Interaction between nutrients, pro-inflammatory cytokines and inflammation

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INTRODUCTION

An invasion of the body by micro-organisms and injury activates the immune system and brings about widespread metabolic changes. Both phenomena are closely interrelated and form part of a complex and co-ordinated response. The objectives of the response are to disadvantage and destroy the invading organism, repair damaged tissue and restore tissue function to normal.

Activation of the immune system results in the release of a complex variety of soluble mediators from cells of the system and hepatocytes [1-3]. The mediators include immunoglobulins, complement proteins and cytokines. Cytokines are a large group of peptides and proteins which are involved in signalling between the cells of the immune system. Cytokines include interleukins (ILs), interferons, colony stimulating factors, tumour necrosis factors (TNFs) and transforming growth factors. A grouping of three cytokines, IL-1, IL-6 and TNF-α, not only mediate and modulate an enhanced level of activity in the immune system but also cause widespread metabolic changes. They belong to a subgroup of cytokines described as pro-inflammatory cytokines as they are key mediators of inflammation. A number of cell types produce IL-1, IL-6 and TNF-α. These include phagocytic leucocytes, T- and B-lymphocytes, mast cells, fibroblasts and endothelial cells [4-6]. Once induced, IL-1 and TNF can stimulate production of each other and of IL-6. Thus, a cascade of pro-inflammatory cytokines occurs after the initial inflammatory stimulus [7]. Subsequently, nitric oxide, hydrogen peroxide and superoxide radicals are produced by phagocytes [8]. These oxidants also enhance cytokine production.

The production of cytokines and oxidant molecules is part of a highly effective mechanism for creating a hostile environment for pathogens within the body [9]. Paradoxically, the high potency of these molecules, which are essential in the body’s defence system, may also damage the host.

The essential nature of cytokines in recovery from inflammatory situations is indicated by the poor prognosis of malnourished patients who have a reduced ability for cytokine production [10, 11]. These patients also exhibit poor wound healing as TNF-α is an important inducer of transforming growth factors that play a crucial part in the process.

This review focuses on the effects of IL-1, IL-6 and TNF-α, the innate systems for protecting the subject from the potentially pathological effects of enhanced cytokine production and the modulatory role which nutrients may exert on such biological events.

CYTOKINES AND THE METABOLIC CONSEQUENCES OF INFECTION AND INJURY

Infection is characterized by fever and wasting of peripheral tissues. Similar changes are associated with injury. The wasting results in loss of tissue lipid, protein and micronutrients. Widespread metabolic changes, which are part of the wasting process, facilitate the delivery of nutrients to the immune system, assist repair of tissues, control cytokine production, protect healthy tissue from the effects of free radicals and other oxidant molecules and remove nutrients from the bloodstream which might assist multiplication of pathogens.

Amino acids, released by increased proteolysis in muscle, skin and bone, provide substrates for the synthesis of cells and soluble mediators by the immune system. Glutamine, released from muscle, glucose derived from increased hepatic gluconeogenesis of amino acids and oleic acid from lipolysis, are major nutrients for cells of the system [12, 13].
Zinc, an important cofactor in DNA synthesis, is released from peripheral tissues and may subsequently support cell division within the immune system [14]. The mechanisms underlying the metabolic changes associated with the wasting process are complex. They involve interaction between cytokines and the hypothalamus and the direct effects of IL-1 and TNF-α on peripheral tissues and liver. Increased production of glucocorticoids and catecholamines occur due to increased activity of the sympathetic nervous system and stimulation of corticotrophin-releasing factor production by the actions of cytokines on the central nervous system [15–17]. Catecholamines, glucocorticoids and cytokines enhance glycogenolysis and gluconeogenesis [18]. Studies in patients and experimental animals have shown that IL-1, TNF-α and agents which induce production of these cytokines stimulate skeletal muscle protein catabolism, increase glutamine synthesis and enhance efflux of glutamine and other amino acids from the tissue [19–23]. An increased supply of substrate for gluconeogenesis is thus provided from skeletal muscle. The extent to which skin and bone provide amino acids is unclear. However, studies in vitro have shown that TNF-α and IL-1 cause bone resorption and inhibition of proteoglycan synthesis in cartilage [24, 25]. Bacterial lipopolysaccharide produces a marked reduction of protein synthesis in the skin and bone of rats in vivo [26]. A rapid increase in plasma concentrations of free fatty acids and triacylglycerols attached to very-low-density and low-density lipoproteins follows administration of IL-1 and TNF-α in vivo. The response is due to a combination of events which include enhanced lipolysis in adipose tissue and increased hepatic lipogenesis [27]. IL-1, TNF-α and glucocorticoids are responsible for the alterations in tissue zinc concentrations that have been observed during inflammation. The cytokines cause decreased concentrations in plasma, muscle, skin and bone, and an increase in liver, kidney, bone marrow and thymus [14, 28]. IL-1, TNF-α and glucocorticoids exert a stimulatory effect upon the synthesis of metallothionein and may be partly responsible for the increases in tissue zinc [29]. The changes in metallothionein facilitate a shift in body zinc from tissues which act as a reservoir (muscle, skin, bone) to tissues where enhanced cellular activity occurs during inflammation (thymus, bone marrow and liver).

Thus, IL-1 and TNF-α directly and indirectly change metabolism to provide substrate for the immune system from endogenous sources (Fig. 1). Such a change of nutrient supply is important, since anorexia, and lethargy, are among the predominant features of infected and traumatized subjects [30].

**Fig. 1. Influence of pro-inflammatory cytokines upon the immune system and on metabolism after invasion of the host by pathogens**

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**DAMAGE TO THE HOST FROM THE INFLAMMATORY RESPONSE TO PATHOGENS**

Paradoxically, although cytokines play an important role in the response to infection and injury, they can exert damaging and lethal effects upon the host. Several biological events enhance cytokine production, increasing the potential for damage to the host. Oxidant molecules up-regulate cytokine production by activation of nuclear transcription factors such as NFκB and NFIL-6; the factors enhance transcrip-
tion of mRNA for IL-1 and TNF-α, and for IL-6 respectively [31–33]. Further enhancement of cytokine production may occur since IL-1 and TNF-α may induce production of IL-6 and further production of themselves and of each other. Induction of nitric oxide and other oxidant molecules from phagocytic cells by IL-1, IL-8 and TNF-α may also cause damage to the host.

Excessive, or inappropriate production of cytokines, has been associated with morbidity and mortality in a wide range of conditions in which the immune system has become activated. These include sepsis, adult respiratory distress syndrome, malaria, meningitis, cancer, cystic fibrosis, systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis and asthma [34–38]. Furthermore, untimely production of pro-inflammatory cytokines has been implicated in the pathogenesis of atherosclerosis, multiple sclerosis and Alzheimer’s disease [39–41].

The deleterious effects that a propensity for cytokine production has upon the host are evident in a study on variable genetic elements within the major histocompatibility complex. Gambian children who were homozygous for a variant of the TNF-α promoter region, which enhances TNF-α production, had seven times the mortality rates from cerebral malaria than children who were heterozygous [42]. In autoimmune hepatitis and pulmonary tuberculosis, similar associations between a genetic predisposition to produce IL-1 and TNF-α, and pathology, have been noted [43, 44].

Further damage to the host may arise from the interaction of viruses with the mechanisms controlling cytokine production. Although IL-1 and TNF are generally antiviral in their actions, replication of HIV is enhanced by NFκB activation. These inflammatory stimuli which enhance IL-1 and TNF production will therefore indirectly increase replication of the virus [45].

ENDOGENOUS MODULATORS OF PRO-INFLAMMATORY CYTOKINE PRODUCTION AND ACTIONS

When an inflammatory stimulus is encountered, a number of metabolic and cellular events occur which can lead to suppression and localization of the production of cytokines and their subsequent actions.

The observation that substances in the urine of febrile patients inhibited cytokine actions indicated that natural inhibitors of cytokine actions are generated during inflammation. Subsequently, a sophisticated array of control systems which modulate production of cytokines and limit their impact, has been identified [46]. The liver, brain, adrenal cortex and immune system play major roles in the control systems (Fig. 2). Natural inhibitors to IL-1 and TNF-α are produced in response to IL-1 and TNF-α. The inhibitor for IL-1, interleukin-1 receptor antagonist, is produced by lymphocytes and phagocytes; its amino acid sequence is very similar to that of IL-1 and it binds to receptors for the cytokine without leading to cellular activation. Interleukin-1 receptor antagonist thus competes with IL-1 for binding to receptors and decreases the sensitivity of cells to IL-1. The inhibitor for TNF-α is the extracellular domain of TNF receptors. These domains are shed into the circulation as soluble TNF receptors after binding of TNF-α to a small proportion of the receptors on the surface of target tissues. The soluble receptors compete with membrane-associated TNF-α receptors, thereby reducing cellular sensitivity to the cytokine. Interleukin-1 receptor antagonist and soluble TNF receptors are present in plasma in concentrations that are well in excess, in molar terms, of concentrations of IL-1 and TNF-α, and may thus exert major inhibitory influences on the biological activity of the two cytokines. Soluble forms of IL-1 receptors have been found in plasma, indicating a further way in which tissue sensitivity to IL-1 may be reduced [47]. In addition to specific inhibitors for IL-1 and TNF, other cytokines down-regulate IL-1 and TNF-α production. Pre-eminent among the inhibitory cytokines are IL-4 and IL-10. In addition to their direct effects on IL-1 and TNF, the inhibitory cytokines exert an indirect influence by enhancing soluble TNF receptor and interleukin-1 receptor antagonist production [47].

Control mechanisms arise from the actions of IL-1 and TNF upon the hypothalamo-pituitary-adrenal axis. Consequently, glucocorticoids are released and suppress cytokine production by enhancing lipocortin production [48, 49]. Glucocorticoids also participate indirectly in the control of cytokine production. They facilitate the release of amino acids from peripheral tissues and, in conjunction with IL-1 and IL-6, stimulate acute phase protein production by hepatocytes [50]. Some of these proteins, such as orosomucoid, α2-macroglobulin, C-reactive protein and...
α₁-antichymotrypsin, inhibit neutrophil activation and production of superoxide radicals and TNF-α [51–53]. Increased production of orosomucoid, caeruloplasmin, and of glutathione, enhances antioxidant defences and limits the stimulatory effects of oxidant molecules on cytokine production.

Acute phase proteins may also enhance cytokine production. Lipopolysaccharide binding protein increases the sensitivity of macrophages to endotoxin and results in enhanced TNF-α production [54]. Local amplification of cytokine production may also occur under the action of fibronectin which accumulates at sites of inflammation. This glycoprotein is highly susceptible to proteolysis. Its fragments have been shown to stimulate fibroblast proliferation and chemotaxis and to stimulate IL-1 and TNF-α production [55].

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**MODULATION OF CYTOKINE BIOLOGY BY NUTRIENTS**

The metabolic aspects of inflammation, described earlier, are mediated by a range of secondary messengers and cell signalling mechanisms, which offers broad scope for nutritional modulation.

Cytokines may have beneficial or detrimental effects, depending upon the context and amounts in which they are produced. During infection they are mostly beneficial; in cancer, chronic inflammatory disease, or in individuals infected with HIV, they may be detrimental. Thus, beneficial dietary manipulation of cytokine production and actions may be designed to facilitate, enhance or suppress events, depending upon the biological or clinical context in which they are operating [9]. Studies using animal models have illustrated that manipulation of the intake of a wide range of nutrients can modulate many deleterious effects of infective and inflammatory states (Table 1).

**MODULATION OF CYTOKINE PRODUCTION AND BIOLOGICAL EFFECTS BY FATS**

Fats may exert modulatory effects by influencing the ability of cells to produce cytokines and the ability of target tissues to respond to cytokines. This topic has been reviewed in detail elsewhere [56, 57]. The fatty acids in dietary fat consist of four main types according to chemical composition. These are saturated fatty acids, such as stearic and palmitic acid which are found in highest concentrations in saturated fats such as beef fat, coconut oil and butter; n-9 monounsaturated fatty acids, such as oleic acid which is present in high concentrations in butter and olive oil; n-3 polyunsaturated fatty acids (n-3 PUFAs) such as linolenic acid, present in soybean oil and eicosapentaenoic acid present in high concentrations in fish oils; and n-6 PUFAs, such as linoleic acid which is present in high concentrations in corn, sunflower and safflower oils.

Extensive studies have been carried out, mostly in animal models, using a number of these fats. The studies include observation of the effects of dietary fat on burn injury, cytokine- and endotoxin-induced anorexia and fever, cytokine- and endotoxin-induced changes in visceral protein metabolism and cytokine production from macrophages. In summary, fats rich in n-3 PUFAs or n-9 monounsaturated fatty acids, or poor in n-6 PUFAs, reduce responsiveness to cytokines [57, 58]. Fats rich in n-6 PUFAs exert the opposite effect. The ability of peritoneal macrophages from rats to produce IL-1 and IL-6 in response to TNF-α is greatly influenced by the dietary intake of linoleic acid and total unsaturated fatty acid intake, respectively. IL-1 production increases to plateau concentrations, within a range representing 1–4% of dietary energy, whereas IL-6 production is positively related to unsaturated fatty acid intake over a wider range of intakes [59].

There is a limited amount of evidence that n-6 PUFA intake may influence pro-inflammatory cytokine production in humans. Monocytes taken from subjects consuming a cholesterol-lowering diet, which involved a reduction in saturated fatty acid intake from 14.1 to 4% of dietary energy, and an increase from 6.1 to 8.8% in n-6 PUFAs, over a 24-week period, exhibited enhanced IL-1 and TNF-α production in response to endotoxin [60]. Furthermore, blood from smokers shows a greater propensity to produce TNF in response to endotoxin, and smokers consuming n-6 PUFA intakes of greater than 5% of dietary energy had 2-fold greater concentrations of C-reactive protein than smokers with a lower intake of n-6 PUFAs [61].

Inflammatory symptoms are improved by fish oil, or n-3 PUFAs, in diseases such as rheumatoid arthritis, psoriasis, asthma, multiple sclerosis, Crohn’s disease and ulcerative colitis [57]. Fish oil supplementation of the diet of patients with pancreatic cancer cachexia arrested weight loss [62]. Fish oil reduces the ability of leucocytes from healthy subjects and rheumatoid patients to produce IL-1, IL-6 and TNF-α [63]. This may partly explain the anti-inflammatory effects of fish oil. γ-Linolenic acid also has a suppressive effect on plasma concentrations of a wide range of cytokines (IL-1, IL-2, IL-4, IL-6, TNF-α and γ-interferon) in patients with
Modulation of cytokine biology by nutrients

INFLUENCE OF PROTEIN AND AMINO ACID INTAKE ON CYTOKINE BIOLOGY

The biochemical changes that occur during inflammation exert a large metabolic demand. Cytokines bring about major changes in protein and amino acid metabolism, whereby amino acids are released from peripheral tissues for nutrition of cells of the immune system and the synthesis of acute phase proteins and glutathione by liver. However, the supply from the peripheral tissues may not always match demands. It has been estimated that, during major infections in man, the amount of protein required to produce and maintain an increase in circulating leucocytes and acute phase proteins is approximately 45 g/day [72].

There may be an enhanced requirement for sulphur and related amino acids after infection and trauma [8]. Severe trauma and infection cause large decreases in plasma glycine, serine and taurine concentrations. These changes may be due to enhanced utilization of glycine, serine and the sulphur amino acids, methionine and cysteine, which are closely related in metabolism. Many substances produced in enhanced amounts, in response to cytokines, are rich in these amino acids. These include glutathione, which consists of glycine, glutamie acid and cysteine; metallothionein, which contains glycine, serine, cysteine and methionine to a composite percentage of 56%, and a range of acute phase proteins which contain up to 25% of these amino acids in their structure. After surgery on uninfected patients, a decrease in the ratio of urinary sulphate to nitrogen occurs, indicating preferential retention of sulphur amino acids in tissue components [73]. TNF-α may play a role in the extensive weight loss observed in patients with cancer and AIDS. In asymptomatic HIV-infected individuals, substantial reductions in glutathione concentrations in plasma and lung epithelial fluid occur, which may indicate a requirement for sulphur amino acids that is not satisfied by diet or endogenous sources [74].

The ability to increase α1-macroglobulin in response to endogenous pyrogen in rabbits, and in response to TNF-α and turpentine abscess in rats, is impaired by low protein diets [75-77]. In rats given a turpentine abscess, the concentration of α1-macroglobulin increased over a wide range of protein intakes of various degrees of adequacy. The ability of rats fed low protein diets to increase serum α1-acid glycoprotein and hepatic glutathione concentrations in response to TNF-α is enhanced by dietary supplementation with glycine and cysteine respectively [76].

In studies in rats given TNF-α, the partitioning of cysteine into hepatic protein and glutathione may depend upon the dietary sulphur amino acid intake. At low levels of intake, incorporation of cysteine into protein is favoured over incorporation into glutathione, to a greater extent than at high levels of intake [73, 78]. Thus, at low intakes of sulphur amino acids, antioxidant defences may become compromised. An insufficient intake of sulphur amino acids will thereby exert a pro-inflammatory influence. In protein-depleted rats given TNF-α,
increases in lung glutathione concentrations were only possible if cysteine and methionine were added to the diet. Infiltration of inflammatory cells into the lung, in response to the cytokine, was noted in the absence of these amino acids from the low protein diet, and was prevented by their addition to the diet [78].

The ability to maintain and enhance tissue glutathione may be of particular importance in controlling cytokine production in response to inflammatory stimuli, since the stimulatory influence of oxidant molecules and TNF-α on NF-κB activity is decreased by glutathione and other sulphur-containing compounds [79, 80]. Furthermore, in rats a non-lethal dose of TNF becomes lethal if the ability of the animal to increase and maintain glutathione synthesis is prevented by administration of diethylnmaleate [81].

Thus, production of cytokines, acute phase proteins and glutathione is influenced by the adequacy of both protein and sulphur amino acid intake. These observations suggest that nutritional strategies concerning the supply of amino acid substrate to individuals responding to cytokines should go beyond consideration of all dietary protein as simply a provider of protein nitrogen; the amino acid proportions in that provision should also be taken into account.

MODULATION OF CYTOKINE BIOLOGY BY OXIDANTS AND ANTIOXIDANT STATUS

Complex antioxidant defences exist within the host. They are distributed in body fluids and within various compartments of the cell. Plasma contains a wide range of substances with antioxidant properties. These include molecules derived directly from the diet, such as vitamin E and other tocopherols, vitamin C, β-carotene and catechins, and proteins and peptides, such as glutathione, caeruloplasmin, albumin and metallothionein, which are synthesized endogenously. Many of these substances act as antioxidants within aqueous compartments of the cell, although vitamin E and other tocopherols are the predominant antioxidants within cell membranes. Superoxide dismutase, catalase and glutathione peroxidase and reductase facilitate the processing of oxidant molecules to harmless by-products. Clearly nutrients can contribute directly and indirectly to the robustness of antioxidant defences and thereby limit the capacity of oxidants released during inflammation to activate nuclear transcription factors and damage tissues of the host (Fig. 3). In this role, nutrients therefore limit pathological aspects of the cytokine-mediated response to infection and injury.

As indicated earlier, alterations in antioxidant status brought about by changes in tissue glutathione may change the intensity of cytokine production by modulating the interaction between oxidants and NF-κB and NFIL-6. Micronutrient intake influences antioxidant defences. Trace elements are present in metallothionein (Zn), caeruloplasmin (Cu), superoxide dismutases (Cu, Se, Zn) and glutathione peroxidase (Se). Thus, dietary copper and zinc intake may influence antioxidant defences and the ability of the defences to be enhanced by the actions of cytokines.

Copper deficiency in rats impairs their ability to increase plasma caeruloplasmin and copper–zinc superoxide dismutase in lung, in response to the dual stress of endotoxin injection and exposure to high concentrations of oxygen. Likewise, the ability of IL-1 to increase plasma concentrations of caeruloplasmin with fully functional oxidase activity is also suppressed by copper deficiency [82]. Deficiencies in zinc impair the ability of IL-1 to induce metallothionein synthesis in rats [83].

Iron status may influence the production of cytokines, by its ability to catalyse free radical formation. The production of TNF-α by mice and IL-1 by rats, in response to endotoxin, is suppressed by desferrioxamine (an iron chelator) and by iron deficiency respectively [31, 84]. Furthermore, inflammatory symptoms in rheumatoid arthritis are exacerbated by intravenous iron dextran [85].

Oxidation of PUFAs, as a result of free radical attack, leads to enhanced ethane and pentane production in respired gases. Swords et al. [86] showed that although endotoxin injections produced no increase in ethane production in well-fed rats, production rates doubled in animals fed a diet deficient in selenium and vitamin E. Other cytokine-mediated responses to inflammatory agents are also modulated by vitamin E intake. In a study in which rats were given diets either containing no vitamin E, a normal amount of vitamin E or four times the normal amount for 3 weeks before injection with endotoxin, deficient animals showed the largest anorexic response to endotoxin, the largest increase in orosomucoid and increased plasma IL-6 concentration [87, 88]. Histological examination of the lungs indicated that although infiltration of the lungs by immune cells was equally intense in all dietary groups receiving endotoxin, differences existed in the saline-injected controls. The deficient controls had 18 and 32% more polymorphonuclear cells in the lungs than the controls receiving diets containing normal or supernormal amounts of vitamin E respectively [87]. The data suggest that vitamin E deficiency sensitizes the animals to the mild inflammatory stimuli encountered during daily activities. Thus, cytokine production in response to mild and chronic or acute and severe exposure to inflammatory agents may be modulated when antioxidant defences are compromised by lack of vitamin E. A similar phenomenon may occur in human subjects. Cigarette smoking provides a chronic inflammatory stimulus to the macrophage population in the lung. Indeed, raised plasma concentrations of acute phase protein and IL-6 have been
Modulation of cytokine biology by nutrients

**Fig. 3.** Interactions between oxidants and antioxidant defences in the activation of nuclear transcription factors during inflammation. Stimulatory actions are indicated by plus signs and inhibitory actions by minus signs. Abbreviation: SOD, superoxide dismutase.

- **Cytokines** + Oxidant molecules
- Cell membrane
- Vit E
- DNA transcription
- HIV replication
- Acute phase protein synthesis
- Cytokine synthesis

**MODULATORY INFLUENCE OF THE AMOUNT AND ROUTE OF NUTRIENT DELIVERY ON CYTOKINE BIOLOGY**

Anorexia is a key feature of the response to pro-inflammatory cytokines. The extent to which correction of appetite loss by nasogastric or parenteral feeding carries risks or benefits is important in patients with an ongoing inflammatory response. Anorexia may be an unfortunate phenomenon associated with the metabolic changes induced by cytokines, or it may be an attempt to selectively avoid nutrients that might disadvantage the response of the host to pathogens. Experimental and observational data suggest that either possibility could be the case. Rats given IL-1 and a choice of casein, lard or a mixture of sucrose and cornstarch, reduced intakes of the protein and fat by 57 and 68% respectively, whereas carbohydrate appetite was unaffected [90].

Beneficial effects on immune function, morbidity and mortality were observed in burned children supplied with additional protein in the form of whey protein. The unsupplemented and supplemented diets contained 16.5 and 23% of energy as protein, respectively. Improvements in neutrophil opsonic index, plasma acute phase proteins, survival and number of days with bacteraemia were noted in children fed the whey protein supplements [91].

However, asymptomatic infected malnourished children often become febrile during nutritional rehabilitation. The appearance of fever may indicate an enhancement of cytokine production, previously held in check by the malnourished state [92]. In malnourished elderly patients showing an impaired ability to produce cytokines, dietary protein supplementation restored and enhanced production [10]. Such an enhancement carries benefits and dangers for the host if it is not part of a carefully coordinated metabolic response that disadvantages the pathogen but protects the host. Indeed, enhanced mortalities have been noted in malnourished infected populations once nutritional supplementation is commenced [93]. Similar phenomena have been observed in studies in animals. Mortality from malaria and bacterial infection is modified by alter-
Mortality in rats from *Plasmodium berghei* malaria was reduced by low protein diets but enhanced by dietary supplementation with a mixture of threonine, valine, leucine and isoleucine [94]. Likewise, mortality in guinea pigs from *Escherichia coli* and *Staphylococcus aureus* infection was increased from 15 to 54% over a range of protein intakes, from an inadequate 5% of total dietary energy as protein to 20% [95]. Similar deleterious effects on mortality from bacteraemia were observed in guinea pigs receiving increased quantities of an adequate diet. While 62% mortality occurred when an adequate quantity was fed (523 kJ day$^{-1}$ kg$^{-1}$), increasing intake to 628 or 732 kJ day$^{-1}$ kg$^{-1}$ resulted in 100% mortality [96]. Enhanced cytokine production rather than increased virulence may underlie these paradoxical effects of dietary supplementation.

Although malnutrition decreases the ability to produce cytokines, a chronic reduction in food intake may bring about the opposite effect. Vaisman et al. [97] showed that monocytes taken from obese patients who received 420 kJ/day for 6 days, showed a 3-fold enhancement in ability to produce TNF-α in response to phyathaemagglutinin or endotoxin stimulation *in vitro* compared with the response before diet restriction. The reason for this paradox may lie in gut physiology. Fong et al. [98] observed the effects of 'bowel rest' on subsequent TNF production in response to endotoxin by feeding healthy volunteers via the enteral and parenteral routes. Peak plasma TNF concentrations were three times greater in subjects fed parenterally than in those fed enterally. Fong et al. suggest that the stimulatory effect was due to an increase in bacterial translocation and endotoxin transfer into the portal circulation when the gut food content decreased. Exposure of Kupffer cells to these inflammatory agents would result in a low level of cytokine production that would sensitize the volunteer's immune system, thereby enhancing TNF production in response to the subsequent endotoxin challenge. An oral intake of 420 kJ/day in the study of obese patients may have been insufficient to prevent translocation and sensitization [97]. A number of studies have shown the clinical advantage of feeding via the enteral rather than the parenteral route if a choice is permitted by the condition of the patient. Part of the effectiveness of the former route may lie in the prevention of sensitization of cells of the immune system within the viscera to inflammatory stimuli.

**CONCLUSIONS**

The essence of survival of an individual, or species, lies in the ability to prioritize physiological processes, particularly those processes that exert a large metabolic demand. Thus, at various times in the life cycle, metabolic processes become focused upon achieving growth, the construction of placenta and foetus, the synthesis of milk components and the repulsion of an invasion by pathogens. For the infected individual, the marshalling of resources to combat the infective agent takes high priority. Other physiological processes can take precedence once the invasion has been repelled and the damage caused by the invader repaired.

The high priority given to combating pathogens is necessary because of the speed with which pathogens multiply once established within the host. In general terms, bacterial cells multiply at least 50 times as rapidly as T-cells under favourable conditions. Thus, the provision of nutrients to allow the immune system to function correctly cannot be left to chance. Cytokines therefore play a crucial role as modulatory agents by which the activity of the system is changed and metabolic activity of the host directed towards provision of nutrients for the system from endogenous sources. The enhanced level of cytokines and free radical production that follows pathogenic invasion, although designed to combat the invader, has the potential to damage the host. Damage, however, is limited by enhancement of the antioxidant defences of the host and activation of systems for retaining cytokine production within healthful confines.

As discussed earlier, previous and concurrent nutrient intake modulate cytokine biology. Nutrients may act at many cellular locations, changing cytokine production and altering the responsiveness of target tissues to cytokines. Fats mainly exert a direct influence at the level of the cell membrane by changing phospholipid fatty acid composition. Protein and individual amino acids facilitate the widespread change in protein metabolism that occurs during inflammation. Sulphur amino acids and other nutrients which influence antioxidant defences may modulate cytokine production indirectly by modulating activation of transcription factors by oxidant molecules produced during inflammation. As a consequence of the nutritional modulation, the host will experience depletion of resources and damage which ranges from being mild and temporary in nature, to severe, chronic and lethal.

The future challenge for the clinician and scientist will be to determine how the nature of the nutrient cytokine interactions, identified in the experimental context, can be employed to achieve a healthful diet and clinical benefit [98–102].

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