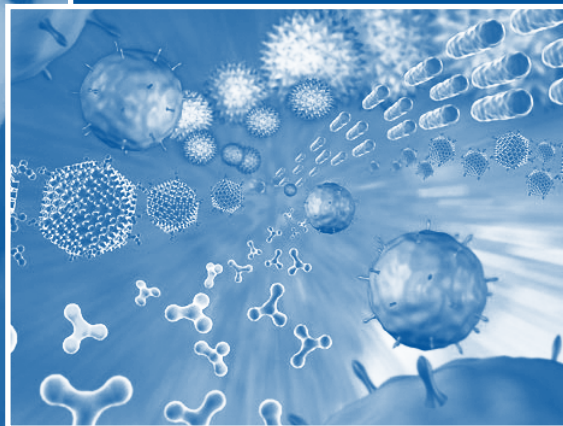
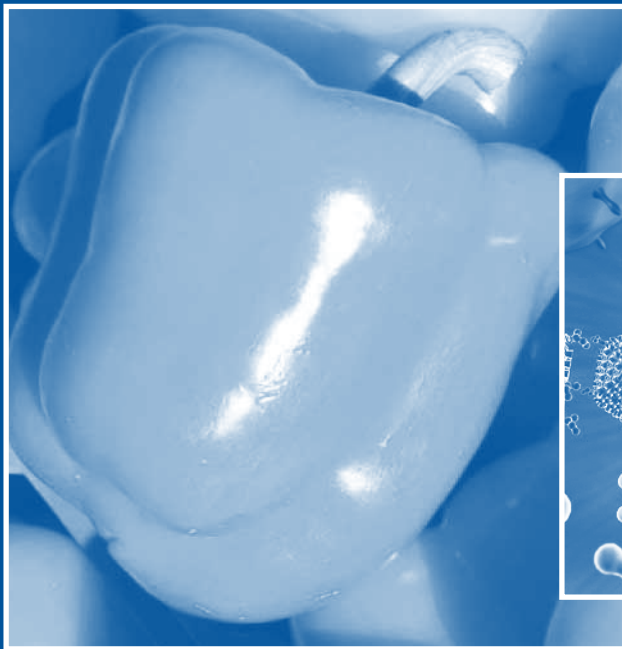


ILSI EUROPE CONCISE MONOGRAPH SERIES

NUTRITION AND IMMUNITY IN MAN



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NUTRITION AND IMMUNITY IN MAN

by
Sandra Gredel

2nd edition



ILSI Europe

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FOREWORD

The immune system has evolved as a defense mechanism against infections and tissue damage and is thus crucial to the maintenance of health on a day-to-day basis. The immune system comprises structural and cellular elements that are dispersed throughout the body. Inappropriate immune regulation can aggravate tissue damage, lead to chronic inflammation and development of allergic and autoimmune diseases. Optimal immune function¹ thus requires a delicate balance between destruction of invading pathogens and avoidance of self-destruction.

To maintain this balance (so-called immune homeostasis) and exert its functions, the immune system requires energy, building blocks and essential vitamins for the production of signalling molecules, proliferation of cells, and synthesis of effector molecules such as antibodies. These processes are very sensitive to deficiencies in macro- and micronutrients, explaining the long-known association of undernutrition with impaired immune function and increased susceptibility to infection. More recently, it has become evident that immune function is also sensitive to microorganisms and food constituents that interact with specific receptors and cells of the immune system and thereby modulate its functions.

Our understanding of the mechanisms regulating immune function, the impact of nutrition on these mechanisms, and the consequences for health maintenance has rapidly expanded in the last decade. It is therefore timely to update the previous ILSI Europe Concise Monograph “*Nutrition and Immunity in Man*” that was published in 1999. The present monograph provides an updated overview of immune function, includes newly discovered elements such as T_{reg} and T_h17 cells, summarises the effects of specific dietary components on immune function, and highlights the resulting impact on health. In that respect, the effects of vitamins and fatty acids on immune function have been updated as well as the effects of pre- and probiotics.

This monograph is intended as a concise introduction to the fascinating but complex field of nutrition and immunity. We are confident that it will serve as a valuable resource for all individuals that take an interest in the impact of nutrition on immune function and its implications for health.

On behalf of the Nutrition and Immunity Task Force
Ruud Albers
Unilever

1. Throughout the text, “immune function” means “the functioning of the immune system”.

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 diseases have been noted throughout history.

Under-nutrition impairs the immune system, suppressing immune function that are fundamental to the efficient protection of the host from bacterial and viral infections. The consequence of this impairment is an increase in both incidence and severity of 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 crucial 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, premature infants, 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 also be present in some instances of “over-nutrition” (such as obesity or high intake 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 improving the functions of 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 or vitamin C, at levels above the Recommended Dietary Allowances (RDA), or with food constituents such as probiotics and prebiotics

could improve immune function in vulnerable segments of the population, such as the elderly, but also in the general population. Functional foods aimed to improve or suppress immune function are more frequently appearing in supermarkets. Diseases like allergy, asthma and inflammatory bowel diseases have their roots in disorders of the immune system. Moreover, the immune system is involved in cardiovascular diseases and cancer. The course of all these diseases can be altered by dietary intervention.

1. 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 effector molecules, cells and tissues is widely dispersed throughout the body (Figure 1). The body has various nonspecific defence mechanisms like skin and mucous secretions. Any organism that breaks through this surface barrier encounters two further levels of defence, the innate and the acquired immune responses. These are the defences under consideration in this monograph and are, together with their specific cells and organs, commonly addressed as the *immune system*.

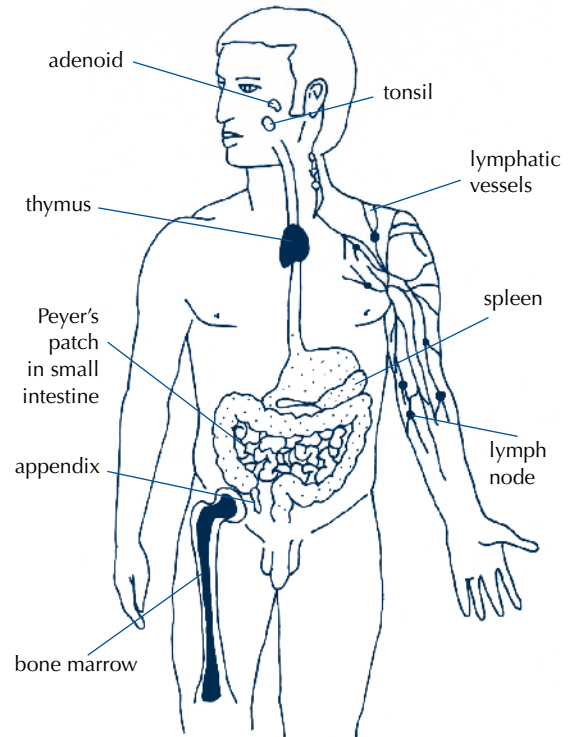
1.1 The functioning of the immune system

The immune system can be divided into innate and acquired (or adaptive) immunity. While the innate immunity is a first line of defence and a generic response, the acquired immunity is specific and requires continuous adaptations to foreign agents. The main distinction between the two lies in the cell types, receptors and mechanisms involved in immune responses. The cross-talk between innate and acquired immunity through specific receptors and mediators enables a powerful host defence.

To perform the task of defending the host against infection, the immune system features three extraordinary capabilities:

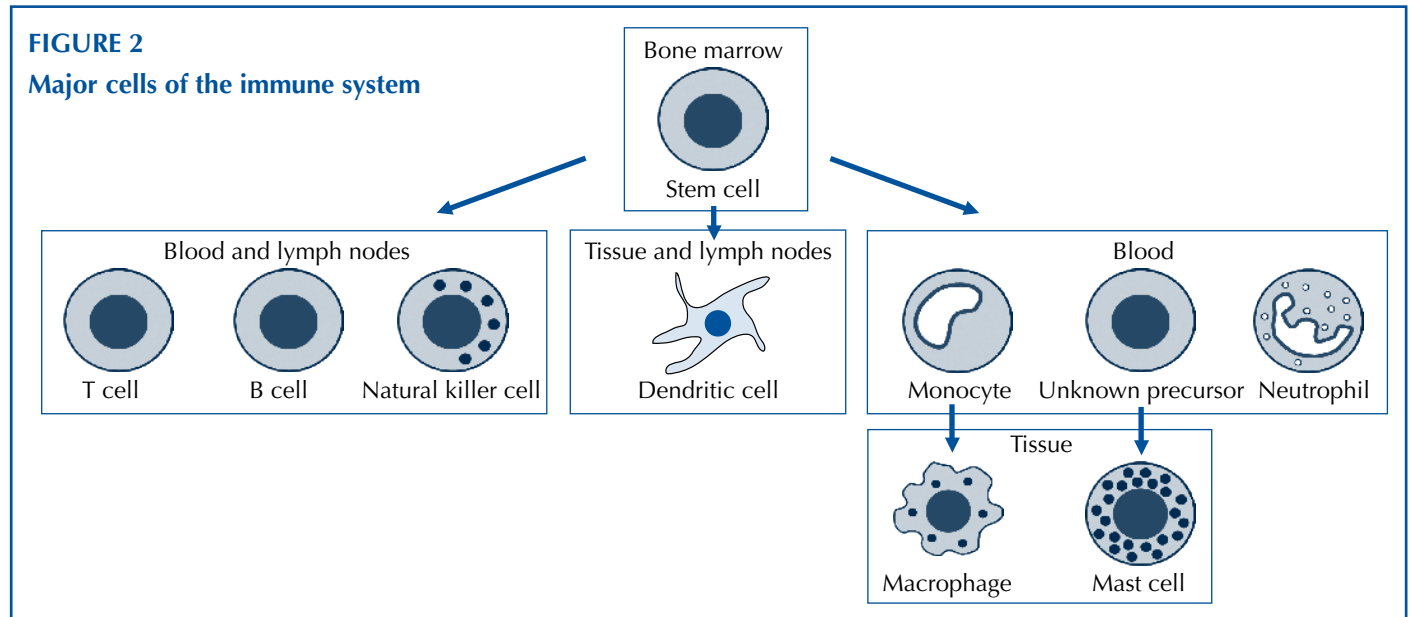
- The ability to distinguish the body's own components from those of foreign invaders (often referred to as the ability to distinguish "self" from "non-self")
- The ability to recognise and respond, in specific ways, to an essentially unlimited number of different molecules

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 system lymphocytes migrate to other immune tissues such as spleen, lymph nodes, and the gut-associated lymphoid-tissues (for example, Peyer's patches in the small intestine).

- The unique capacity to respond with an accelerated and enhanced response on re-exposure to a previously encountered foreign agent (i.e., 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 that carry these distinctive marker molecules that denote self. However, any encounter with certain foreign marker molecules (called *antigens*, from *antibody generator*) activates cells of the immune system, causing them to mount a defensive response. During this response, pathogens are destroyed and their antigens are presented to immature immune cells. Thus, these cells are stimulated to differentiate into specialised cells equipped with specific receptor structures that allow them to recognise and interact with their individual targets. A few of these specialised cells, called *memory cells*, remain functional even after the response to a foreign agent is completed. Thus, the next time the immune system meets with the same antigen, it can respond to it quickly and effectively.

1.2 Major cells of the immune system

The principal defensive “soldiers” of the immune system are a class of mobile white blood cells called leukocytes. There are two distinct types of leukocytes: *phagocytes*, including macrophages, neutrophils and dendritic cells; and *lymphocytes*, including B cells, T cells and natural killer cells (Figure 2).

Phagocytes engulf and destroy microbes or other particles. They are part of the innate immune system and include monocytes/macrophages, neutrophils and dendritic cells. Monocytes circulate in the blood as precursors of macrophages and differentiate into macrophages after leaving the circulation to migrate into tissues throughout the body. Macrophages and neutrophils express receptors such as the *Toll-like receptors* that help them to recognise constituents common to many pathogens (see Box 1).

BOX 1

Receptors that recognise “foreign” molecular structures

The prime task of the innate immune system is not to recognise every possible antigen, but to identify a few, highly conserved molecular structures that are characteristic for all microorganisms. These structures are recognised by specific receptors called *pattern-recognition receptors* (PRR). The structure of these receptors is invariant, in contrast to the extremely diverse structures of the B and T cell receptors. PRR recognise typical patterns found exclusively in microbial pathogens. These patterns, called *pathogen-associated molecular patterns* (PAMP), must comply with three important requirements:

- Expressed only by pathogens and not by their host
- Shared by entire classes of pathogens
- Essential for the survival or pathogenicity of the microorganisms

An important class of PRR is the family of Toll-like receptors. They recognise PAMP such as lipopolysaccharides found on all Gram-negative bacteria, double-stranded RNA of viruses, and many other structures. Once the PRR identifies a specific PAMP, the appropriate effector cells are triggered to perform their effector functions immediately. PRR such as the Toll-like receptors are an important link between immunological signals and nutrient-associated regulation of gene expression leading to enhanced antimicrobial defence (for example, vitamin D).

Pathogen-specific molecules binding to these receptors trigger the immune cells to engulf and kill the pathogen and to induce the secretion of chemical mediators such as *cytokines* and *chemokines* by these phagocytes (see Box 2). Some nutrients, e.g. vitamin D, mediate the Toll-like receptor activation by inducing the synthesis of antibacterial peptides within macrophages.

Dendritic cells are antigen-sampling cells of the peripheral tissue and are equipped for antigen capture, processing and presentation to T cells, which then differentiate into active,

immunogenic T cells. Due to their functional properties, dendritic cells are located along the body surfaces that line the border of the body with the environment, such as the skin and the mucosa of the respiratory and the gastrointestinal tracts.

BOX 2

Cytokines

Cytokines are proteins made by various types of immune and non-immune cells and affect the behaviour of other cells. Each cytokine has multiple effects on different cell types. Cytokines produced by leukocytes and having effects mainly on other white blood cells are termed interleukins (IL). Cytokines act selectively via specific cytokine receptors on the cells they affect. Receptor binding induces activities in the cell, such as growth, differentiation or death.

Cytokines produced at the onset of the immune response act on other immune cells and thereby determine the type of immune response (inflammation, antibody response) that develops. The different subgroups of T lymphocytes in particular contribute via their cytokine secretion profile to immunoregulation:

- T helper 1 (T_h1): IL-2 and interferon- γ (stimulation of inflammatory processes)
- T helper 2 (T_h2): IL-4, IL-5, IL-9 and IL-13 (stimulation of antibody responses)
- T helper 17 (T_h17): IL-17 (mediator in inflammatory and autoimmune diseases)
- T regulatory (T_{reg}): IL-10, transforming growth factor- β (inhibition of inflammatory processes)

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.

Chemokines are members of the cytokine family. They act as chemoattractant proteins and stimulate the migration and activation of cells, especially phagocytes and lymphocytes. Chemokines play a central role in inflammatory processes.

BOX 3

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 process them for elimination.

Collectively, the B cells can produce 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, which produce the specific antibody, are primed and activated. If the same antigen is encountered again, the B cells (memory cells) can respond by producing large quantities of the appropriate antibody very quickly.

T cells are another subset of lymphocytes. Characterised by their capacity to produce activating or suppressing cytokines, they are divided into helper T cells (e.g. T_h0 , T_h1 , T_h2 , T_h17) and regulatory T cells (see Box 4). A third group of T cells, the cytotoxic T cells, is well equipped to kill virally infected cells.

Like B cells, T cells act in response to specific antigens. They can recognise antigens through receptors on their surface, the T cell receptors. Part of the T cell receptor is an antigen-specific molecule that acts like an antibody, binding to the specific antigen. When the antigen is bound, it activates the T cell and the cascade of immune reactions occurs. For instance, the activation of T_h2 cells controls the proliferation and differentiation of B cells that have bound the same antigen.

B cells are a class of lymphocyte and originate from the bone marrow. Upon stimulation by antigens, B cells develop into cells that 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 (see Box 3).

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 cells to develop into functionally different T cell types (see Box 4).

Natural killer cells are able to recognise and kill target cells rapidly. Target cells include virally infected cells and tumour cells. Target cell recognition and the ensuing killing function of natural killer cells is not regulated by antigen-dependent mechanisms but by inhibitory and activating receptors on these cells. Receptors are triggered by contact with potential target cells.

1.3 The immune system of the gut

The gut immune system or the *gut-associated lymphoid tissue* (GALT) is an important part of the total immunological capacity of an individual. The GALT prevents the passage of bacteria and food antigens from the gastrointestinal lumen through the epithelium of the intestinal mucosa. It does allow, however, the translocation of minute amounts of viable and dead bacteria as important immunological information to the systemic immune system. Immune cells of the gut are organised in different compartments, such as lymph nodes, lymph follicles and Peyer's patches (Figure 3).

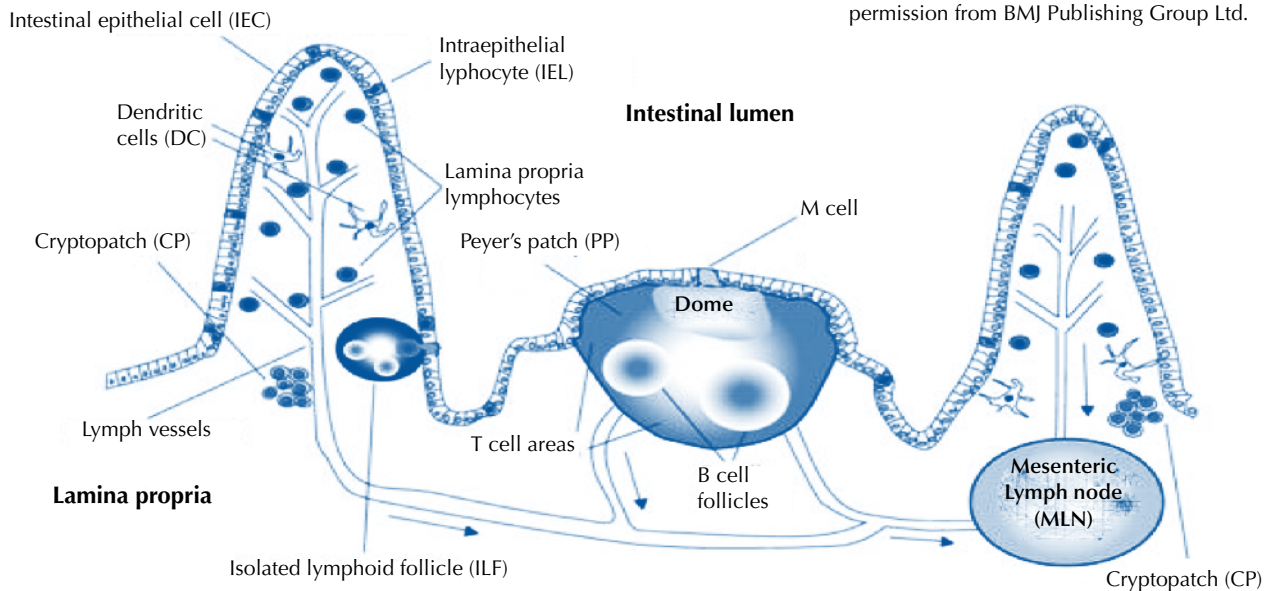
Single immune cells are distributed within the intestinal mucosa and between epithelial cells. To cope with various challenges, the GALT has developed at least two strategies. First, it provides for immune exclusion by secreting antibodies to inhibit the colonization of disease-causing bacteria and to prevent mucosal infections. Second, the GALT possesses mechanisms to avoid overreaction to innocuous substances from occurring on mucosal surfaces. The latter phenomenon is called *oral tolerance* and largely explains 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” (see ILSI Europe Concise Monograph “*Food Allergy*”).

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

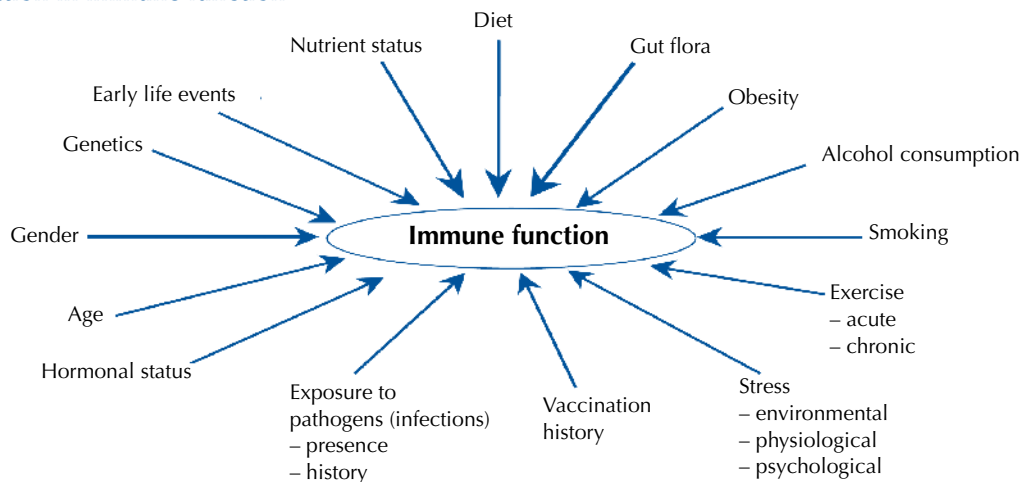
1.4 The development of the immune system

The immune system is not constant but is subject to several changes during a person’s lifetime. Changes are induced by a number of environmental factors (Figure 4), with

FIGURE 3
Gut-associated lymphoid tissue



Reproduced from ‘Modulating the intestinal immune system: the role of lymphotoxin and GALT organs’ Spahn, T.W., Kucharzik, T. 53:456-465, 2004 with permission from BMJ Publishing Group Ltd.

FIGURE 4**Sources of variation in immune function**

the biggest changes occurring in infancy and childhood. As the embryo is generally not confronted with antigens while in the womb, certain aspects of the innate and acquired immune system are not fully matured at birth. The immunoglobulin levels of newborns are low (except for maternal immunoglobulin G, which is transferred to the unborn child via the placenta) and their T cells produce a range of cytokines dominated by T helper 2 (T_h2) lymphocyte-specific cytokines, which enhance antibody production by B cells. During the first year of life, the cytokine pattern changes to a more balanced T helper 1 (T_h1)/ T_h2 cytokine ratio that supports cellular immune responses and the elimination of intracellular pathogens. An imbalance between T_h1 and T_h2 cytokines would increase the risk of autoimmune or allergic responses.

Furthermore, the barrier function of the gut mucosa and oral tolerance against food antigens develop over time. Within the first seven years of life, the organs of

the lymphoid system grow faster than the entire body and then their relative size diminishes until they reach a relative size similar to that in adults, approximately at the age of 12 years.

The immune system in the elderly is often characterised by dysregulation of immune responses. Cellular immune responses may be decreased in the elderly, resulting in a higher sensitivity to infections. By contrast, antibody production is comparable between the healthy elderly and younger adults. However, impairment of immunocompetence in the elderly may not be due to a primary decline of immune function, but rather due to latent nutritional deficits. Thus, the dysregulation of immune responses in the elderly could be due to cumulative immunological processes throughout life, and any changes in nutrition, physical activity and general health (Figure 4) may further contribute to this.

BOX 4

Why does an immune response have to be regulated?

An immune response cannot be too strong, one might suppose. Is it not the point to kill and eliminate harmful pathogens as fast and efficiently as possible?

Precisely not.

What happens when a self-reactive helper T cell, which has escaped deletion in the thymus, enters the circulation and attacks healthy body cells? Without adequate immune suppression it would proliferate and start an auto-immune response targeted against the body's own cells.

The same mechanism of immune suppression, however, could in another situation suppress the required immune response against tumour cells, which also show properties in common with the body's own cells.

Or, what happens when dietary protein fractions pass through the intestinal wall and come into contact with intestinal leukocytes? Without regulatory mechanisms and the induction of oral tolerance this would induce food allergy, an immune response against harmless food constituents.

The immune cells that are most important in controlling the intensity and duration of an appropriate immune response are the regulatory T cells. They can be identified by distinct surface markers and by a specific pattern of cytokine secretion. Immunoregulation is a continuous balance between stimulation and suppression of immune effector cells. Other cells may also be implicated in immune regulation, like B cells that produce specific IgA antibodies to food antigens in the gut of mammals.

2. DIETARY FACTORS WHICH ALTER THE IMMUNE RESPONSE

The RDA for a nutrient indicates the average daily dietary intake level considered sufficient to meet the requirements of nearly all (97–98%) healthy individuals. However, for most nutrients their role in supporting an optimal immune response has not been considered when defining the RDA. Therefore, the RDA for a specific nutrient may not be at a level that allows the best immune response. In consequence, for many nutrients it is still an open question whether nutrient intakes at higher levels than the current RDA could improve immune responses.

2.1 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 function¹. Such malnutrition, which is primarily a problem in developing countries, substantially increases the risk of childhood mortality from infection. Protein-energy malnutrition is often accompanied by deficiencies of micronutrients such as vitamin A, vitamin E, vitamin B₆, vitamin C, folate, zinc, iron, copper and selenium. Most host defence mechanisms are impaired in malnutrition, even if the nutritional deficiency is only moderate in severity. The rapidly proliferating T cells responding to pathogens are especially affected, resulting in a decrease in their numbers. Severe and chronic malnutrition leads to atrophy of the thymus and other lymphoid organs.

Both obesity and its treatment seem to have clear but not yet precisely defined effects on the immune response. Obese people are more likely than people of normal weight to develop different types of infections, and obesity is associated with an increased risk of various types of cancer. Further, molecules produced specifically in adipose tissue (adipokines) generate a pro-inflammatory environment in different body tissues, which increases the risk of chronic inflammatory diseases. Although some observational evidence clearly suggests an adverse effect of obesity on the immune system, experimental data from human studies are less clear. For instance, a few studies have reported impaired immunological functions including lymphocyte proliferation, delayed-type hypersensitivity, and/or impact on the maturation and bactericidal capacity of macrophages. However, other studies showed no differences between obese and normal weight subjects. Therefore, whether the relation between obesity and infection is either causal or simply an association generated by confounding factors (such as diabetes mellitus) is still an open question.

Certain weight reduction strategies lead to alterations in immune responsiveness. Currently, there is no clear picture on the consequences of weight reduction in obese subjects because both suppressive and stimulatory effects on various immune responses have been reported. Resolution of this issue is hindered by the limited number of studies and flawed study designs (e.g. lack of control subjects, heterogeneity between the different weight loss approaches). Because obesity and weight loss programmes affect an increasing number of subjects in wealthy and developing societies, any impact of obesity and intentional weight loss on the immune response is expected to become more marked in the future.

2.2 The amount and quality of dietary fat can influence the immune function

Most research into how fat in the diet can influence the functioning of the immune system has focused on specific types of fatty acids, but total fat intake may also be important. In Western countries, fat usually contributes to 35-40% of the total energy intake. Fatty acids have several functions in immune cells (see Table 1) and changes in total fat intake can influence the immune response in humans. For instance, reducing the fat intake from 36% to 25% of total energy enhances lymphocyte responsiveness as well as the capacity of natural killer cells to destroy tumour cells. Fat is also one of the major membrane constituents.

Fatty acids can be divided into distinct families that differ in structure and dietary origin: saturated and unsaturated fatty acids. Saturated fatty acids (SFA) contain no double carbon-carbon bonds in their structure. Fatty acids that contain double bonds are termed unsaturated: monounsaturated if there is one double carbon-carbon bond and polyunsaturated if there are two or more double bonds. Polyunsaturated fatty acids (PUFA) can be further classified by the position of the double bonds into two families: n-3 (omega-3) and n-6 (omega-6).

The parent n-3 and n-6 PUFA, α -linolenic acid and linoleic acid, respectively, cannot be synthesised by man and they must be supplied by the diet. These are, therefore, regarded as essential fatty acids. The parent n-6 PUFA, linoleic acid, is found primarily in plant oils such as maize or sunflower oil, while α -linolenic acid, the parent n-3 PUFA, is found in linseed (flax), canola or soy oils. To influence the immune system, these parents have to be converted into their long chain derivatives (LCPUFA): arachidonic acid (AA) of the n-6 family, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) of the n-3 family.

Table 1

Role of fatty acids in immune cells

Fatty acids:

- Provide energy for immune cells
- Are components of cell membrane phospholipids and affect membrane structure and function
- Regulate gene expression, for example via signalling processes
- Are precursors for the eicosanoids and other lipid mediators

Dietary linoleic acid is readily converted into AA but the conversion of α -linolenic acid into EPA and DHA is limited. There are, however, good dietary sources of preformed EPA and DHA, such as oily fish.

Once incorporated into the membranes of immune cells, LCPUFA can be converted into tissue hormones called eicosanoids, a family of biological regulators that includes the prostaglandins and leukotrienes (see Box 5). Depending on the type of PUFA in the diet, especially the amount of n-3 LCPUFA, immune cells produce different quantities and kinds of eicosanoids with very different effects on the immune response.

Fatty acids are important in the functioning of the immune system because they also affect the fluidity of membranes. The latter decreases with the chain length and increases with the degree of unsaturation 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. Moreover, LCPUFA seem to be natural ligands of a certain class of anti-inflammatory transcription factors called peroxisome proliferator-activated receptors.

BOX 5

Eicosanoids

Eicosanoids belong to a family of tissue hormones derived from cell membrane-associated long-chain polyunsaturated fatty acids (LCPUFA) and are comprised of, for example, prostaglandins and leukotrienes. The type of polyunsaturated fatty acids (PUFA) in cell membranes is influenced by dietary fat. A wide variety of biological activities have been ascribed to eicosanoids, including modulation of the intensity and duration of inflammatory and immune responses.

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

Prostaglandins derived from n-6 LCPUFA (for example, prostaglandin E2) appear to have potent regulatory functions for various types of immune cells. At low concentrations, prostaglandin E2 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 E2.

In general, diets rich in n-3 PUFA tend to inhibit excessive immune responses, which are associated with chronic inflammatory diseases such as rheumatoid arthritis. However, immune responses required to protect against pathogens seem not to be adversely affected. Diets rich in n-6 PUFA have a diverse effect on immune responses, including pro- and anti-inflammatory responses.

BOX 6

Assessment of the immune status

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 2% of total immune cells and therefore might not give a fully representative picture. Furthermore, immune cells associated with the gut are normally not accessible in humans. Currently, no single marker allows conclusions to be drawn about the functioning of the whole immune system. Selected markers may be indicative for specific aspects of immune function (e.g. response to vaccination for resistance to infections), but global assessment of diet-induced changes of the functioning of the immune system requires a thorough methodological approach targeting a spectrum of markers. Ideally, immune measures that are used as biomarkers should be biologically relevant and sensitive, as well as feasible under normal study conditions. Based on these criteria a recent expert group classified immunological markers into three categories:

High suitability: Markers from this category are considered highly suitable because they measure an integrated *in vivo* response to an immune challenge. Markers belonging to this category are the vaccine-specific serum antibody production, the delayed-type hypersensitivity response, the concentration of secretory immunoglobulin A (sIgA) in relevant fluids, and the response to attenuated pathogens.

Medium suitability: A number of *ex vivo* markers are available if the application of “high” category markers is not possible. These markers provide mechanistic understanding of the effect of an intervention. Markers include natural killer cell activity and phagocyte oxidative burst. The combination of T cell proliferation, expression of T cell activation markers, and key cytokine production can be applied to assess T lymphocyte function. The measurement of antigen-specific antibody production serves to assess B cell function.

Low suitability: Some *ex vivo* markers are considered to be of low suitability, largely because of the lack of a clear association between a change in marker and a change in susceptibility to infection.

Combining markers with high and medium suitability is currently the best approach for measuring immunomodulation in human nutrition intervention studies.

2.3 Deficiencies in vitamins and trace elements can impair the immune response

Deficiencies of several micronutrients have been shown to reduce the immune response, as summarised in Table 2. Some of the methods used to measure responses in the immune system are discussed in Box 6.

Vitamin A

Dietary vitamin A occurs mainly in liver, egg yolk and milk. Some carotenoids (see Section 2.4) found in vegetables and fruit can be converted in the body into vitamin A. Vitamin A deficiency is rare in Western societies, but it is a major public health problem in many parts of the developing world. Physicians and scientists have recognised for hundreds of years that the “dry eye” disorder caused by vitamin A deficiency is linked to high morbidity and mortality from infectious diseases.

More recently, clinical trials in developing countries have shown that supplementation with this vitamin reduces child mortality by 30% and is one of the most cost-effective interventions to improve public health. These clinical trials have further indicated that vitamin A supplementation reduces the severity of diarrhoeal diseases in childhood. However, clinical trials of vitamin A supplementation in children with respiratory virus infection showed equivocal results and should be investigated further. Furthermore, it is important to consider the toxicity of vitamin A when given as a supplement. It is much safer to increase the consumption of food rich in this vitamin.

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

Table 2**Effects of deficiency or insufficiency in micronutrients or phytochemicals on the immune response**

Micronutrient	Effects of deficiency or insufficiency
Vitamin A	Loss of mucosal epithelial barrier function Impaired neutrophil and macrophage function Decreased natural killer cell number and lytic activity Diminished antibody response
Vitamin D	Decreased production of antibacterial peptides
Vitamin E	Impaired B- and T-cell-mediated immunity Increased oxidative damage in immune cell membranes
Vitamin B ₆	Decreased lymphocyte responsiveness Impaired antibody production
Vitamin C	Decreased resistance to infection Impaired proliferation of T cells
Zinc	Impaired T cell development Impaired lymphocyte responsiveness Decreased resistance to infection
Selenium	Increased oxidative damage in immune cell membranes Decreased cytokine production Decreased resistance to viruses Decreased antibody production
Carotenoids	Decreased natural killer cell activity Decreased production of cytokines Impaired function of phagocytes
Flavonoids	Immunomodulating effects

Other consequences of vitamin A deficiency are the compromised integrity of the lining of the pulmonary, gastrointestinal and urinary tracts. Thus, pathogenic bacteria can more easily penetrate the epithelial barrier and cause more severe infection and exacerbated inflammation. For instance, vitamin A supplementation can limit diarrhoea by restoring intestinal integrity. Recently, retinoic acid, a metabolite of vitamin A, was

shown to be produced uniquely by specific intestinal immune cells, but not by the same immune cell type from other lymphoid organs. Retinoic acid directs the migration of antigen-specific T cells from the periphery back to the gut, where they first encountered their antigen. Therefore, all these data emphasise the importance of an adequate vitamin A intake for the regulation of immune processes in the gut.

Vitamin D

Vitamin D is a hormone, and its precursor can be synthesised in the skin by sunlight exposure. The precursor is first metabolised in the liver and then in the kidney to its biologically active form of vitamin D. However, latitude, season, skin pigmentation, aging and sunscreen use all may decrease cutaneous vitamin D production. Dietary sources of vitamin D precursor are oily fish, cod-liver oil and egg yolk.

It is estimated that one billion people worldwide have vitamin D deficiency or insufficiency. In recent decades, accumulated observations have indicated that vitamin D-deficient people suffer more frequent and more serious respiratory infections than people with adequate plasma vitamin D levels. The frequent incidence of respiratory infections in the winter season could also originate from a latent vitamin D deficiency, since solar radiation at latitudes above 45° is considerably lower in winter than in summer.

Vitamin D is an important immune system regulator. Receptors for this vitamin occur in most cells of the body, including immune cells. Liver cells, kidney cells and macrophages have the enzymatic capacity to make the biologically active form of vitamin D. Interestingly, Toll-like receptor stimulation in macrophages enhances both the conversion of the vitamin D precursor into the active form and the expression of the vitamin D receptor. Vitamin D in macrophages regulates the production of an endogenous antibiotic called cathelicidin, and modulates the pattern of cytokine secretion. Both cathelicidin and the cytokines enhance the defence against pathogens. Obviously, vitamin D is a key link between Toll-like receptor activation and antibacterial responses in innate immunity. Results from epidemiological as well as clinical studies further suggest a reduced risk for certain types of autoimmune diseases with higher serum vitamin D status. Having discussed whether the RDA for vitamin D

was adequate for the general population, the Institute of Medicine increased it to 600 IU by the end of 2010.

Vitamin E

Vitamin E occurs in a variety of plant foods. Vegetable oils such as wheat germ, maize and soybean oils are especially rich in vitamin E. Experimental 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 much higher than recommended levels has been shown to enhance certain aspects of immune function. Taking into account only controlled trials with human subjects, vitamin E at high concentrations seems to enhance the cellular immune response and to decrease prostaglandin E₂ production in the elderly. As high concentrations of prostaglandin E₂ inhibit T cell function and proliferation, this could be, together with the prevention of oxidative damage in immune cell membranes, a mechanistic explanation for an enhanced immune function with vitamin E supplementation in the elderly. However, effects of vitamin E supplementation have been shown to be variable and dependent on the intake level of vitamin E, dose, age, smoking, housing conditions, and others. This may be the reason why a protective effect of vitamin E against respiratory infections in the elderly could not be demonstrated in randomised controlled trials.

Vitamin B₆

Vitamin B₆ is widely distributed in foods, with rich sources including fowl, fish, liver, cereals and pulses. It has been known since the 1940s that deficiencies in vitamin B₆ impair immune function. This effect is not surprising because vitamin B₆ is essential for a wide variety of reactions necessary for the synthesis and metabolism of amino acids (the building blocks of protein), and there is a need for increased protein synthesis during the immune response.

Human studies demonstrate that deficiency of vitamin B₆ impairs both antibody production and T cell activity. Lymphocyte growth and maturation are also altered, and natural killer cell activity is decreased. Although supplementation of vitamin B₆ corrects both the deficiency and these impairments in immunity, doses above the RDA do not produce additional benefits in healthy adults.

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.

The mechanisms whereby vitamin C has effects on the immune system are not well understood. Due to its antioxidant activity, it could protect the immune cells from oxidative damage. In addition, a few organs 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. Vitamin C is also highly concentrated in immune cells and its concentration is rapidly reduced during infection. It modulates the functions of phagocytes, proliferation of T lymphocytes, production of cytokines and gene expression of monocyte adhesion molecules.

Animal studies indicate that immune responses to infection are abnormal in vitamin C deficiency. In particular, 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 in vitamin C deficiency. Therefore, there is much interest in the possibility that high doses of vitamin C (1 g/day or more) may be of value in preventing some types of infections, especially respiratory infections. This

interest is mainly due to the propagation of high vitamin C intakes by Linus Pauling. Numerous controlled trials have been conducted in human volunteers to evaluate the effect of vitamin C on the common cold. They show that people who regularly take 200 mg/day of vitamin C or more have slightly shorter colds (about 10%) than those who do not. Vitamin C supplementation has, however, no effect on the incidence of colds in the normal population. Only among people that are regularly stressed by physical activity (like marathon runners) or are exposed to a sub-arctic environment, can vitamin C supplementation reduce the incidence of the common cold.

Zinc

Major dietary sources of zinc are meat, dairy products, seafood and cereals. Cells of the immune system contain a large number of enzymes that need zinc to function, so it is not surprising that zinc deficiency has profound effects on immune function.

Zinc deficiency is widespread in many parts of the developing world. In these populations, supplementation of zinc decreases the morbidity and mortality of children by reducing their risk of contracting diarrhoea and acute respiratory infections. In humans, experimentally induced mild zinc deficiency mainly affected T cell functions. It resulted in an imbalance between T cell subpopulations, decreased production of cytokines (interleukin-2, interferon- γ) and attenuated natural killer cell activity. Zinc deficiency in the elderly is also associated with impaired immune responses, which can be restored by zinc supplementation. By contrast, a systematic analysis of published clinical trials concluded that currently there is no convincing evidence that zinc may be effective for treatment of the common cold.

There are several ways in which zinc deficiency and supplementation affect the immune system. First, zinc is needed for the biological activity of thymulin, a thymus-specific hormone that promotes T cell functions such as

cytotoxicity or cytokine production. Second, zinc affects signal transduction pathways that control gene expression of various immunoregulatory cytokines. Third, zinc is a cofactor of several enzymes involved in antioxidant responses that contribute to reduced oxidative damage in immune cells.

It is known that an intake of zinc that is twice the recommended daily intake has no adverse effect on the immune system of healthy adults. However, when given in quantities higher than twice the RDA, zinc may impair immunity.

Selenium

Dietary selenium occurs in protein-rich foods such as meat, fish, nuts and seeds. Selenium is essential for an optimal immune response and influences both the innate and acquired immune system. It has a key role in the redox balance, including the protection against DNA damage. Selenium is also an important cofactor of a group of enzymes that contribute to the protection of 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. However, evaluation of the direct effects of selenium is difficult because of interactions between selenium and another antioxidant, vitamin E.

In a human study, healthy men with marginal selenium intakes received supplemental selenium for several weeks. Selenium supplementation (50 and 100 µg/day) improved the cellular immune response, whereas the humoral immune responses were not altered. Further, it resulted in a more rapid clearance of a live attenuated polio vaccine. The presented data suggested that a higher selenium intake would contribute to an enhanced immune function.

Moreover, the morbidity and mortality from several viral infections could be reduced by selenium supplementation. Examples are HIV, polio, and Keshan disease (affecting the heart muscle). The latter is endemic in some parts of China and appears to be due to a combination of a Coxsackie virus infection and a dietary deficiency of selenium and vitamin E. Keshan disease has been nearly eradicated in China by selenium supplementation, even though the virus is presumably still present in the environment.

Other minerals

In addition to zinc and selenium other minerals and trace elements are important for the normal functioning of the immune system. These include iron, copper, magnesium and manganese. Iron is an example of a nutrient, which is not only required for an adequate immune response but also for an optimal growth of pathogens. As long as iron deficiency does not impair immune function, iron supplementation may only benefit pathogenic bacteria. Therefore, supplementation of this trace element has to be considered on an individual basis.

2.4 Phytochemicals can alter the immune response

Progress of nutrition research over the last decade clearly suggests that, besides essential nutrients, non-nutritive constituents such as phytochemicals have a strong impact on human health. These phytochemicals are represented by a number of chemically diverse substances. So far, mainly carotenoids and flavonoids have been investigated for their immunomodulatory potential.

Carotenoids

Carotenoids are yellow, orange and red compounds found in fruits and vegetables. Examples are β -carotene, which is widely distributed in plants, and lycopene, a carotenoid found in tomatoes. Like vitamins C and E, carotenoids are antioxidants, and, additionally, β -carotene is a precursor of vitamin A.

Although animal studies have clearly shown an enhancing effect of β -carotene on the immune system, results from human studies are inconsistent. Epidemiological studies suggest that diets rich in carotenoids reduce the risk of respiratory infections. A high dietary intake of carotenoids is further inversely associated with inflammatory markers suggesting that carotenoids possess an anti-inflammatory activity. Some studies have shown that β -carotene supplementation may be beneficial for individuals with a compromised immune system. In particular, a recovery of declined natural killer cell activity in the elderly to normal levels was observed following β -carotene supplementation. Furthermore, in volunteers with a low carotenoid intake, β -carotene or carotenoid-rich food were able to enhance various immune responses. By contrast, in healthy adults with adequate carotenoid intake and normal immune responses supplementation with carotenoid-rich foods did not further modulate immune responses.

Overall, although the underlying mechanisms are currently not known, carotenoids may exert immunomodulatory effects in humans. Also, adequate intake levels as well as differences in the immunomodulatory potential between the various carotenoids are still not known.

Flavonoids

Flavonoids occur in all plant foods and include several thousands of compounds with well-defined chemical structures. They are responsible for the red and blue colours in plant foods as well as for some typical flavours of plants.

So far, experimental and clinical data are rare. Interestingly, the majority of *in vitro* studies suggest that flavonoids have immunosuppressive effects. First clinical data from a human intervention trial suggested that a subgroup of flavonoids, the anthocyanins, possesses anti-inflammatory activities at dietary relevant doses (equivalent to the intake of 100 g bilberries). Molecular studies have indicated that flavonoids interfere with signal transduction in immune cells. However, it is important to know that, in these tests, flavonoids were applied at concentrations that are unlikely to be achieved in the human body after a flavonoid-rich meal. Nevertheless, these phytochemicals have a potential to modulate immune responses and should be studied more closely in humans.

2.5 Probiotics, prebiotics and dietary fibre

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. They are the primary stimulus for the intestinal immune system and are necessary for normal immune development. When the balance of organisms in the gut is disrupted or altered by disease or by the use of antibiotics, local immune defences are impaired.

By definition, a *probiotic* is a live microorganism that, when administered in adequate amounts, confers a health benefit on the host. Other approaches complementary to probiotics, which are being investigated, are prebiotics and synbiotics. A *prebiotic* is a non-digestible selectively fermentable food constituent that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the large intestine that confer benefits upon host well-being and health. A *synbiotic* is a mixture of a probiotic combined with a prebiotic whose aim is the establishment and increased survival of health-promoting bacteria.

Probiotics

Probiotic organisms are found in fermented foods, including traditionally cultured dairy products such as yogurt and new types of fermented milks specifically designed to contain bacteria of potential benefit to health. The organisms included in commercial probiotics are primarily lactic acid bacteria of the genera *Lactobacillus* and *Bifidobacteria*. Because these organisms only temporarily colonise the intestinal tract, regular consumption may be necessary for optimal benefits. Both innate and acquired immune responses can be modulated by probiotics in a strain- and dose-dependent way.

There are several ways in which probiotics affect the host defence system. One way is by contributing to the “barrier effect” of the intestinal bacteria, which creates an environment hostile to some pathogenic bacteria. Another way relates to the metabolic products produced by lactic acid bacteria, such as bacteriocins and lactic acid itself, which inhibit the growth of pathogenic organisms. Some probiotic strains also adhere to the epithelial wall of the intestine, thus preventing pathogenic bacteria from adhering to the same receptors, or they compete with pathogens for nutrients that are in limited supply.

An additional way by which probiotics may promote health is by altering the immune system at the local (gut) as well as at the systemic level. Direct interaction between probiotics and immune cells seems to be mediated via Toll-like receptor signalling (Box 1). Alteration of immune function after the ingestion of specific probiotics has frequently been reported in various experimental systems. As an example, probiotics can counteract the increase in gut permeability that would otherwise occur after exposure to foreign antigens like viruses. In humans, strain-specific immunomodulatory effects have also been observed. Within each strain, different subclasses are present with

specific immunomodulatory activities. Immunological markers responsive to probiotics include phagocytosis and antibody production. However, long-term effects of probiotic supplementation have not been studied.

Probiotics may be of value in the prevention and treatment of various clinical conditions that involve abnormal populations of gut microbes and malfunction of immune responses. Examples of conditions in which probiotics may be beneficial are acute diarrhoea caused by rotavirus, inflammatory bowel diseases or allergic diseases, for which a limited number of probiotics have shown a beneficial effect in specific subpopulations of allergic subjects.

In summary, the immunomodulatory potential of specific probiotics is now clearly demonstrated. However, it is still 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 little is known about the underlying immunological mechanisms. It is important to realise that, just as different vitamins do not exert the same effects, different probiotic strains have different effects, which is the reason why general conclusions about probiotics as a group are not meaningful. The nature of the interactions between individual probiotics and the immune cells and tissues in the gut continues to be the subject of intense debate.

Prebiotics and dietary fibre

Prebiotics are present in the normal diet at intakes of 2–10 g/day. They include inulin, fructooligosaccharides, galactooligosaccharides and lactulose. Prebiotics alter the composition of the intestinal microbiota to one in which the proportions of bifidobacteriae and lactobacilli are increased. The term *dietary fibre* describes plant food constituents such as cellulose and resistant starch, and includes some prebiotics. Prebiotics and dietary fibres

have in common that they are not hydrolyzed in the small intestine and reach the colon. There, they serve as energy and carbon sources for the colonic microbiota and thus increase the bacterial mass in the intestine. Short-chain fatty acids, including butyrate, are by-products of bacterial fermentation in the gut. These short-chain fatty acids have a beneficial effect on intestinal cells. High concentrations improve symptoms of inflammatory bowel disease, e.g. by inhibiting the production of pro-inflammatory cytokines.

Evidence from animal and human studies suggests that prebiotics specifically increase the numbers of beneficial microorganisms in the colon. Along with these changes, prebiotics improve immune responses against pathogens as well as reduce inflammatory responses in animal models of inflammatory bowel disease. However, prebiotics primarily affect the gut-associated immune system, which is difficult to study in humans.

It was shown that a mixture of prebiotics significantly reduced the incidence of contact dermatitis in atopic infants, suggesting that these prebiotics alter postnatal immune development. The same prebiotic mixture also increased fecal antibody concentrations in formula-fed infants.

In summary, the composition and the activity of the intestinal microbiota can be changed by the intake of probiotics, prebiotics and dietary fibre. Primarily an increase in the numbers of lactobacilli and bifidobacteriae can be expected, which improves gut immunity and may affect the entire immune system. Besides these indirect effects, probiotics, prebiotics and their degradation products may have direct effects on the immune system.

3. 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 various inflammatory conditions, viral and bacterial infections, and food allergies.

3.1 Inflammatory conditions

Many diseases are originally caused or accompanied by chronic inflammation. The most common of these diseases are listed in Table 3. There is evidence that diet may affect the pathogenesis of these diseases. The most promising candidates are the n-3 LCPUFA, good sources of which are fish oils and oily fish such as mackerel, herring, salmon or fresh tuna. LCPUFA in the cell membrane can serve as a source of tissue hormones such as prostaglandins and leukotrienes. When these are derived from n-3 LCPUFA, they exert anti-inflammatory effects. They also change the pattern of signalling molecules like the cytokines, which are involved in the pathogenesis of chronic inflammatory diseases.

Dietary patterns including a high intake of vegetables and fruit are also inversely associated with the risk of chronic inflammation. There is further evidence that vitamin C, vitamin E, selenium, carotenoids and flavonoids have an anti-inflammatory potential. Low serum concentrations of these nutrients are correlated with an increased risk of contracting heart disease, asthma or rheumatoid arthritis.

TABLE 3**Examples of diseases with an inflammatory background**

Diseases	Characteristics
Obesity/metabolic syndrome	Production of pro-inflammatory cytokines, such as TNF- α and IL-6, by adipose tissue
Atherosclerosis	Inflammatory disease of the arteries resulting in the arterial deposition of plaques
Asthma	Chronic inflammation of the lung mucosa accompanied by a contraction of the smooth muscle layer in the bronchi
Contact dermatitis and psoriasis	Inflammatory skin diseases characterised by T cell differentiation towards T _H 2 phenotype (contact dermatitis) or failure of regulatory processes during inflammation (psoriasis)
Rheumatoid arthritis	Autoimmune disease characterised by a chronic inflammation of the synovial membrane in the joints
Crohn's disease and ulcerative colitis	Inflammatory bowel diseases characterised by acute and chronic inflammation of the gut

Heart disease

Numerous dietary factors have been correlated 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 deposition of arterial plaques. The immune system is involved in the pathogenesis of atherosclerosis through interaction between its white blood cells (monocytes and macrophages) and cells of the arterial wall. Dietary factors influence the immunological processes underlying the pathogenesis of atherosclerosis. Epidemiological and clinical studies have indicated that the risk of heart disease can be reduced by increased intakes of PUFA and dietary antioxidants (vitamin C, vitamin E). n-3 LCPUFA may inhibit the development of atherosclerosis by blocking the production of cytokines,

which promote inflammation (see Box 7), and of other substances that play roles in the complex process of local inflammation and arterial injury that leads to the development of plaques. Although supplemental antioxidants, such as vitamin E, can enhance immune response in subgroups of the elderly, randomised controlled trials show that vitamin E supplements do not reduce the risk of heart disease.

Evidence from population studies revealed that a high intake of vegetables and fruit is inversely associated with the risk for heart disease. Along with such a dietary pattern, reduced markers of inflammation have been observed in these studies.

BOX 7

The inflammatory response

Inflammation is the body's response to entry by infectious 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. Acute inflammation is an appropriate and effective means of fighting an infection. Chronic inflammation, however, is characterised by a loss of self-tolerance and regulation and can cause severe damage to tissues.

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 that 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 that contribute to tissue injury.

Symptoms: Celsus in the first century said that 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.

Inflammatory bowel diseases

Crohn's disease and ulcerative colitis are the most common forms of inflammatory bowel diseases (IBD). Crohn's disease is characterised by patches of inflamed tissue reaching deep into the wall of the entire gut, whereas inflammation in ulcerative colitis is primarily located in the mucosa of the colon. The cause of these diseases is not known. Heredity and the gut microbiota seem to be

involved in the process of occasional acute inflammations (e.g. salmonella or rotavirus infections) which, if not under appropriate control, can become chronic.

In the inflamed areas of the gut mucosa, the vitamin C concentration is decreased and the oxidative damage of lipids is increased. In a study with Crohn's disease patients, supplementation with a combination of vitamin C, vitamin E, fish oil and β -carotene reduced the production of inflammatory proteins by blood monocytes. The n-3 LCPUFA from fish oil may have been the most effective component in the applied combination. Several studies have confirmed that patients with IBD may be able to reduce the use of corticosteroids if they are supplemented with n-3 LCPUFA.

Because the gut microbiota is involved in the etiology of IBD, rebalancing the gut flora by increasing the numbers of lactobacilli and bifidobacteriae may be beneficial. In fact, the use of prebiotics and probiotics currently seems to be the most promising dietary approach to improvement of IBD symptoms. For example, in ulcerative colitis patients treated with a synbiotic, markers of gut inflammation were reduced and the inflamed tissue regenerated. In another study, ulcerative colitis patients were brought into remission more quickly when they took a prebiotic. However, more research is needed to confirm these results and to define the most effective strains and prebiotics, and combinations thereof (see Box 8).

Asthma

A few studies have suggested that the intake of specific food groups modulates asthma risk. The dietary intake of fish, especially of oily fish containing n-3 LCPUFA, may be protective against asthma. It has been hypothesised, although not proven, that high intakes of n-6 and, especially, low intakes of n-3 PUFA might have contributed to the increased prevalence of asthma. It is believed that the production of mediators involved in allergic responses is affected by the balance between the two types of PUFA.

BOX 8**Functional foods for “immune modulation”**

Within the last decade, the food industry developed the concept of functional foods (see ILSI Concise Monograph “*Concepts of Functional Foods*”). Functional foods beneficially affect one or more target functions in the body, beyond adequate nutritional effects. This specific effect has to be proven in well-designed human studies. Functional foods have to improve the state of health or well-being and/or to reduce disease risk. Adequate markers of target functions and biological responses have to be defined. Related to the immune system, such markers include “vaccination response” or “cytotoxic activity of natural killer cells” (see Box 6).

These markers could be enhanced or suppressed. Depending on the individual immune status, one or the other effect could be suitable. Functional foods with an immune-enhancing potential could be of value for individuals marginally deficient in a specific nutrient or for individuals that consume immunosuppressive nutrients (e.g. fat) in excess. But, some individuals with adequate nutrition are also interested in boosting the immune system by increasing the intake of specific nutrients. Examples of functional foods are yogurt that are supplemented with immunomodulatory probiotics.

Because the immune system is a complex and delicately regulated system, care has to be taken not to disturb this balance. More research is needed to understand how single nutrients, as well as combinations of nutrients at doses higher than the recommended dietary intake levels, affect the immune system in healthy individuals with a normal functioning immune system. More information is also needed about the variation of immune responses in healthy individuals and how this impacts susceptibility to infections.

Further, genotype, gender and age effects on the sensitivity of the immune system to dietary interventions have to be investigated in more detail. This will allow deeper understanding of whether and how enhanced immune responses through functional foods translate into improved immunocompetence.

However, the evidence from clinical trials in adults with n-3 LCPUFA is not conclusive, although there is a possible benefit in children. A high intake of vegetables and fruit (especially apples) does seem to reduce the risk of asthma. Potential beneficial constituents in these foods are the phytochemicals, including flavonoids.

3.2 Viral and bacterial infections**Measles**

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 USA, where vitamin A deficiency is ordinarily considered rare, many children show biochemical evidence of vitamin A deficiency during measles infection. Children in US 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 hospitalised for severe measles.

HIV and AIDS

There is evidence that nutritional status is an important determinant of survival in individuals infected with human immunodeficiency virus (HIV). In the later stages of the disease, severe malnutrition is common, and wasting is one of the most prominent characteristics of advanced disease. The nutritional deficiencies observed

in HIV-infected individuals, especially deficiencies in vitamins A, B₆ and B₁₂, have been associated with deficits in immune function (very low level presence of helper T cells) and accelerated disease progression. Recent research indicates that selenium deficiency may be an important predictor of decreased survival in patients with the acquired immunodeficiency syndrome (AIDS). Some intervention studies reported that the mortality of AIDS patients with low helper T cell counts was reduced when they took vitamins and/or trace element supplements, but other studies did not find any effect of micronutrient supplementation. In developing countries, however, vitamin A seems to reduce mortality, improve growth and reduce diarrhoea of HIV-infected children.

Respiratory infections

Several micronutrients are associated with respiratory infections, as already discussed: vitamins A, C, D, and E, selenium and zinc. Vitamin A restores the integrity of the mucosa in the pulmonary tract, and vitamin D fosters the production of the endogenous antibiotic cathelicidin. Both mechanisms could protect the body from colonization and proliferation of pathogens. Data from clinical studies also demonstrated that low serum vitamin D concentrations in northern countries are associated with acute respiratory tract infections. Vitamin E and selenium protect immune cells from oxidative damage and, hence, could reduce the risk of contracting respiratory infections or alleviate the symptoms thereof. Results from a randomised controlled trial with healthy volunteers demonstrated that selenium supplementation enhances the elimination of polioviruses and stimulates cellular immune responses. Supplementation with zinc reduces the incidence of respiratory infections in zinc-deficient persons, mainly in developing countries. As previously noted, vitamin C is an antioxidant with no effect on the incidence of the common cold in people with normal nutrition, but the duration of the infection was slightly reduced with

supplemental vitamin C at a dose of 200 mg/day or more. In people with vitamin C deficiency or with high physical or cold stress, vitamin C reduced the incidence of the common cold.

Diarrhoea

Several systematic reviews on studies in both developed and developing countries have shown that certain probiotics significantly shorten the duration of diarrhoea in young children. In most studies, the clinical effects were accompanied by an increase in the immune response. Lactobacilli, for example, reduced the stool frequency and the duration of diarrhoea in children. This effect is dose-dependent, with higher doses of probiotics causing a more efficient reduction in diarrhoea.

Vitamin A enhances the regeneration of damaged mucosa epithelium and the phagocytic activity of neutrophils and macrophages. Additionally, vitamin A supplementation restores the ability of gut immune cells to produce antibodies (IgA and IgG) against bacterial toxins, which is compromised in vitamin A deficiency. Clinical studies support the view that multiple low doses of vitamin A supplementation reduce the incidence and duration of diarrhoea episodes, especially in malnourished children.

3.3 Food allergy

Heredity and environmental factors are major predisposing factors in allergy. The chance of a genetically susceptible individual developing sensitivity to a food protein depends on many factors, including exposure to the potential food allergen from diet, and an antecedent episode of viral gastro-enteritis (see ILSI Europe Concise Monograph “*Food Allergy*”).

Probiotics are a potential tool in the prevention and treatment of food allergy because of their ability to promote oral tolerance and endogenous barrier mechanisms, alleviate intestinal inflammation, and to beneficially affect the intestinal microbiota composition. Initial clinical studies in children with atopic diseases suggested a beneficial effect of *Lactobacillus rhamnosus* GG. However, more recent studies reported conflicting outcomes. Clearly, demonstration of beneficial effects of probiotics depends on defined probiotic strains and doses as well as on the clinical setup (differences in target groups, countries, intervention schemes, criteria to define atopic diseases).

3.4 Cancer

It has long been thought that the immune system could play a role in the recognition of and the reaction to tumours. Since the 1980s, several studies have revealed that subjects with a low natural killer cell activity had an increased cancer risk. Furthermore, the increased incidence of certain types of cancer in HIV-infected individuals has suggested a relationship between immunosuppression and development of certain tumours.

A current hypothesis proposes that the immune system and cancer cells interact in three ways. First, the immune system recognises cancer cells and eliminates these cells (cancer immunosurveillance). Second, the proliferation of cancer cells is held in check by the immune system (equilibrium). Third, cancer cells with dampened immunogenicity are not recognised by the immune system and develop more easily into clinically apparent cancers (escape). Primarily due to methodological reasons, to date there is no evidence from human studies that enhancing immune function by dietary means will reduce the risk of certain tumours.

4. BENEFITS AND RISKS OF ALTERING THE IMMUNE RESPONSE BY NUTRITIONAL MEANS

From the nutritional standpoint, a well-balanced diet should support effective immune function, and the concept of promoting health or treating disease by altering the immune response by dietary means shows great promise. However, there are still many questions to be answered about optimal intakes of nutrients and whether enhanced immune responses really translate into increased resistance to infections.

Potentially beneficial approaches include the reduction of total fat intake, the improved quality of dietary fat (decreasing the ratio of SFA to PUFA), the compensation of micronutrient deficiencies in some elderly, and the use of probiotics or prebiotics. 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 overactive 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. The use of a single high dose of vitamin A in the treatment of children with measles is a good example. In other cases however, the correction of a nutrient deficiency might be harmful.

BOX 9

Regulation of health claims on foods related to immune function

Regulation (EC) No 1924/2006 harmonises nutrition and health claims for food products in the European Community. The European Food Safety Authority (EFSA) evaluates the totality of available scientific evidence and advises the European Commission on the admissibility of specific health claims. The evaluation is established on a case-by-case basis because the type, level, etc. of scientific evidence needed depends on the context of specific claims.

EFSA has drafted a guidance document for the scientific requirements for health claims related to gut and immune function. That document was discussed with scientific experts at a workshop in December 2010. From the examples provided, it is obvious that claims need to clearly define the nature of the specific aspects of the immune system subject to the claim, e.g. defense against pathogens or response to allergens. Moreover, a mere change in immune function markers is not necessarily considered a beneficial health effect. Exceptions to this could be prevention of UV-induced suppression of skin immunity and improved responsiveness to vaccination. However, in general it needs to be demonstrated that changes in immune function result in beneficial health outcomes such as less frequent or less severe infections or less diarrhoea. At the same time, legislation on foods does not allow prevention or treatment of disease claims because these are confined to medicines. Therefore, health claims for food products must be based on effects on risk factors or biomarkers, not solely on disease outcomes, although the latter can help to establish the relevance of effects on risk factors or biomarkers.

For EFSA opinions on specific health claims and for the most up to date guidance on substantiation of claims related to immune function, consult the EFSA website:

<http://www.efsa.europa.eu/en/ndatopics/topic/nutrition.htm>

The supplementation of iron in malaria regions could increase the incidence of malaria and lead to a more severe course of the disease.

The improvements in immune responses that 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 or multimineral supplements are well within the safe range. To date, most studies show that supplements do not enhance the immune response in healthy, well-nourished adults and elderly with normal levels of physical activity but are of benefit to malnourished subjects and those engaging in extreme physical activity. What has been observed is a boost of 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 assumption.

Vitamin E is generally regarded as one of the safest nutrients, even when administered in doses greater than those normally consumed. A controlled trial of vitamin E supplementation in the elderly demonstrated that the immune-enhancing effects of a comparatively 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. Interestingly, the intake of vitamin E at doses of 400 mg/day and higher are associated with increased mortality. Thus, for vitamin E, as for other nutrients, there may be a level of intake that has optimal effects on the immune response, and on overall health. This intake level has still to be defined.

In relation to vitamin D, current data indicate that many people in Western countries have low intakes of this vitamin. Higher intakes of vitamin D could improve resistance to infections as well as immunoregulatory processes.

Many minerals, including those that influence the immune response, have narrow ranges of safety. Although small increases in the intake of these minerals could 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 industrialised 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 RDA of 12–15 mg/day) can impair the immune response and interfere with copper nutrition.

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.

The consumption of food supplemented with probiotics is unlikely to be of risk, as confirmed by a large number of studies with healthy subjects.

5. 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 that protect the body against potentially harmful foreign agents. Nutritional factors can influence immune functioning in many ways and at many levels. It is therefore important to consider the immunological relevance of effects observed. Specific *in vivo* measures such as response to vaccination can for instance indicate improved resistance to infection, but due to the complexities of the system, no single assay or marker allows conclusions to be drawn about the functioning of the immune system as a whole. Thus, scientists have established criteria to determine relevant biomarkers, which in combination 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 LCPUFA), several vitamins (especially vitamins A, D, E, B₆ and C), carotenoids, flavonoids, trace minerals (especially zinc and selenium), prebiotics and probiotics.

Research suggests that altering the immune response by dietary means might be of value in the reduction of risk and/or the treatment of a wide variety of disorders, including inflammatory diseases, heart disease, viral and

bacterial infections, asthma and food allergies, and cancer. 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 might be associated with unusual dietary patterns or the prolonged use of supplements at high concentrations. Nevertheless, dietary approaches aimed at modifying the immune response may one day prove to be of real value in both the maintenance of health and the treatment of disease.

6. GLOSSARY

Allergen: Antigen (see below) that provokes an allergic reaction.

Antibody: Protein molecule (immunoglobulin) produced and secreted by B lymphocytes in response to an antigen, which is capable of binding to that specific antigen. There are five classes of antibodies: IgM, IgG, IgE, IgA and IgD.

Antigen: Substance that provokes an immune response.

Antioxidant: Substance that can delay or inhibit oxidation.

Atherosclerosis: Degenerative disease of the 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: Disease in which the body's immune defences react to the body's cells (self antigens) as though they were foreign, leading to destructive effects.

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

Cellular immune response: Interactive immune response that involves T cells and other immune cells.

Controlled trial: Study that investigates the effect of a test substance. Subjects are randomly allocated to different groups. One group receives the test substance, whereas the other (the control group) receives an inactive placebo. Ideally, the treatment should be double-blinded, that is, neither the investigators nor the subjects should know during the study whether a subject belongs to the treated or the control group.

Epidemiologic study: Study that is conducted to assess risk factors for diseases (for example, heart disease). The investigators search for differences in lifestyle factors like housing, stress, diet, physical activity or smoking between patients with a specific disease and persons without this disease. An epidemiologic study can be conducted prospectively (lifestyle factors of the study group are recorded and the disease incidence is noted during the course of study) or retrospectively (persons with and without the specific disease are admitted into the study and interviewed about their past lifestyle).

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

Functional food: Food that is designed to exert an additional benefit to health, beyond that of meeting basic nutritional needs.

Humoral immune responses: Immune response that is mediated by secreted antibodies.

Inflammation: General term for the reaction of tissues to injury or infection, or sometimes a localised immune response; characterised clinically by heat, redness, swelling and pain.

Leukocyte: White blood cell family that includes lymphocytes, monocytes/macrophages and neutrophils.

Leukotriene: Tissue hormone derived from long-chain PUFA, which possesses diverse biological actions in the immune system.

Lymphocyte: Class of antigen-specific white blood cells that includes B cells, T cells and natural killer cells.

Macrophage: Type of phagocytic cell present in tissues.

Monocyte: Class of white blood cells, which is precursor to macrophages.

Morbidity: State of being diseased.

n-3 PUFA: Polyunsaturated fatty acids with the first double bond between the third and the fourth carbon atoms from the methyl end; they are found in vegetable oils such as canola oil; n-3 long-chain (LC) PUFA are found in oily fish and fish 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.

Neutrophil: White blood cell (50–60% of circulating leukocytes), also called granulocyte.

Peyer's patches: Lymph node-like structures that are interspersed at intervals just beneath the epithelium of the small intestine.

Phagocyte/Phagocytic cell: Cell that has the capability of ingesting other cells, foreign material or bacteria.

Polyunsaturated fatty acid (PUFA): Fatty acid with two or more double bonds in its carbon chain.

Prostaglandin: Tissue hormone derived from long-chain PUFA, which possesses diverse biological actions in the immune system.

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

T cells (or T lymphocytes): Subset of lymphocytes defined by their development in the thymus. T cells induce and regulate specific immune responses after stimulation by specific antigens.

Tissue hormones: In contrast to hormones, which are produced in one organ and act systemically, tissue hormones are locally produced and then act in specific organs.

7. 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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