter with certain foreign marker molecules (called *antigens,* from *anti*body *gen*erator) activates cells of the immune system, causing them to mount a defensive response. During this response, immature immune cells are stimulated to differentiate into specialized cells capable of responding to the specific antigen. These cells are equipped with special receptor structures that allow them to recognize and interact with their individual targets. A few of these specialized cells, called *memory cells*, remain functional even after the response to a foreign agent is completed. Thus, the next time the immune system meets up with the same antigen, it can respond to it quickly and effectively.

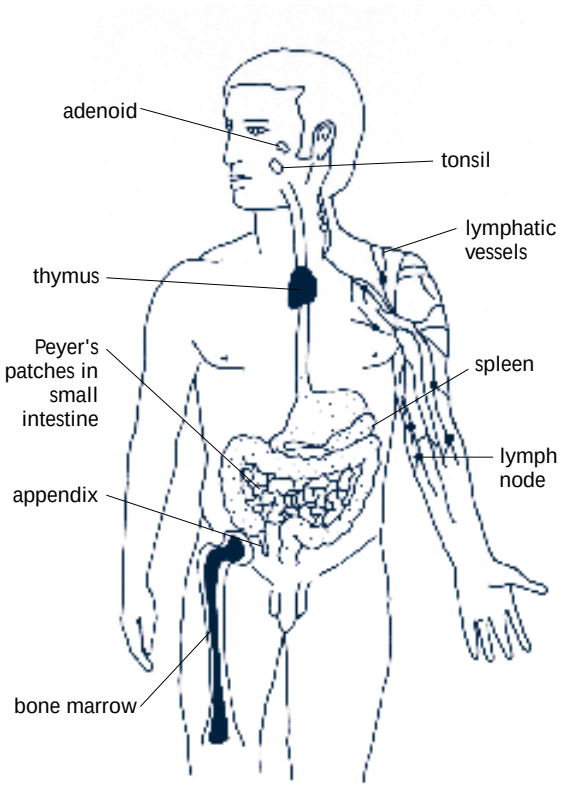
The principal defensive "soldiers" of the immune system are a class of mobile white blood cells called lymphocytes. There are two distinct types of lymphocytes with the special characteristics of specificity and memory: B cells and T cells (Figure 2).

B cells originate from the bone marrow. Upon stimulation by antigens, B lymphocytes develop into cells which produce antibodies. Antibodies are complex proteins called immunoglobulins. Each B cell produces one type of antibody which reacts specifically to a single variety of antigen. B-cell-stimulating antigens are usually protein molecules.

Some of the activities of the B cells are under the control of T cells. Like B cells, T cells originate in the bone marrow but they undergo important stages of development in an organ called the thymus. Specific signals drive the undifferentiated T cell to develop into functionally different T cell types.

"Helper" T cells regulate the immune response by secreting signalling molecules called *cytokines* (see Box 1). Cytokines bind to target cells and mobilize other cells and substances, producing a complex variety of defensive responses. "Suppressor" T cells can reduce the activity of other functional cells (see Box 2).

FIGURE 1
The distribution of the immune system



Thymus and bone marrow are the tissues for maturation of immune cells. T lymphocytes mature in the thymus and B lymphocytes in the bone marrow. Through the blood stream lymphocytes migrate to other immune tissues such as spleen, lymph nodes, and the gut-associated lymphoid-tissue (for example, Peyer's patches in the small intestine).

BOX 1

Cytokines

Cytokines are small soluble proteins made by various types of cells that regulate the behaviour of the cell itself or of other cells. Each cytokine has multiple activities on different cell types. They act selectively via specific cytokine receptors on the cells they affect. Receptor binding induces activities in the cell, such as growth, differentiation or death. Immune cells produce a typical range of cytokines. For example:

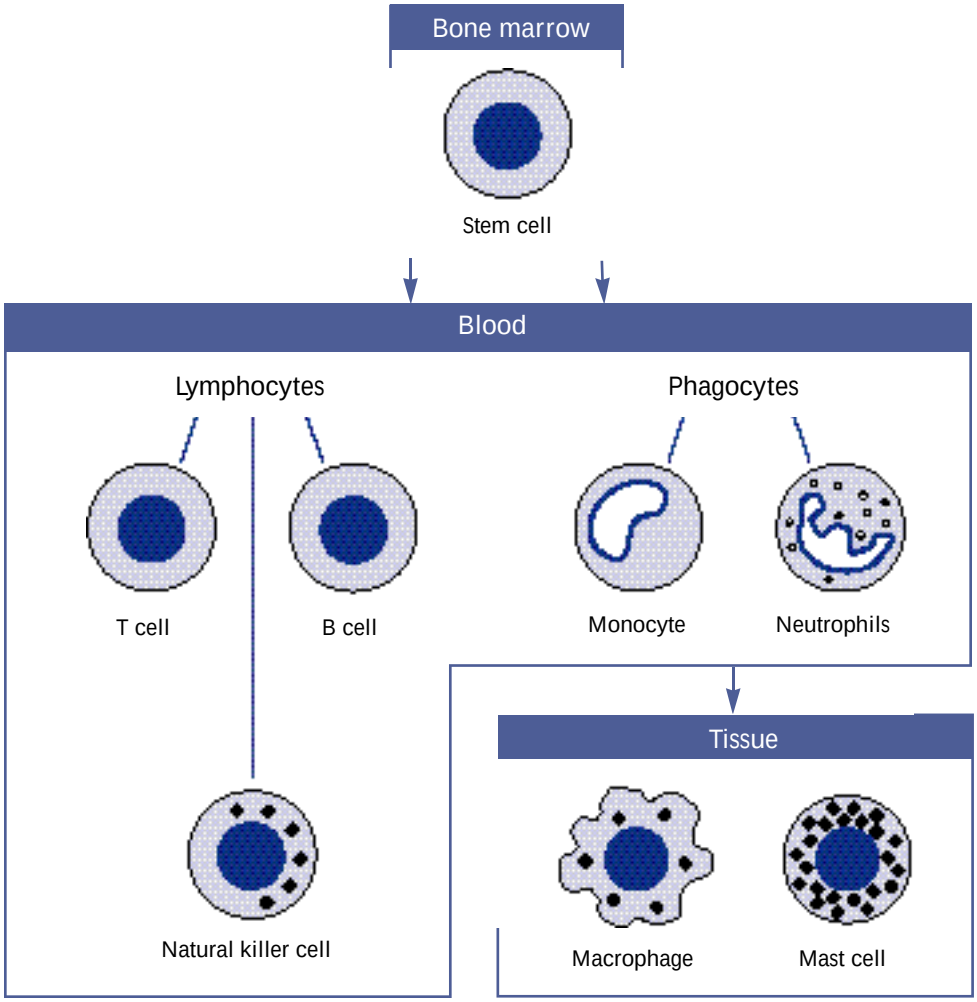
- T lymphocytes produce cytokines such as interleukin-2 and interferon-γ.
- Monocytes and macrophages primarily secrete cytokines such as interleukin-1 and tumour necrosis factor α.

Most cytokines act in concert with others to cause their physiological effects. Besides immune cells, cytokines may also affect non-immune cells in tissues such as brain and liver.

Another important part of the immune system is located in the gut, the so-called gut-associated lymphoid tissue (GALT). This lymphoid tissue has a distinctive biology related to its exposure to antigens from food but also to the antigens associated with the many microbes normally resident in the gut. This is discussed in more detail later (see Box 8).

Besides the specific immune mechanisms, non-specific immune mechanisms complete the immunological defence system. They can help eliminate infections by mechanisms which do not involve antibody production (see Box 3).

FIGURE 2
Major cells of the immune system



The major cells of the immune system arise from stem cells in the bone marrow. Stem cells are able to produce specialized lymphocytes and phagocytes.

BOX 2

More about B and T cells

Each B cell is programmed to make one specific antibody which is capable of reacting with one specific antigen in a lock-and-key fashion. When a B cell encounters its triggering antigen, it gives rise to many daughter cells, which manufacture and secrete large quantities of the specific antibody that matches that antigen. The antibodies bind to the antigen molecules and prepare them for elimination.

Collectively, the B cells can produce the many thousands of different types of antibodies that an individual needs to counteract the great variety of antigens that may be encountered during a lifetime. B cells express specific membrane-bound antibodies on their surfaces as antigen receptors, thus permitting their proliferation following interaction with antigens. When a particular antigen is encountered for the first time, the B cells that produce the appropriate antibody are primed and activated. If the same antigen is encountered again, the corresponding B cells (memory cells) are ready prepared to respond and can produce large quantities of the appropriate antibody very quickly.

Like B cells, T cells act in response to specific antigens. They can recognize antigens through receptors on their surface – the "T cell receptor". Part of the T cell receptor is an antigen-specific molecule that acts like an antibody, binding to the specific antigen. When the antigen binds to the T cell receptor, it activates the T cell to control the proliferation and differentiation of B cells that have bound the same antigen. These B and T cells interact specifically, triggering the T cells to produce molecules on their surfaces which stimulate B cells. T cells also secrete cytokines which activate B cells.

BOX 3

Non-specific immune help

Besides the acquired and specific part of the immune system that is mediated by B and T cells and their soluble products, there is a non-specific part that enables the body to rapidly eliminate bacteria and viruses at first contact. This includes:

- Phagocytes: These large white blood cells engulf and destroy microbes or other particles. Phagocytes include macrophages and neutrophils. Macrophages mature continuously from circulating monocytes and leave the circulation to migrate into tissues throughout the body. Macrophages and neutrophils express surface receptors that help them recognize constituents common to many pathogens. Bacterial molecules binding to these receptors trigger the cells to engulf and kill the bacterium and to induce the secretion of chemical mediators by these phagocytes.

- Natural killer cells: These cells form a third group of lymphocytes that differs from T and B cells in their function. They make up a small fraction of the immune cells in the blood. These cells do not bear antigen-specific receptors but are able to recognize and kill abnormal cells spontaneously. Target cell recognition and the ensuing killing function of natural killer cells is regulated by inhibitory and activating receptors on natural killer cells. These receptors are triggered by contact with potential target cells.

DIETARY FACTORS WHICH ALTER THE IMMUNE RESPONSE

High and low energy intakes adversely affect the immune response

It is well known that severe malnutrition, especially wasting malnutrition in children, leads to impairments in immune function. Such malnutrition, which is primarily a problem in developing countries, substantially increases the risk of childhood mortality from infection. Most host defence mechanisms are impaired in protein-energy malnutrition, even if the nutritional deficiency is only moderate in severity. T cells are especially affected, resulting in a decrease in their numbers.

Both obesity and its treatment may have effects on immune function, but their roles are not fully understood. Obesity is associated with impairments in host defence mechanisms (Table 1). For example, the responsiveness of both T and B lymphocytes to chemicals which induce cell growth may often be reduced in overweight people. This situation is thought to mimic those immunological processes *in vivo* after stimulation by specific antigens.

Certain weight reduction strategies lead to alterations in immune responsiveness. Although data are limited, most studies indicate that weight loss through low-calorie diets (400–1200 kcal / day) is associated with decreases in several measures of T cell, B cell and other immune cell functions. It is not known, however, whether these alterations in immune function are due to weight loss *per se* or to other factors such as changes in the amount or type of fat consumed or due to inadequate intake of essential nutrients. Because obesity and weight loss programmes affect an increasing number of subjects in wealthy societies, the impact of total energy intake on the immune response will soon become more severe.

The amount of dietary fat can influence immune functions

Most research into how fat in the diet may influence the functioning of the immune system has focused on specific types of fatty acids, but total fat intake may also be important (Table 1). Animal studies indicate that diets high in fat may depress the immune response and increase the risk of infection, and high-fat diets often result in diminished T cell activity.

TABLE 1

Effects of total energy and fat on the immune response

Dietary factor	Effects
High energy intake	Impaired lymphocyte responsiveness
High fat intake	Suppression of T cell functions and of natural killer cell activity
PUFA	Source for the generation of tissue hormones; also influence cell membrane fluidity
n-6 PUFA	Promote chronic inflammation
n-3 PUFA	Inhibit chronic inflammation and tend to suppress immunity

PUFA = Polyunsaturated fatty acids

In Western countries, fat usually contributes 35–45% of the total energy intake although some individuals may eat less, and some more, than this. Changes in total fat intake can influence the immune response in humans. The responsiveness of T lymphocytes, isolated from blood, to chemicals which induce cell growth was increased when the fat content of the diet was reduced from 30% or 40% to 25% of total energy. An increase in T lymphocyte responsiveness occurred in elderly subjects after fat intake was reduced from 36% to 27% of total energy. The capacity of natural killer cells to destroy tumour cells was increased when fat intake was reduced from 32% to 22% of total energy in healthy men. Overall, several indices of the immune response increase when the percentage of energy from fat is decreased.

Fat composition can influence immune function

Fatty acids can be divided into distinct families that differ in structure and dietary origin. Fatty acids which contain double bonds are termed unsaturated, and are further classified by the position of the double bonds, that is, n-3 or n-6 (see Box 4). Saturated fatty acids do not contain double bonds in their structure. The principal roles of fatty acids are as energy sources and as membrane constituents. In addition, certain fatty acids have specific roles, and are therefore regarded as essential nutrients.

Fatty acids are important in the functioning of the immune system because they are structural components of cell membranes. The fluidity of membranes is affected by the chain length and degree of saturation of the incorporated fatty acids. Fluidity is important for the expression of cell surface structures such as receptors, which play crucial roles in immune function.

A particular family of unsaturated fatty acids known as polyunsaturated fatty acids (PUFA) can potently alter the functioning of immune cells. There are two classes of PUFA: the n-6 series (found primarily in vegetable oils) and the n-3 series (found in fish oils and also in certain vegetable oils such as canola, soy, and linseed). These fatty acids can be converted by immune cells into tissue hormones, for example, prostaglandins (see Box 5). Depending on the type of PUFA in the diet, immune cells produce different quantities and kinds of prostaglandins with very different effects on the immune response. In addition to their effects on tissue hormone levels, PUFA may exert some of their effects by other mechanisms.

In general, diets rich in n-3 PUFA tend to inhibit the immune response, whereas those rich in n-6 PUFA tend to promote immune responses which lead to inflammation (see Box 6). For example, a supplement of flaxseed oil designed to provide 20 g/day of the n-3 fatty acid α-linolenic acid reduced the magnitude of indicators of the immune response in healthy young men. In another study, supplementation with 18 g/day of fish oil (equivalent to 5 g of long-chain n-3 PUFA) suppressed several indices of the non-specific and specific immune response. However, there have been relatively few human studies.

The ratio of n-6 to n-3 PUFA may be more important than the absolute amount of each of these classes of fatty acids in the diet. This ratio has changed greatly in recent decades, because vegetable oils rich in n-6 PUFA have displaced other fats in most Western diets.

BOX 4

Fat in the diet

Major fatty acids	Typical fat source
Saturated fatty acids	Beef fat, palm oil
Unsaturated fatty acids	
Monounsaturated fatty acids	Olive oil, canola oil
Polyunsaturated fatty acids (n-6)	Most vegetable oils
Polyunsaturated fatty acids (n-3)	Fish oil

Nutritional guidelines recommend that total fat intake should be equal to or less than 30% of total energy intake. Saturated fat intake is recommended to be less than 10% of total energy intake. Polyunsaturated fat should constitute up to 10% of total energy intake (of this, 10–20% should be n-3 and the rest n-6). The balance of dietary fat should be monounsaturated.

Deficiencies in vitamins, carotenoids and trace minerals can impair the immune response

Deficiencies of several micronutrients have been shown to reduce the immune response, as summarized in Table 2. Some of the methods used to measure responses in the immune system are discussed in Box 7.

Vitamin A

Dietary vitamin A occurs mainly in liver, egg yolk and milk. Some carotenoids found in vegetables and fruit can be converted in the body to vitamin A. Vitamin A deficiency is rare in technologically advanced societies, but it is a major public health problem in many parts of the developing world. Physicians and scientists have recognized for hundreds of years that xerophthalmia (the “dry eye” disorder caused by vitamin A deficiency) is linked to high morbidity and mortality from infectious diseases. Experimental observations and clinical trials in the 1920s and 1930s led to the reputation of vitamin A as the “anti-infective” vitamin. More recently, clinical trials in developing countries where vitamin A deficiency is prevalent have shown that supplementation with this vitamin reduces child mortality by 20–30%. Vitamin A capsule distribution is recognized as one of the most cost-effective interventions to improve public health in developing countries.

Vitamin A appears to play a particularly important role in the body's defences against the measles virus. Recent studies suggest that high-dose vitamin A supplementation is of significant value in preventing complications of severe measles and reducing mortality from this disease.

BOX 5

Prostaglandins

Prostaglandins are a family of tissue hormones derived from cell-membrane-associated polyunsaturated fatty acids. The type of polyunsaturated fatty acids in cell membranes is influenced by dietary fat. A wide variety of biological activities has been ascribed to prostaglandins, including modulating the intensity and duration of inflammatory and immune responses.

The principal precursor for the prostaglandins is the n-6 PUFA arachidonic acid. However, the two classes of n-6 and n-3 PUFA compete in prostaglandin formation, resulting in different families of prostaglandins and other tissue hormones. In addition, n-3 PUFA suppress the production of n-6 PUFA-derived prostaglandins.

Prostaglandins derived from n-6 PUFA (for example, prostaglandin E_2) appear to have potent regulatory functions for various types of immune cells. At low concentrations, prostaglandin E_2 is believed to be necessary for certain aspects of immunity. However, at a higher concentration several functions of immune cells are suppressed. The content of these prostaglandin precursors in cell membranes can be modified by altering the dietary composition of PUFA, thereby influencing the quantity of the produced prostaglandin E_2.

An adequate supply of vitamin A is needed for the normal development of many types of blood cells, including lymphocytes. In vitamin A deficiency, the numbers of these cells may be decreased and their functioning may be abnormal. Networks of cytokines which influence immune responses may also be altered during vitamin A deficiency, and antibody responses to antigens may be modified.

BOX 6

The inflammatory response

Inflammation is the body's response to entry by infective agents, to physical injury or to contact with antigens (for example, allergens on the skin). Blood supply to the area increases, allowing immune cells and other protective substances greater access to the area affected.

Some of the factors in the inflammatory response are as follows:

- Cells: The main cell types seen in an acute inflammatory response are the phagocytes, particularly the neutrophils; therefore these are also known as inflammatory cells. In chronic inflammation, activated T cells and macrophages also contribute to the inflammatory process.
- Mediators: In the acute inflammatory response which follows injury or infection of the body, phagocytes release chemical mediators such as cytokines and prostaglandins. The combined local effects of these mediators attract inflammatory cells to the area, resulting in the inflammatory response. In chronic inflammation, T cells and macrophages release mediators which contribute to tissue injury.
- Symptoms: Celsus in the first century said the signs of inflammation are "rubor et tumor, cum calore et dolore", that is, redness and swelling, heat and pain – all of which reflect the activities of cytokines and other mediators.
- Dietary factors: Polyunsaturated fatty acids (PUFA) can potently alter the functioning of phagocytes and T cells. There is some evidence that PUFA may affect diseases associated with chronic inflammation, such as asthma and rheumatoid arthritis. PUFA are a source of tissue hormones, for example, prostaglandins and leukotrienes. Depending on the type of PUFA in the diet, immune cells produce different kinds of tissue hormones with very different effects on the immune response. For example, one group of PUFA, the n-3 fatty acids, has anti-inflammatory effects. PUFA change the secretion pattern of signalling molecules like the cytokines, which are also involved in the pathogenesis of chronic inflammatory diseases.

TABLE 2

Effects of micronutrients on the immune response

Micronutrient	Effects
Vitamin A deficiency	Impaired antibody production Impaired lymphocyte responsiveness
ß-Carotene supplementation	Increased natural killer cell activity Increased production of signalling molecules
Vitamin E deficiency	Impaired antibody production Impaired lymphocyte responsiveness Impaired function of phagocytes Increased virulence of viruses
Vitamin C deficiency	Impaired inflammatory responses Impaired function of phagocytes
Vitamin B_6 deficiency	Decreased lymphocyte responsiveness Impaired antibody production Impaired T cell responses
Zinc deficiency	Impaired T cell development Impaired lymphocyte responsiveness Decreased resistance to infections
Selenium deficiency	Impaired antibody production

Carotenoids

The carotenoids are yellow, orange and red compounds found in fruits and vegetables. Examples are ß-carotene, which is widely distributed in plants, and lycopene, a carotenoid found in tomatoes. Like vitamins C and E, carotenoids are antioxidants.

Carotenoids have been reported to affect the immune response in animals and humans. They increase the population of specific lymphocyte subgroups, enhance the activity of natural killer cells, stimulate the production of various cytokines and activate phagocytic cells. Of particular interest is the possible capacity of lycopene to enhance the potency of the immune system.

Although animal studies have clearly shown an enhancing effect of ß-carotene on the immune system, results from human studies are inconsistent. Some studies have shown that ß-carotene supplementation may be beneficial for individuals with compromised immune systems, but it does not stimulate immune responses of healthy adults with adequate ß-carotene intake. In healthy young men, ß-carotene supplementation prevented the suppression of the immune response that would otherwise have resulted from exposure to long-wave ultraviolet light. In healthy elderly people, ß-carotene supplementation has been shown to enhance natural killer cell activity but to have no effect on indices of T-cell-mediated immunity.

BOX 7

Assessment of immune status

A wide variety of methods are used to assess the function of various components of the immune system and to detect nutrient-immunity interactions. Because the immune response is complex, no single assay is sufficient for a meaningful assessment of effects on immune function. Assessment of immune function *in vivo* requires measurement at several levels and may include measurement of specific antibodies arising from immunization, measurement of immunoglobulin concentrations in the blood, and determination of the absolute and relative (percentage) number of various lymphocyte subgroups (for example, helper and suppressor T cells). A wide range of *in vitro* tests measure immune function as a reflection of immune response *in vivo*.

In general, studies of human immune function and nutrition have tended to focus almost exclusively on immune cells circulating in the blood. A disadvantage is that these account for only 1% of total immune cells and therefore may not give a fully representative picture. They are usually studied through *in vitro* systems which have been designed primarily to assess T cell function. Other cells, such as B cells, are also affected by nutrition, and their functioning should also be evaluated more closely.

Nutritional deficiencies may affect several aspects of the immune response in different ways, so no single measure can provide a complete picture of the effects of nutrition on immune functioning.

Immunological methods currently used to assess the immune status are:

- Counting the numbers of immune cells circulating in the blood
- Measuring immune cell functions such as growth, production of antibodies and cytokines, phagocytosis, or killing activity of natural killer cells.

In the future, immune parameters may be of value as biomarkers in human nutritional intervention studies. There is a need for biomarkers which indicate that a change has occurred in the immune system and that provide information about the biological significance of the observed changes. Ideally, immune measures that are used as biomarkers should be specific and sensitive and relate to specific clinical signs. The relevant methods will be those that are capable of detecting biologically significant changes in either direction, that is, those that compromise immunity as well as those that enhance it. However, it is important to appreciate that a change in a marker in the absence of a clinical response may still be relevant, perhaps signalling that the immune system has been altered with respect to future antigenic challenges.

Immunological methods may also be of value in the assessment of nutritional status. Changes in immunological function are among the first detectable effects of a nutritional deficiency. By the use of immunological techniques it may be possible to identify nutritional deficits before they become detectable by classical biochemical methods.

Vitamin E

Vitamin E occurs in a variety of plant foods. Vegetable oils such as wheat germ oil, corn oil and soybean oil are especially rich in vitamin E. Many studies have shown that vitamin E deficiency impairs several aspects of the immune response, including B- and T-cell-mediated immunity. An unusual feature of vitamin E is that it is one of the few nutrients for which supplementation with higher than recommended levels has been shown to enhance certain aspects of immune function in both animals and humans. Both B- and T-cell-mediated immune responses appear to be affected by vitamin E supplementation. Animal experiments have also shown increased resistance to infectious diseases with vitamin E supplementation.

The mechanism by which vitamin E exerts its effects on the immune system is not yet clear. There is compelling evidence suggesting that vitamin E acts by reducing prostaglandin synthesis and/or by preventing the oxidation of PUFA in cell membranes.

Recent trials in healthy elderly people have shown that supplementation with vitamin E (at doses of 60, 200 or 800 mg/day) significantly improves certain *in vivo* indices of immune function, for example, increased specific antibody production in response to vaccination. A reduction in the incidence of self-reported infections was also observed, suggesting that vitamin E supplementation may stimulate the immune system to resist infectious diseases. The most effective dose was 200 mg/day. At the present time, however, the optimal dose of vitamin E for stimulating age-depressed immune functions remains to be determined.

Vitamin C

Major dietary sources of vitamin C are vegetables and fruit. Like vitamin E, vitamin C is an antioxidant. Unlike vitamin E, however, vitamin C is a water-soluble substance found in body fluids rather than in cellular lipids and membranes. Vitamin C acts as a major antioxidant in the aqueous phase and also reinforces the effects of other antioxidants, such as vitamin E, by regenerating their active forms after they have reacted with free radicals. Certain organs in the body concentrate vitamin C to levels far higher than those found in blood. One of these organs is the thymus, which plays a crucial role in immunity mediated through the actions of T lymphocytes and phagocytes.

Animal studies indicate that normal responses to infection do not occur during vitamin C deficiency. Vitamin C plays an important role in the function of phagocytes, and the failure of these cells to perform normally may contribute to the impairment of the response to infection that is seen in vitamin C deficiency.

There is much interest in the possibility that high doses of vitamin C (l g/day or more) may be of value in preventing some types of infections, especially respiratory infections. Numerous controlled trials have been conducted in human volunteers to evaluate the effect of vitamin C on the common cold. In general, these trials have shown that people who regularly take 1 g/day or more of vitamin C have shorter and milder colds than those who do not. It is unclear from the results, however, whether vitamin C supplementation can reduce the number of colds that people experience. In some trials, participants who took vitamin C had fewer colds than those taking placebos, but in other trials no such difference was found. One analysis

associated vitamin C supplementation with a reduced risk of colds in men and boys from population groups with relatively low vitamin C intakes, but not in those with nutritionally adequate diets.

It is possible that vitamin C supplementation may reduce the incidence of colds only in specific high-risk population subgroups. A recent re-analysis of data from previously published studies showed that vitamin C supplementation reduced the number of colds experienced by groups of people who exercise heavily. For example, the incidence of post-race respiratory infections in marathon runners was twice as high in those who did not take vitamin C supplements as in those who did. The differences between individual studies may reflect underlying vitamin C status, which was not controlled for in all studies.

Vitamin B_6

Vitamin B_6 is widely distributed in foods, with rich sources including fowl, fish, liver, cereals and pulses. It has been known since the 1940s that deficiencies of vitamin B_6 impair immune function. This effect is not surprising, since vitamin B_6 is essential for a wide variety of reactions necessary for the synthesis and metabolism of amino acids (the building blocks of protein). Many of the substances produced during the immune response, such as antibodies, are proteins.

Animal and human studies indicate that deficiencies of vitamin B_6 modify both antibody production and T cell activity. Lymphocyte growth and maturation are altered, and antibody production may be indirectly impaired. Although elimination of vitamin B_6 deficiency corrects these impairments in immunity, high doses of this vitamin above the RDA do not produce additional benefits in healthy adults.

Zinc

Major dietary sources of zinc are meat, dairy products, cereals and vegetables. The role of zinc in the functioning of the immune system has been studied extensively. Cells of the immune system require a large number of enzymes that need zinc to function, so it is not surprising that zinc deficiency has profound effects on immune function.

In animals, zinc deficiency impairs the immune system at a number of points. Deficiency profoundly suppresses the function of the thymus, which is crucial for the development of T cells. Lymphocytes become less responsive to chemical signals to grow. In addition, T-cell-dependent B cell functions and resistance to infections are impaired. Zinc deficiency increases morbidity and mortality after challenge with various pathogenic bacteria. Patients with acrodermatitis enteropathica (a disease caused by an inherited defect in the intestinal absorption of zinc) have immune defects similar to those seen in animals with dietary zinc deficiency. Wound healing is impaired in zinc deficiency. It has recently been shown in experimentally induced zinc-deficient humans that zinc deficiency results in an imbalance between T cell sub-populations.

It is believed that an intake of zinc which is twice the RDA (12-15 mg/day) is safe and has no effect on the immune system of healthy adults. However, when given in higher quantities, zinc will impair immunity. This has been demonstrated for both phagocytic cell and lymphocyte function, but the mechanism of these effects is not clear.

Selenium

Dietary selenium occurs in protein-rich foods such as meat, fish, nuts and seeds. Its role in the immune response has not been clearly established. Selenium is an important component of an enzyme which protects cells from oxidative damage. Because phagocytes generate large amounts of reactive oxygen species, selenium may be a factor in protecting phagocytes from an excess of such oxidants. In animals, selenium deficiency significantly suppresses specific immune functions. In contrast, a moderate increase in selenium intake appears to enhance the immune response. In a human study, a selenium intake of twice the RDA had an adverse effect on immune function. However, evaluation of the direct effects of selenium is difficult because of interactions between selenium and vitamin E.

Keshan disease is a disease which affects heart muscle. It is endemic in some parts of China, affecting primarily women of childbearing age and children. It appears to be due to a combination of a viral infection, possibly with a Coxsackie virus, and a dietary deficiency of selenium. Keshan disease has been nearly eradicated in China by selenium supplementation, even though the virus is presumably still present in the environment.

To gain insight into Keshan disease, researchers used an animal model of Coxsackie virus–induced myocarditis (inflammation of the heart muscle). Both selenium deficiency and vitamin E deficiency enhanced myocardial damage and allowed a normally benign infection to become virulent. A number of factors appear to be involved, including changes in the viral genome and a lack of antioxidant activity normally provided by vitamin E.

In addition to zinc and selenium, other minerals may be important for the normal functioning of the immune system. These include iron, copper, magnesium and manganese.

PROBIOTICS – THE CONCEPT OF BENEFICIAL GUT BACTERIA

The bacteria of the gut play important roles in several functions related to the digestion of food and the establishment and maintenance of the gut immune defence barrier (see Box 8). When the balance of organisms in the gut is disrupted or altered by disease or by the use of antibiotics, local immune defences may be impaired.

In both human and veterinary medicine, supplements containing desirable bacteria are sometimes given in an effort to replace or augment the normal gut species. Such supplements are called *probiotics*. By definition, a probiotic is a live microbial food ingredient that is beneficial to health. Probiotics may have benefits both for healthy people and for those with medical problems; most of the research interest in probiotics focuses on their value in the maintenance of digestive health.

Other approaches complementary to probiotics which are being investigated are *prebiotics* and *synbiotics*. A prebiotic is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon. A synbiotic is a mixture of probiotics plus prebiotics whose aim is the implantation and increased survival of health-promoting bacteria. Any of these approaches may indirectly induce immune effects. Preliminary data support the validity of these concepts, but more research is needed to confirm these observations.

BOX 8

The immune system of the gut

The ability of the immune system to distinguish true threats from harmless substances is put to a particularly severe test in the gut. Huge amounts of foreign substances pass through the human gut (an adult eats more than a tonne of food per year!). Therefore, it is not surprising that the gut immune system or the *gut-associated lymphoid tissue* (GALT) comprises an important part of the total immunological capacity of an individual. The vast bulk of this foreign material consists of harmless food components; mounting an immune response against these substances would be counterproductive. At the same time, however, small amounts of truly threatening agents, such as disease-causing bacteria and viruses, are also likely to be present in the digestive tract. The gut immune system needs to respond decisively to these agents.

Immune cells of the gut are organized in different compartments, such as lymph nodes, lymph follicles and Peyer's patches. Single immune cells are distributed within the intestinal mucosa and between epithelial cells. The immune cells of the GALT may be more susceptible to nutritional effects than the immune cells in general circulation because they are exposed to high concentrations of dietary constituents. Until recently, however, it was not possible to study in humans the impact of diet or single nutrients on the GALT.

To cope with various challenges, the GALT has developed two strategies. First, it provides for immune exclusion by secreting antibodies to inhibit the colonization of disease-causing bacteria and to prevent the penetration of harmful antigens from the digestive tract into the bloodstream. Second, it possesses mechanisms to avoid overreaction to innocuous substances occurring on mucosal surfaces. The latter phenomenon is called oral tolerance and largely appears to explain why most people show no adverse immune reactions to foods. However, in some individuals the immune system initiates an inappropriate and exaggerated immune response towards food constituents, which is known as "food allergy".

Indigenous bacteria may also contribute to protection at mucosal surfaces by creating a "barrier effect" against pathogens, known as colonisation resistance. This barrier effect involves several mechanisms, including competition for receptors at mucosal surfaces and for metabolic substrates and production of regulatory factors such as short-chain fatty acids and bacteriocins (antibiotic proteins produced by bacteria).

Probiotic organisms are found in fermented foods, including traditionally cultured dairy products such as yogurt and kefir and newer types of fermented milks specifically designed to contain bacteria of potential benefit to health. The organisms included in commercial probiotics include lactic acid bacteria (both lactobacilli, such as *Lactobacillus acidophilus* and *Lactobacillus casei*, and cocci, such as *Enterococcus faecium*) and bifidobacteria. Because these organisms only temporarily colonize the intestinal tract, regular consumption is necessary for optimal benefits.

One way in which probiotics may promote health is by contributing to the "barrier effect" of the intestinal bacteria, which creates an environment hostile to some pathogenic bacteria. Some of the metabolic products produced by lactic acid bacteria, such as bacteriocins and lactic acid itself, may inhibit the growth of

pathogenic organisms. Some probiotic strains may also adhere to the epithelial wall of the intestine, thus preventing pathogenic bacteria from adhering to the same receptors, or they may compete with pathogens for nutrients that are in limited supply.

An additional mechanism by which probiotic bacteria may promote health in the digestive tract is by altering the local immune response. Survival of the bacteria during intestinal transit or adhesion to epithelium, or both, seem to be important for modifying the host's immune reactivity. Alteration of immune function after the ingestion of probiotic lactic acid bacteria has frequently been reported in various experimental systems. For example, yogurt, which contains live *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, has been shown to enhance several parameters of immunity in experimental animals.

Studies with another probiotic microorganism, *Lactobacillus* GG, have shown that this organism can counteract the increase in gut permeability that would otherwise occur after exposure to viruses or foreign antigens. This organism also stimulates immune response to specific antigens.

In humans, strains of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* have been shown to enhance phagocytosis within the body for several weeks after ingestion in fermented milk products. The increase in phagocytosis coincided with elevated recovery of the probiotic bacteria in the faeces. A study in human volunteers was designed to determine whether consumption of a fermented milk product containing *Lactobacillus acidophilus* could induce changes in the intestinal flora and alter the immune response. Volunteers who received the fermented milk for three weeks showed an increase in *Lactobacillus acidophilus* and counts of bifidobacteria in their faeces. In response to a challenge with a *Salmonella typhimurium* strain with reduced pathogenicity, they also showed a more than fourfold rise in antibody against the organism when compared with a control group challenged with the same microorganism but not given the fermented milk. These results indicate that lactic acid bacteria which persist in the gut can act to boost the antibody response.

Probiotic bacteria may be of value in the treatment of clinical conditions that involve abnormal populations of gut microbes, increased gut permeability and altered gut mucosal barrier functions. Examples of situations in which probiotics may be of therapeutic value include acute diarrhoea caused by rotavirus.

In summary, it is an open question as to whether and how the observed changes in immune function are related to health effects. In many studies only symptoms have been measured and nothing is known about the underlying immunological mechanisms. The nature of the interactions between probiotics and the immune cells and tissues in the gut remains the subject of intense investigation.

REDUCTION OF DISEASE RISK BY DIETARY MODIFICATION OF THE IMMUNE SYSTEM

Researchers are actively investigating how dietary modifications that influence the immune system can be used to reduce the risks of various diseases or to improve their management. The diseases include viral infections, asthma and allergy, cancer, heart disease and autoimmune diseases.

Viral infections

Vitamin A has been used effectively in the treatment of measles in vitamin A-deficient children. This is one example of nutritional enhancement of the immune system that has become an accepted part of standard medical practice. Trials in developing countries have demonstrated significant decreases in measles-associated pneumonia and mortality in children given vitamin A supplements compared with children given a placebo. These findings have led the World Health Organization to recommend vitamin A therapy for children with measles in developing countries. However, the benefits of vitamin A do not seem to be limited to deprived populations. Even in the United States, where vitamin A deficiency is ordinarily considered rare, many children show biochemical evidence of vitamin A deficiency during measles infection. Children in U.S. hospitals who were treated with vitamin A for severe measles experienced shorter and less severe illness. These findings prompted the American Academy of Pediatrics to recommend vitamin A therapy for infants and young children hospitalized for severe measles.

Although the mechanism by which a relative deficiency of vitamin A affects measles infection is not known, it is believed to involve a decrease in the infected person's immunity. Vitamin A–treated measles patients have been shown to have increased numbers of lymphocytes and increased levels of measles-specific antibodies, indicating that immune function is enhanced.

The encouraging results from studies of measles have prompted investigations of the effect of vitamin A supplementation on other infections. However, given the wide range of immune responses to different types of pathogens, it is doubtful that vitamin A would be of value in all infectious diseases. Clinical trials in developing countries have indicated that vitamin A supplementation reduces the severity of diarrhoeal disease in childhood but has little impact on childhood pneumonia. Vitamin A deficiency has been associated with increased severity of respiratory virus infection, but clinical trials of vitamin A supplementation in children with this disease have had equivocal results.

There is evidence that nutritional status may be an important determinant of survival in individuals infected with human immunodeficiency virus (HIV), the AIDS virus. In the later stages of the disease, severe malnutrition is common, and wasting is one of the most prominent characteristics of advanced disease. Although nutritional factors are not likely to be the most important determinants of the disease, they may influence initial susceptibility to HIV infection. The nutritional deficiencies observed in HIV-infected individuals, especially deficiencies of vitamins A, B_6 and B_{12}, have been associated with deficits in immune function (lower counts of helper T cells) and accelerated disease progression. Recent research indicates that selenium deficiency may be an important predictor of decreased survival in AIDS patients. Further studies are

needed to determine whether supplementation with vitamins and / or selenium is of value in the treatment of HIV-infected patients.

Several studies of young children have shown that some probiotics significantly shorten the duration of rotavirus diarrhoea in both developed and developing countries. In most studies, the clinical effects were accompanied by an increase in the immune response.

Asthma and allergy

Heredity is a major predisposing factor in allergy, but environmental factors, including diet, also play a role. The chances of a genetically susceptible individual developing sensitivity to a food protein depend on many factors, including exposure to the potential allergen, permeability of the gut and an antecedent episode of viral gastro-enteritis.

Probiotics may be a useful tool in the treatment of food allergy because of their ability to promote endogenous barrier mechanisms and alleviate intestinal inflammation. Lactobacilli of the types normally found in the intestinal tract and included in probiotics may modify the effects of food proteins on the immune response. Therefore, probiotics may be a promising tool to provide protection against potentially harmful dietary antigens during childhood, as has been demonstrated in children under the age of two.

A few studies have suggested that dietary intake of fish, especially oily fish containing n-3 PUFA, may be protective against asthma. It has been hypothesized, although not proven, that recent increases in the ratio of n-6 to n-3 PUFA in the diet (because of the increased use of vegetable oils rich in n-6 PUFA) may have contributed to the increased prevalence of asthma. In several countries, there are social and regional differences in the prevalence of asthma and other allergic diseases which have been associated with differences in the consumption of PUFA. It is believed that the production of mediators involved in allergic responses is affected by the balance between the two types of PUFA.

Cancer

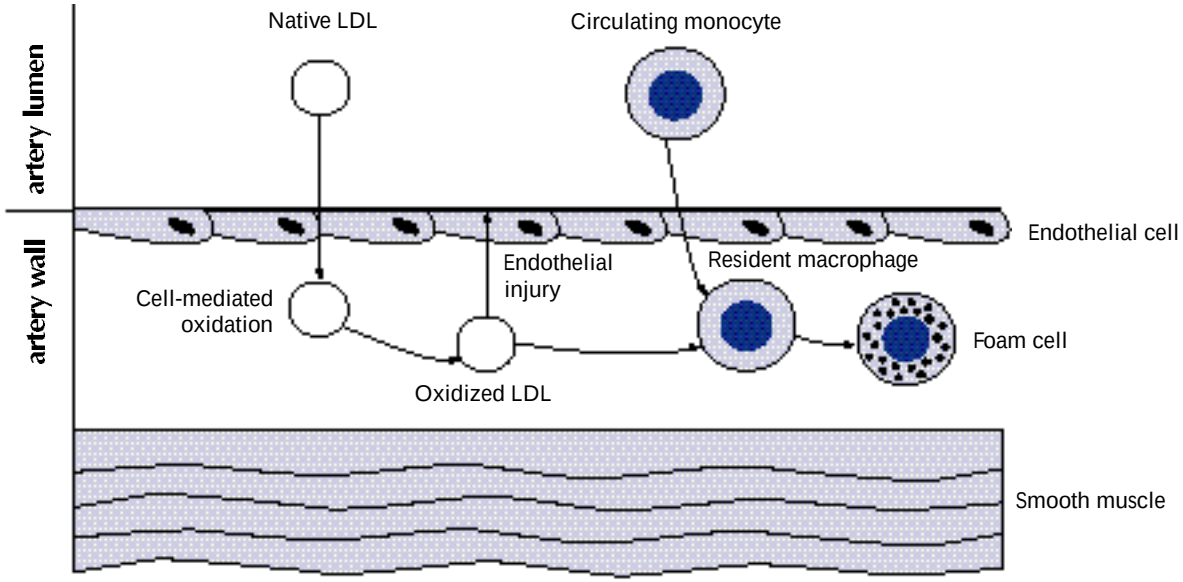
It has long been thought that the immune system could play a role in recognizing and reacting against tumours. Furthermore, the increased incidence of suppression of the immune system associated with infection by HIV has suggested a relationship between immune suppression and the development of certain tumours. However, T-cell-deficient individuals do not develop more tumours than do normal individuals. The probable reason for this is that most tumours do not express distinctive antigenic molecules necessary to initiate a specific immune response.

Despite the knowledge that natural killer cells are able to kill tumour cells, there is no evidence that enhancement of natural killer cell activity by dietary intervention is able to reduce the risk of certain tumours.

Heart disease

Numerous dietary factors have been linked with increases or decreases in the risk of heart disease. Atherosclerosis is a major cause of mortality from heart disease. It is an inflammatory disease of the arteries resulting in the arterial deposition of plaques. The immune system is involved in the pathogenesis of atherosclerosis through interaction between its white cells (monocytes and macrophages) and cells of the arterial wall (Figure 3). Dietary factors influence the immunological processes underlying the pathogenesis of atherosclerosis. Population studies and clinical evidence have indicated that the risk of heart disease may be reduced with increased intakes of n-3 PUFAand antioxidants.

FIGURE 3
Major events in atherosclerosis



Native LDL from the artery lumen enters the artery wall where it can be oxidized. Oxidized LDL stimulates monocytes to enter the artery wall. Monocytes differentiate into macrophages which take up oxidized LDL and become foam cells. Foam cells release lipids and enzymes that enhance the progression of arterosclerotic lesions.

n-3 PUFA may inhibit the development of atherosclerosis by blocking the production of cytokines which promote inflammation (see Box 6) and other substances which play roles in the complex process of local inflammation and arterial injury that lead to the development of plaques.

Vitamin E also has protective properties which may be partly attributable to its ability to alter interactions of immune cells with the endothelial cells lining the inner surfaces of arteries. Vitamin E also prevents oxidation of low-density lipoproteins (LDL – lipoprotein molecules which transport fat and cholesterol in the body). The oxidation of LDL is believed to contribute to plaque formation by several mechanisms. Oxidized LDL adversely affects arterial cells and is removed from circulation by macrophages, which are then transformed into “foam cells”. These come to rest in the arterial wall. Foam cell formation is a key step in the early stages of plaque development which may also promote the proliferation of smooth muscle cells, thus thickening the arterial wall and reducing the diameter of the affected

artery. Oxidized LDL may also promote the formation of blood clots and impair the flexibility of arteries. All of these factors can increase the progression of atherosclerosis. It has been demonstrated that supplementation with high doses of vitamin E (up to 800 mg per day) inhibits the oxidation of LDLin human subjects. This effect may be at least partly responsible for the inverse associations between vitamin E supplementation and heart disease risk seen in population studies. However, despite experimental evidence, the antioxidant hypothesis alone does not explain the protective effect of antioxidants such as vitamin E. Several additional mechanisms may underlie the role of antioxidants in preventing the clinical manifestations of coronary artery disease.

Autoimmune disease

Autoimmune disease occurs when the immune response is mounted against the body's cells. The consequence is that the active immune cells cause chronic inflammatory injury resulting in severe tissue damage. It is not known what triggers autoimmunity, but both environmental and genetic factors are important. Examples of autoimmune disease are insulin-dependent diabetes mellitus and rheumatoid arthritis.

Fish oils containing n-3 PUFA have been shown to have significantly beneficial clinical, immunological and biochemical effects in a number of animal models of autoimmune diseases. These observations suggest that diets enriched in n-3 PUFA might be of some therapeutic benefit in autoimmune diseases in humans.

Some studies in populations also suggest that diets high in n-3 PUFA may inhibit autoimmune diseases. For example, Greenland Inuits have unusually high n-3 PUFA intakes and high ratios of n-3 to n-6 PUFA (1:1) in their diets because of their high intake of fats from marine mammals and fish. They have very low rates of autoimmune and inflammatory disorders compared with individuals consuming Western diets (who have ratios of n-3 to n-6 PUFA of 0.04-0.1:1). This is likely due, at least in part, to the effects of different kinds of PUFA on the synthesis of prostaglandins and leukotrienes involved in immune responses, but there may also be genetic differences in the metabolism of essential fatty acids by Inuits.

There have been a few preliminary trials to test the effect of supplementation with fish oils rich in n-3 PUFA in patients with autoimmune and other diseases involving immune disorders. The results indicate that fish oil supplementation may be beneficial in patients with rheumatoid arthritis and Crohn's disease (which affects the lower gut).

BENEFITS AND RISKS OF ALTERING THE IMMUNE RESPONSE BY NUTRITIONAL MEANS

Ideally, our lifestyle (diet, physical activity, psyche) should enable the immune system to operate at its genetically determined optimal level of activity. From the nutritional standpoint, a well-balanced diet should support effective immune function. If this is unattainable, however, the concept of promoting health or treating disease by altering the immune response by dietary means shows great promise. There are still many questions to be answered about optimal concentrations of nutrients and the biological significance of nutritionally modified immune responses. Potentially beneficial approaches include:

- high-dose vitamin A supplementation in children with measles to reduce the risk of complications
- the use of large doses (600 mg/day or more) of vitamin C to reduce the incidence of respiratory infections in high-risk individuals, such as those exposed to intense physical stress
- the use of vitamin E supplements (at doses of at least 200 mg/day) to improve immunity in the elderly and to reduce the risk of coronary heart disease
- supplementation with vitamins and minerals to boost immunity in the elderly
- increasing the ratio of n-3 to n-6 PUFA to reduce symptoms of autoimmune and inflammatory diseases and possibly to protect against heart disease
- reducing fat intake to activate immune response
- the use of probiotic bacteria to enhance immune defences in the gut, stimulate the immune system and/or treat food allergies.

The potential benefits of such approaches must be balanced against the potential risks. The greatest risk resulting from dietary modulation of the immune response would be associated with nutritional interventions by people with over-active immune systems (for example, those with allergies, chronic inflammatory diseases, autoimmune diseases) in the absence of adequate medical supervision. For some approaches, the risks are likely to be negligible. This is especially true for the correction of nutritional deficiencies. For example, the elimination of malnutrition among children in developing countries would be expected to greatly improve their resistance to infectious diseases, and it would not be expected to have any harmful results. Enhancement of immunity through judicious short-term use of a high-dose nutritional supplement also appears to be acceptably safe, since long-term adverse effects are unlikely. The use of a single high dose of vitamin A in the treatment of children with measles is a good example.

Similarly, the improvements in immune responses which occur when elderly people are supplemented with low doses of multiple vitamins and minerals are also unlikely to be accompanied by adverse effects. The beneficial effects of low-dose supplementation are probably due to the correction of mild deficiencies, and the doses of nutrients in ordinary multivitamin/multimineral supplements are well within the safe range. To date, most studies show that supplements do not stimulate the immune response in healthy, well-nourished individuals with normal levels of physical activity but are of benefit to malnourished or elderly subjects as well as those engaging in extreme physical activity. What has been observed is a boost of the

immune response to levels seen in normal healthy subjects. In these risk groups, the benefits clearly outweigh the potential risks. In normal subjects, there are mostly no benefits and, for most nutrients, no risks. However, more studies are needed to confirm this.

The use of probiotic bacteria found in traditionally fermented foods is also unlikely to be risky, although this has not been well studied in humans. Fermented dairy products such as yogurt and kefir, which contain living lactic acid bacteria, have a long history of safe use by a wide variety of cultural groups.

There is greater reason for concern about therapies that involve the prolonged use of high doses of nutritional supplements or unusual dietary patterns to alter immune responses. In these instances, the possibility of adverse effects – either on the immune response itself or on other physiological functions – must always be balanced against the potential benefits.

Many minerals, including those which influence the immune response, have narrow ranges of safety. Although small increases in the intake of these minerals may have beneficial effects on immunity, large increases can be harmful. For example, there is ample evidence that low zinc intake impairs immune function and that mild zinc deficiencies are relatively common, even in industrialized societies. Therefore, it might be expected that zinc supplementation would be beneficial. However, the prolonged consumption of high amounts of zinc (more than twice the RDAof 12–15 mg / day) can impair immune responses and interfere with copper nutrition.

Vitamin E is generally regarded as one of the safest supplements, even when administered in doses far greater than those normally obtained from food. A recent controlled trial of vitamin E supplementation in the elderly demonstrated that the immune-enhancing effects of a moderately high dose of vitamin E (200 mg / day) were superior to those obtained at either lower or higher doses (60 or 800 mg / day, respectively). All of the doses tested in this study were considerably higher than usual dietary intakes of vitamin E. Typical intakes of vitamin E are about 10 mg / day. It is difficult to increase vitamin E intake above this value by dietary means, because most of the foods richest in this vitamin are undesirably high in fat and energy. Thus, for vitamin E, as for other nutrients, there may be a level of intake that has optimal effects on the immune response, with diminishing benefits at higher intakes.

SUMMARY

Relationships between nutrition and infection have been observed since antiquity, and the role of the immune system in these relationships has been appreciated since the 1960s. Clinically meaningful effects of nutrition on immune function are not limited to malnourished children in developing countries; they can be observed among people of all ages throughout the world.

The immune system consists of an intricate array of defence mechanisms which protect the body against potentially harmful foreign agents. Nutritional factors may influence immune functioning in many ways and at many levels. Because of the complexity of the immune system, no single assay can assess the effects of changes in nutrition on immune function. Scientists are currently searching for biomarkers which give information about the immunological significance of various dietary factors.

Dietary factors that influence immune responses include total energy intake (both as it pertains to malnutrition and to obesity and dieting), total fat intake, the types of fatty acids ingested (especially n-3 and n-6 PUFA), several vitamins (especially vitamins A, B_6, C and E), carotenoids, trace minerals (especially zinc and selenium) and probiotic bacteria.

Preliminary research suggests that altering the immune response by dietary means may be of value in the reduction of risk and / or the treatment of a wide variety of disorders, including viral infections, asthma and allergy, heart disease and autoimmune diseases. A few such therapies, like the use of vitamin A in the treatment of measles, have already become an accepted part of modern medical practice. However, for most dietary factors this approach is still under investigation. The potential benefits of dietary modulation of the immune response must be balanced against the potential health risks that may be associated with unusual dietary patterns or the prolonged use of supplements at high concentrations. Nevertheless, nutritional therapies aimed at modifying the immune response may one day prove to be of great value in both the maintenance of health and the treatment of disease.

GLOSSARY

Allergen: A substance (antigen, see below) that provokes an allergic reaction.

Antibodies: Substances produced by B cells that react with antigens and prepare them for destruction.

Antigen: A substance that triggers an immune response.

Antioxidant: Any substance that can delay or inhibit oxidation.

Atherosclerosis: A degenerative disease of arteries in which there is thickening caused by the accumulation of material (plaque) beneath the inner lining, eventually restricting blood flow. The plaque characteristically contains cholesterol and macrophages.

Autoimmune disease: A disease in which the body's immune defences react to the body's cells as though they were foreign, leading to destructive effects.

B cell (or B lymphocyte): Asub-set of lymphocytes that can develop into antibody-producing cells.

Controlled trial: A study to investigate the effect of a treatment. Subjects are randomly allocated to either of two groups. One group receives the treatment under investigation whereas the other (the control group) receives an inactive placebo. Ideally, the treatment should be double-blind, that is, neither the investigators nor the subjects should know during the study whether a subject belongs to the treated or the control group.

Crohn's disease: A chronic inflammatory disease of the gut. The cause is unknown.

Cytokine: A biologically active peptide synthesized mainly by lymphocytes or monocytes and macrophages. Cytokines act as regulatory molecules that alter the function of target cells in immunological reactions.

Enzymes: Proteins which catalyse metabolic reactions, speeding them up without themselves being used up in the reaction. Each enzyme is specific for a given substrate and / or reaction.

Fatty acids: Organic acids with a hydrocarbon chain of varying length; constituent of fats, specifically, triacylglycerols and related compounds.

HIV: Abbreviation for human immunodeficiency virus (the virus that causes AIDS).

Hormone: Chemical substance produced in the body that controls and regulates the activity of certain cells and organs.

Inflammation: General term for the reaction of tissues to injury or infection, or sometimes a localized immune (allergic) response; characterized clinically by heat, redness, swelling and pain.

Leukotrienes: Tissue hormones derived from PUFA which possess diverse biological actions in the immune system.

Macrophage: Type of phagocytic cell present in the tissue.

Morbidity: The state of being diseased.

n-3 PUFA: Polyunsaturated fatty acids with the first double bond between the third and fourth carbon atoms from the methyl end. n-3 PUFA are found in fish oils and some types of vegetable oils.

n-6 PUFA: Polyunsaturated fatty acids with the first double bond between the sixth and seventh carbon atoms from the methyl end. n-6 PUFA are found in vegetable oils such as soybean oil.

Phagocytic cell: A cell that engulfs and destroys other cells, particles or bacteria.

Polyunsaturated fatty acid: A fatty acid with two or more double bonds in its carbon chain.

Probiotics: Live microbial food ingredients that are beneficial to health.

Prostaglandins: Tissue hormones derived from PUFA which possess diverse biological actions in the immune system.

PUFA: Abbreviation for polyunsaturated fatty acid.

Recommended Dietary Allowances (RDA): Average daily intake of a nutrient specified at levels appropriate to maintain good health.

T cells (or T lymphocytes): A sub-set of lymphocytes defined by their development in the thymus. T cells induce, regulate and effect specific immune responses after stimulation by antigen.

Tissue hormones: In contrast to normal hormones (hormone, see above) which are produced in one organ and act systematically, tissue hormones are locally produced all over the body and act locally.

FURTHER READING

A complete list of references used to compile this concise monograph is available from ILSI Europe. More detailed information on this subject can be found in the texts below.

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