Dietary manipulation of the inflammatory response

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Inflammation involves a complex interaction of cells and soluble mediators. These components interact to produce a situation in which immune cells are attracted to the inflammatory locus and activated. Cytokines are among the potent soluble mediators produced during inflammation and include the interleukins (IL) 1–8, tumour necrosis factors (TNF), and interferons (Male *et al.* 1989). In addition to activating the immune system, a number of these molecules bring about metabolic changes in the subject which lead to the provision of nutrients for the activated immune system. The cytokines involved in this process are IL-1 and -6 and TNF-α and -β (Grimble, 1990).

An inflammatory stimulus, such as invasion of tissue by bacteria, viruses or parasites, or tissue damage incurred by trauma, surgery or burns, will induce production of IL-1, IL-6 and TNF from a range of immune cells. These cells include phagocytic leukocytes, T and B lymphocytes, mast cells and non-immune cells such as fibroblasts and endothelial cells (Moissec & Ziff, 1986; Le *et al.* 1987; Dinarello *et al.* 1988; Gordon & Galli, 1990). Once induced, IL-1 and TNF can induce each other's and IL-6 production, and IL-6 can induce that of IL-1. Thus, a cascade of cytokines, which are capable of producing metabolic and immune effects, occurs (Old, 1987; Heinrich *et al.* 1990).

Inflammatory stimuli not only bring about cytokine production, free radicals are also released (Farante *et al.* 1988). These may enhance production of TNF and other cytokines. Clark *et al.* (1989) showed that experimental conditions which lead to enhanced free radical production also lead to increased TNF production, both in vitro and in vivo.

The metabolic actions of cytokines provide the mechanisms for limiting the extent and duration of cytokine production, via a number of routes (Fig. 1). These mechanisms arise from the actions of IL-1 and TNF on the hypothalamo–pituitary adrenal axis. Consequently glucocorticoids are released and have the ability to suppress cytokine production (Sherry & Cerami, 1988). They also arise from the action of cytokines on peripheral tissue causing release of amino acids, and by direct action on hepatocytes (Perlmutter *et al.* 1986). Cytokines also act indirectly on liver by creating a hormonal milieu for enhancing production of acute-phase proteins. Some of these substances, such as orosomucoid, α-2-macroglobulin and α-1-antichymotrypsin have the ability to directly inhibit neutrophil activation and production of TNF (Costello *et al.* 1984; Scuderi *et al.* 1989). The increased production of acute-phase proteins, such as orosomucoid and caeruloplasmin (*EC* 1.16.3.1; CP), and of glutathione, enhance antioxidant defences and may thereby limit the stimulatory effects of free radicals released concurrently with cytokines. Acute-phase proteins are not entirely suppressive of cytokine production, since one such protein, lipopolysaccharide-binding protein, increases the sensitivity of macrophages to endotoxin and results in enhanced TNF production (Schumann *et al.* 1990).

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
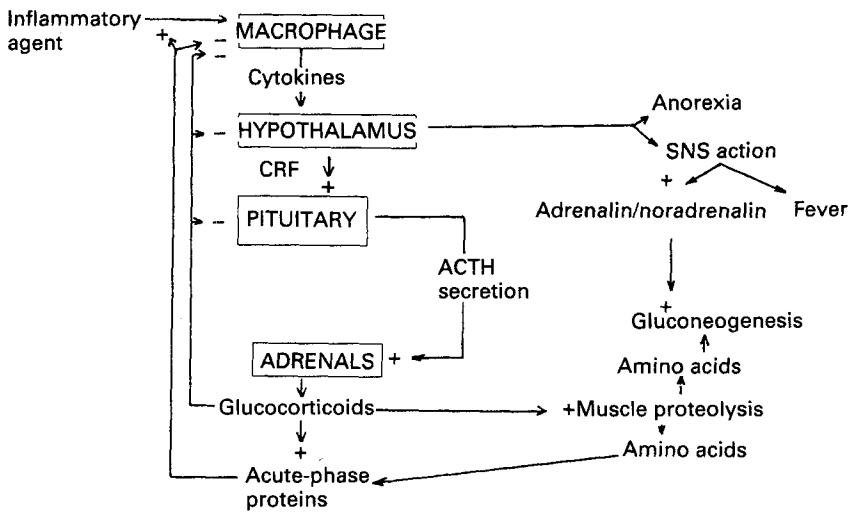
Fig. 1. Control loops in cytokine biology.
+, stimulates; −, inhibits.

production (Keenan *et al.* 1982; Kauffmann *et al.* 1986). Paradoxically, although cytokines are central to an effective inflammatory response in combating invasion of the body, they have the potential for being lethal or tissue damaging (Beutler & Cerami, 1986; Tracey *et al.* 1986; Kelley, 1990). Thus, dietary manipulation of cytokine biology can be aimed at enhancing or suppressing cytokine activity.

MODULATION OF CYTOKINE BIOLOGY BY NUTRIENTS

The cytokine-driven aspects of inflammation, with their widespread metabolic changes and dependence on secondary messengers and signalling, offer broad scope for nutritional modulation. This potential has only been partially realized. Kjeldsen-Kragh *et al.* (1991) found that a number of indices of inflammation were decreased when rheumatoid patients changed from an omnivore to a vegetarian diet. Improvements were noted within 1 month of changing to the diet. The precise nutrient responsible for the improvement is difficult to identify since a vegetarian diet would differ from that consumed by omnivores in terms of its fat and micronutrient content.

Efforts to modify inflammatory responses, in a clinical setting, by alterations in specific nutrients have concentrated on fats, but this class of nutrients is by no means the totality of what is theoretically possible.

INFLUENCE OF FATS

Studies on healthy individuals and patients have been limited to the influence of fish oil preparations on cytokine production, or on inflammatory symptoms in diseases in which cytokine production is likely. Endres *et al.* (1989) demonstrated that a 6-week period consuming 15 g eicosapentaenoic acid as fish oil/d was sufficient to reduce the ability of monocytes to produce IL-1-α and -β and TNF-α and -β in response to an endotoxin stimulus, by more than 30%. The effect persisted for 10 weeks after the subjects had returned to their normal diet. Inflammatory symptoms of rheumatoid arthritis, psoriasis,

Crohn's disease and ulcerative colitis are all ameliorated by fish oil preparations (Kremer *et al*. 1987; Bittiner *et al*. 1988; McCall *et al*. 1989; Solomon *et al*. 1990). The extent to which the amelioration is directly related to reduced cytokine production is, however, unknown.

The modulatory effects of a wide range of fats have been studied in experimental animals. Guinea-pigs experienced a smaller metabolic response to burn injury if fed on fish oil than safflower oil, and pigs and rats are protected from the effects of exposure to large doses of endotoxin by fish oil (Alexander *et al*. 1986; Brown *et al*. 1987; Murray *et al*. 1990). We have demonstrated that fish oil, and a range of saturated fats, including coconut oil, butter and suet, can suppress many metabolic effects of TNF in rodents. The effects influenced include increases in liver zinc content, in the rate of protein synthesis in lung and liver, and in the concentration of plasma CP (Bashir & Grimble, 1992; Mulrooney & Grimble, 1992a).

The modulatory effects of fats extend beyond the actions of cytokines on visceral tissue to the central nervous system. Guinea-pigs and rats fed on fish oil for 6 weeks experienced a smaller fever and lesser degree of anorexia after receiving IL-1-α and -β than animals fed on diets rich in *n*-6 polyunsaturates. Coconut oil and butter were also able to ameliorate the anorectic effects of TNF-α (Hellerstein *et al*. 1989; Pomposelli *et al*. 1989; Mulrooney & Grimble, 1992a). The ability of hypothalamic slices to produce prostaglandin E2 (PGE_2), when incubated with endotoxin or TNF-α was also reduced in rats fed on diets containing coconut oil rather than maize oil (Bibby & Grimble, 1990).

It is tempting to think that the modulatory effects of fats on actions of cytokines are mediated by alterations in prostanoid metabolism since similar modulatory effects on appetite and fever can be obtained by cyclo-oxygenase inhibitors, and fats rich in *n*-3 polyunsaturated fatty acids, such as fish oil, or poor in linoleic acid, such as butter, coconut oil or suet, may inhibit PGE_2 production. However, there is substantial evidence against direct involvement of prostanoids in the actions of cytokines on liver metabolism (Sobrado *et al*. 1983; Johnston, 1985; Revhaug *et al*. 1988; Evans *et al*. 1989). Furthermore, although butter and coconut oil are equally poor in their linoleic acid content, the former fat is far more suppressive of the actions of TNF. One of the major differences between these saturated fats is that butter has a high content of the monounsaturated fatty acid, oleic acid. Supplementation of a diet containing coconut oil with an equivalent amount of oleic acid to that found in butter, resulted in as great a suppression of the actions of TNF as caused by butter (Table 1; Mulrooney & Grimble, 1992b).

MODULATORY EFFECTS OF PROTEIN AND AMINO ACIDS

The studies of Keenan *et al*. (1982) gave the earliest indication that cytokine production is suppressed by malnutrition in patients, and that feeding protein could improve production. The suppressed ability of polymorphonuclear leucocytes (PMN) from mal-nourished patients to produce leucocyte endogenous mediator, was enhanced by feeding protein supplements. A number of animal studies have shown that low-protein diets impair the ability to mount a normal hepatic response to inflammatory stimuli. The increase in α-2-macroglobulin in response to endogenous pyrogen in rabbits, and to TNF and turpentine injection in rats, was impaired by a low-protein diet (Bell & Hoffman-Goetz, 1983; Jennings & Elia, 1990; Grimble *et al*. 1992). The impaired ability of protein-

Table 1. *Influence of various fats and oleic acid on the actions of recombinant human tumour necrosis factor in rats*

Dietary fat*	Appetite change (%)	Liver zinc (%)	Plasma CP (%)	Protein synthetic rate (%)	
				Liver	Lung
Maize oil	−62	+24	+252	+88	+32
Fish oil	−26	+2	+125	+22	−46
Coconut oil	−44	+22	+143	+50	+208
Butter	−41	+8	+88	−20	+4
Coconut oil + oleic acid	−39	+5	+119	+17	−22

CP, caeruloplasmin (*EC* 1.16.3.1).
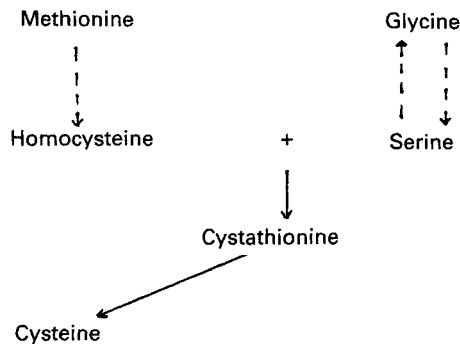* All diets contained 100 g lipid/kg of which 10 g was maize oil.

Fig. 2. Metabolic relationships between sulphur amino acids and glycine and serine.

depleted guinea-pigs to increase α-1-acid glycoprotein in response to IL-1 was restored by infusion with an amino acid solution used for total parenteral nutrition in patients (Drabik *et al.* 1987).

Severe trauma and infection bring about a number of major changes in plasma amino acids. Large decreases in glycine, serine and taurine occur in these states (Askanazi *et al.* 1980; Jeevanandam *et al.* 1990; Paaw & Davis, 1990). While these changes may be in part due to increased renal losses, they may result from enhanced utilization of a closely related group of amino acids. These are the sulphur-containing amino acids cysteine and methionine, and glycine and serine (Fig. 2). The production of many substances, that require amino acids from this group for their synthesis, is increased during inflammation. These substances include glutathione, which is comprised of glycine, glutamic 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. This hypothesis has been discussed in detail elsewhere (Grimble, 1990). The hypothesis was examined by feeding young rats one of a series of diets containing 80 g casein/kg supplemented with isonitrogenous amounts of alanine, glycine, serine, cysteine or taurine, before injection with TNF. The concentration of protein fed was insufficient to support growth and to mount a complete hepatic response to TNF. The results (Table 2) indicate that cysteine is of prime importance in

Table 2. *Influence of supplemental amino acids in a low-protein diet on the metabolic response of rat to tumour necrosis factor*

	Zinc (µg/g)		Liver protein (mg/g)		GSH (mg/g)		Lung GSH (mg/g)		Plasma α-2-macroglobulin (units)	
Injection . . .	S	T	S	T	S	T	S	T	S	T
Diet										
200 g Casein/kg	34	42	158	216	24	29	5·7	5·4	1·9	16·7
80 g Casein: +Ala	31	29	178	162	5	8	4·1	2·4	3·4	9·7
+Gly	13	19	166	173	3	8	nd		4·3	10·0
+Ser	24	29	183	174	8	7	6·6	4·2	nd	
+Cys	22	31	148	211	19	25	nd		3·0	7·8
+Tau	29	29	172	166	7	6	5·5	4·1	nd	

S and T, saline (9 g sodium chloride/l) and tumour necrosis factor injection respectively; GSH, glutathione; nd, not determined.

facilitating an increase in liver glutathione, Zn and protein content. Supplementing the diets with taurine, a major end-product of cysteine metabolism, was unable to increase cysteine availability sufficiently to have a major impact on these liver components. However, the smaller fall in lung glutathione which occurred might indicate a helpful effect of taurine on the animal's glutathione pool.

The influence of the supplemental amino acids is, however, complex since cysteine is not able to restore the response of α-2-macroglobulin to normal. Furthermore, the influence which the supplemental amino acids had on the increase in acute-phase protein concentrations, particularly CP, suggests that the amino acids may produce an indirect effect on hepatic metabolism, related to antioxidant status, rather than simply to provision of substrate for protein and glutathione synthesis. A highly significant negative correlation between CP and hepatic glutathione, and CP and lung glutathione occurred in animals treated with TNF (r −0·54, $P<0.002$; r −0·47, $P<0.02$; Figs 3 and 4). Both substances are part of the animals' antioxidant defences. Animals consuming the low-protein diet supplemented with alanine have low concentrations of hepatic glutathione and are unable to increase them in response to TNF. Subsequently lung glutathione concentrations fall, and there is a compensatory increase in the CP response in an attempt to maintain antioxidant defences. Addition of cysteine to the diet restores the CP response to normal.

Thus, in a situation of malnutrition, the availability of S-amino acids may influence antioxidant defences and, thereby, effect the pattern of acute-phase protein production in an indirect manner.

The fall in plasma taurine which occurs in severe inflammatory conditions may, therefore, reflect increased S-amino acid utilization for glutathione synthesis since both substances are produced from cysteine.

MODULATORY EFFECTS OF MICRONUTRIENTS

Micronutrients are involved in the inflammatory response in a number of roles. Trace elements are present in several acute-phase proteins and other proteins which undergo
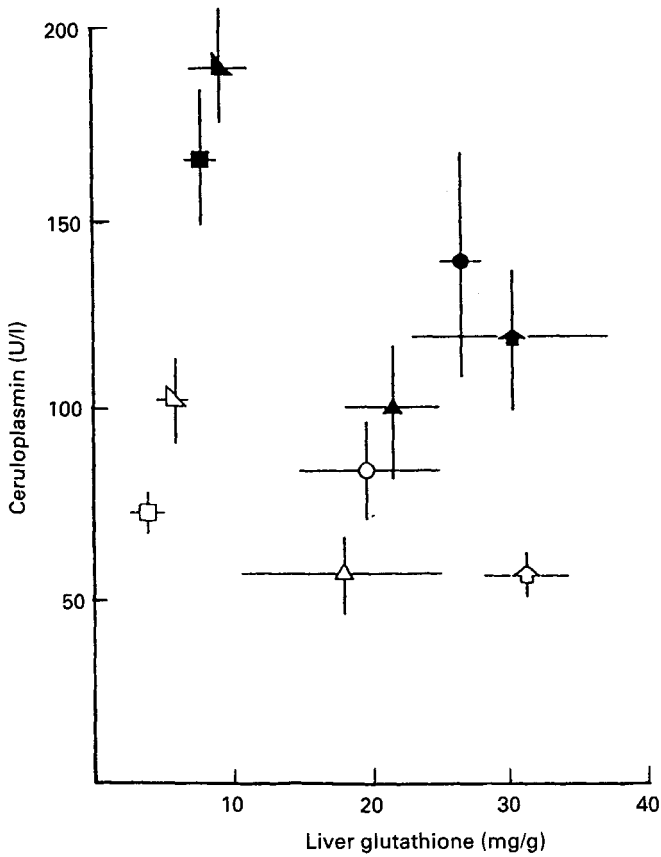
Fig. 3. Influence of glycine and cysteine on the response to tumour necrosis factor (TNF) in rats fed on an 80 g casein/kg diet; ($\triangle$, $\square$, $\triangle$, $\bigcirc$, $\diamond$), saline (9 g sodium chloride/l); ($\blacktriangle$, $\blacksquare$, $\blacktriangle$, $\bullet$, $\spadesuit$), TNF; ($\triangle$, $\blacktriangle$), +6 g alanine/kg; ($\square$, $\blacksquare$), +5 g glycine/kg; ($\triangle$, $\blacktriangle$), +glycine+cysteine; ($\bigcirc$, $\bullet$), +4 g cysteine/kg; $\diamond$$\spadesuit$, +8 g cysteine/kg.
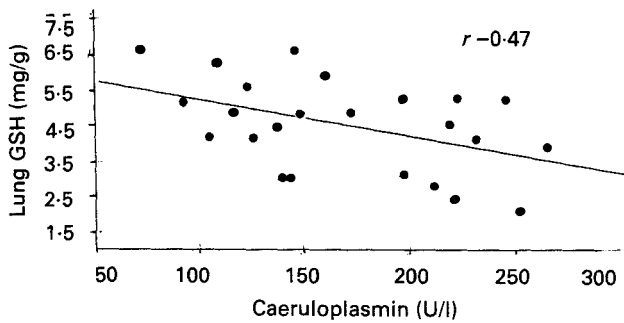

Fig. 4. Relationship of caeruloplasmin (*EC* 1.16.3.1) to lung glutathione (GSH) in rats given tumour necrosis factor (TNF).

increased synthesis as a result of cytokine production. These proteins include metallo-thionein (Zn), caeruloplasmin (copper), haemoglobin (iron), manganese superoxide dismutase (EC 1.15.1.1) (Mn) and Cu–Zn superoxide dismutase (Cu and Zn).

The question of whether deficiencies in trace elements interfere with the production of these proteins during inflammation has been addressed in any detail only for Cu and Zn. The ability of rats to increase plasma caeruloplasmin and Cu–Zn superoxide dismutase in lung, in response to the dual stress of endotoxin and high oxygen concentrations, is impaired by Cu deficiency (Spence *et al.* 1986). Likewise the ability of IL-1 to increase plasma concentrations of fully functional CP is also suppressed (Barber & Cousins, 1988). Deficiencies in Zn impair metallothionein synthesis in response to IL-1 and endotoxin (Huber & Cousins, 1988).

Many of the proteins mentioned previously, are components of antioxidant defences, thus, deficient production may compromise these defences. In addition to the resulting tissue damage, enhanced cytokine production may occur as the result of the stimulatory effect of free radicals. Clarke *et al.* (1989) examined the effects of substances which alter free radical production, and the antioxidant environment, on TNF production by mice infected by *Plasmodium vinckei*. Alloxan which is a free radical generator increased TNF production fivefold, whereas butylated hydroxyanisole, a free radical scavenger, and desferrioxamine, an iron chelator, inhibited TNF production. The effect of Fe seques-tration may explain why peritoneal macrophages of Fe-deficient rats have a reduced ability to produce IL-1 (Helyar & Sherman, 1987). It may also explain why treatment of anaemic rheumatoid patients with Fe-exacerbated inflammatory symptoms, particularly since TNF has been identified in synovial fluid of rheumatoid patients (Winyard *et al.* 1987).

Vitamin E is an important component of antioxidant defences. Oxidation of polyun-saturated fatty acids, as a result of free radical attack, leads to enhanced ethane and pentane production in respired gases. Sword *et al.* (1991) showed that although endotoxin injections produced no increase in ethane production in well-fed rats, production rates doubled in animals fed on a diet that was deficient in selenium and vitamin E.

The influence of vitamin E status on the response of rats to endotoxin injections was examined. The results are shown in Table 3 (Troughton & Grimble, 1992). Animals were given diets containing no vitamin E, a normal amount or five times the normal amount for 3 weeks before injection. Histological examination of the lungs indicated infiltration of the lungs by immune cells which was more severe in the deficient animals than in those receiving the normal or enhanced amount of vitamin E. The deficient animals experi-enced the largest anorexic response to endotoxin and the largest increase in oroso-mucoid. These findings may indicate increased cytokine production in animals whose antioxidant defences have been compromised by lack of vitamin E.

Vitamin A status may also influence cytokine production, although a possible mechanism by which it may do so is unclear. Macrophages from Indian children receiving a supplement of 100 000 IU produced nine times as much as macrophages of children not receiving supplementation (Bhaskaram *et al.* 1989). It is not clear whether the observed effects of the vitamin are of pharmacological or nutritional significance since the supplementation dose is by necessity much greater than habitual intakes. Indeed, Moroguchi *et al.* (1985) demonstrated that mice given an amount of vitamin A that was sixteen times the normal intake resulted in a doubled IL-1 production by peritoneal

Table 3. *Influence of vitamin E status of rats on the response to* Escherichia coli *endotoxin*

Dietary vitamin E (mg/kg) ...	0		50		250	
Injection ...	S	E	S	E	S	E
Food intake						
(g/24 h post injection)	23	3	27	13	24	17
Liver wt (g/kg body-wt)	40	51	37	51	41	53
Plasma α-1-acid						
glycoprotein (units/ml)	22	256	14	157	18	163
Plasma vitamin E (ng/ml)	0·32		0·76		0·97	
Erythrocyte vitamin E (ng/ml)	0·41		0·73		1·12	

S and E, saline (9 g sodium chloride/l) and endotoxin injection respectively.

macrophages, in response to endotoxin, in vitro. The vitamin may have an as yet undefined role in cytokine production since Bowman *et al.* (1990) found decreased interferon production and natural killer cell activity in vitamin A-deficient rats.

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