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The anti-cachectic effect of fatty acids

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Patients with advanced cancer frequently exhibit progressive weight loss and this is associated with a shorter survival time and reduced quality of life. Indeed, some patients appear to die of severe wasting rather than as a result of vital organ involvement by tumour (Warren, 1935; DeWys *et al.* 1980; Oveson *et al.* 1993*b*). Severity of weight loss varies markedly with tumour type; for example, some patients with advanced breast cancer actually increase their weight, whereas almost all patients with pancreatic cancer become severely wasted. In a recent survey of patients with unresectable pancreatic cancer we found that 85 % of patients had unintentionally lost weight by the time of diagnosis and that near to the time of death the group as a whole had lost approximately 25 % of their pre-illness weight (Wigmore *et al.* 1997*c*). Clearly, in a proportion of individuals with pancreatic cancer such severe weight loss contributes to their demise, and thus it is patients with pancreatic cancer that we have used as a paradigm for cancer cachexia.

The term cachexia is derived from the Greek words 'kakos', meaning 'bad' and 'hexis', meaning 'condition'. The syndrome is characterized by anorexia, early satiety, changes in taste perception, weight loss, weakness, anaemia and oedema (Fearon & Carter, 1988). Cachexia is not exclusive to cancer, but is also seen in a variety of inflammatory conditions such as sepsis, acquired immunodeficiency syndrome and rheumatoid arthritis (Grunfeld & Feingold, 1992; Roubenoff *et al.* 1992; Cangiano *et al.* 1996).

Mechanisms of weight loss in cancer

For loss of weight to occur there must be a reduction in energy intake, an increase in energy expenditure or a combination of the two. In pancreatic cancer it would appear that both reduced intake and increased expenditure apply (Falconer *et al.* 1994; Wigmore *et al.* 1997*d*). In uncomplicated starvation there is an adaptation to conserve protein and reduce energy expenditure. In cancer cachexia these adaptations do not appear to compensate adequately, and a situation more akin to the so-called 'metabolic response to trauma' develops, with continuing breakdown of body stores and increased energy expenditure (Falconer *et al.* 1994; Brennan, 1997). A wide spectrum of changes in nutrient metabolism is seen in weight-losing cancer patients. Insulin resistance, glucose intolerance, increased glucose production and consumption, and increased Cori cycle activity have all been demonstrated (Chlebowski *et al.* 1982; Edén *et al.* 1984; Holroyde *et al.* 1984; Shaw & Wolfe, 1987). A decrease in

lipogenesis is seen due to decreased lipoprotein lipase (EC 3.1.1.34) activity (Jeevanandam *et al.* 1986; Vlassara *et al.* 1986). Protein turnover is altered (Fearon *et al.* 1988; Melville *et al.* 1990) and this may be closely related to the development of an hepatic acute-phase response.

At diagnosis about 40 % of patients with advanced pancreatic cancer display an acute-phase protein response. Close to the time of death this proportion rises to 80 % (Falconer *et al.* 1995). The acute-phase protein response is an alteration in the balance of protein production by the liver, usually in response to injury, trauma or infection, in an attempt to aid the prevention of ongoing tissue damage, the eradication of infecting organisms and the activation of repair processes (Baumann & Gaudie, 1994). The presence of an acute-phase protein response in pancreatic cancer patients, as measured by an elevated serum C-reactive protein level, is strongly associated with a shorter survival (Falconer *et al.* 1995). It has been suggested that an imbalance between the amino acid composition of acute-phase proteins and skeletal muscle, the body's labile amino acid reserve, helps drive the accelerated wasting seen during an acute-phase response (Reeds *et al.* 1994).

Overall, these metabolic changes result in a diversion of nutrients away from peripheral tissues and increased expenditure of energy. In the acute situation, such as trauma or infection, the net effect is presumably beneficial in supplying the nutrients and proteins to aid the defence of the body, but in a chronic condition such as cancer these changes can lead to accelerated loss of lean tissue.

Anorexia in patients with advanced cancer can often be due to obstruction of the gastrointestinal tract, pain, depression, anxiety, steatorrhoea, constipation, general debility and the effects of treatments such as opiates, radiotherapy and chemotherapy. However, there remain many patients with advanced cancer in whom there is no overt cause of a reduced food intake. Weight loss can begin early in the course of malignant disease and the degree of wasting may correlate poorly with tumour burden. Thus, it would appear that, in some individuals, the anorexia and metabolic changes of cachexia are driven by mediators produced either by the tumour directly or by the body in response to the tumour.

Mediators of the cachectic state

Cytokines, including tumour necrosis factor, interleukins-1 and -6, ciliary neurotrophic factor and interferon- γ have been shown to induce some of the features of cachexia following

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administration to animals or human subjects (Michie *et al.* 1988; Starnes *et al.* 1988; Hellerstein *et al.* 1989; Strassmann *et al.* 1992; Espot *et al.* 1996). Elevated serum levels of tumour necrosis factor and interleukin-6 and the soluble receptors for tumour necrosis factor have been found in cancer patients, and in some instances these have correlated with severity of disease or weight loss (Aderka *et al.* 1991; Knapp *et al.* 1991; Kurzrock *et al.* 1993; Falconer *et al.* 1994; Preston *et al.* 1995; Staal-van den Brekel *et al.* 1995). However, often the pattern of symptoms and metabolic changes produced by exogenous cytokines differs from that of classical cachexia, and antibody-blocking experiments have shown only a limited ability to reverse these changes (Mahoney *et al.* 1988; Langstein & Norton, 1991; McNamara *et al.* 1992). Thus, the relevance of cytokines within the circulation may only be limited. Increased production of tumour necrosis factor and interleukin-6 by isolated peripheral-blood mononuclear cells of patients with cancer has also been observed and is in keeping with a local action for these cytokines (Aderka *et al.* 1985; Falconer *et al.* 1994). In pancreatic cancer such enhanced cytokine production correlates well with hypermetabolism and an acute-phase response (Falconer *et al.* 1994). Most of the pro-inflammatory cytokines, but primarily interleukin-6, have been shown to induce the hepatic acute-phase protein response (Heinrich *et al.* 1990; Oldenburg *et al.* 1993; O'Riordain *et al.* 1995; Espot *et al.* 1996). Thus, cytokines are likely to work *in vivo* at a local level through a complex network of interrelationships, they stimulate acute-phase protein production and probably also play a wider role in cachexia.

The source of pro-inflammatory cytokines in cancer cachexia is not clearly established. Tumour cells may produce pro-inflammatory cytokines themselves (Wigmore *et al.* 1994) and host peripheral-blood mononuclear cells may produce these cytokines in response to the presence of the tumour (Falconer *et al.* 1994). In addition there would appear to be amplification loops involving the tumour, with interaction of two or more cytokines (Yasumoto *et al.* 1995). It is also possible that the host further modulates the response to the cytokine network since neuroendocrine hormones will affect the production of acute-phase proteins (O'Riordain *et al.* 1995). Different clones of cancer cell lines produce similar patterns of cytokines in mouse models but have very different effects on host weight (Soda *et al.* 1994). It appears that this may be due to the production of other tumour-specific cachectic factors in association with conventional cytokines.

Changes in neuroendocrine hormone levels and target-organ sensitivity are also observed in cachexia. In weight-stable patients with pancreatic cancer, increased insulin secretion has been found with peripheral insulin resistance (Gullo *et al.* 1993). However, in trials in which weight-losing patients were included, a markedly reduced insulin response to feeding was seen. Changes in insulin production seem to be unrelated to loss of pancreatic tissue (Schwartz *et al.* 1978; Fox *et al.* 1985; Cersosimo *et al.* 1991). Elevated cortisol and glucagon levels have also been described (Schaur *et al.* 1979; Burt *et al.* 1983; Holroyde *et al.* 1984). These changes may be stimulated by cytokines (Michie *et al.* 1988; Starnes *et al.* 1988) and may tend to amplify the acute-phase response (Baumann & Gaudie, 1994). Infusion

of hydrocortisone or cortisol, glucagon and adrenalin in human subjects produces many of the features of the acute-phase response, including increased energy expenditure, negative N balance, C-reactive protein production and glucose intolerance (Bessey *et al.* 1984; Watters *et al.* 1986).

The role of leptin (the recently identified protein produced by adipocytes which regulates food intake and body weight) in cachexia remains to be clarified. The production and end-organ effects of leptin are modulated by cytokines and glucocorticoids, thus it may have a part to play in mediating cachexia (Grunfeld *et al.* 1996; Schwarz *et al.* 1997).

It is also possible that novel tumour-specific factors may mediate weight loss in cancer. A 24 kDa glycoprotein found in the urine of cachectic cancer patients has recently been characterized. This causes enhanced skeletal muscle proteolysis when given to mice, and appears distinct from known cytokines (McDevitt *et al.* 1995; Todorov *et al.* 1996; Cariuk *et al.* 1997). A lipid-mobilizing factor similar to zinc- α_2 -glycoprotein (an acute-phase protein) has also been isolated from the urine of cachectic cancer patients. This produces marked lipolysis in mouse models and in human adipocytes cultured *in vitro* (Tisdale, 1996).

Treatment of weight loss in cancer

The best way to cure cancer cachexia is to cure the cancer. However, this is only an option for the minority of patients. The next most obvious way to treat this phenomenon would be to supplement nutritional intake. However, studies of hyperalimentation in cancer cachexia using enteral or parenteral supplementation have been disappointing, producing only limited weight gain, mainly of water and fat (Nixon *et al.* 1981; Cohn *et al.* 1982; Evans *et al.* 1985; Klein *et al.* 1986; Lipman, 1991; Ng & Lowry, 1991). Oral supplementation is often limited by anorexia and early satiety, but even when a limited increase in energy and N intake has been achieved this has not led to significant weight gain or clinical benefit (Oveson *et al.* 1993a).

Numerous other agents have been suggested to be useful in cachexia, such as the anti-serotonergic agent cyproheptadine, the pro-kinetic agent metoclopramide, the corticosteroid dexamethasone, the progestogens medroxyprogesterone acetate and megestrol acetate, the gluconeogenesis inhibitor hydrazine sulphate and the psychotropic agent tetrahydrocannabinol, but none has lived up to its promise (Chlebowski *et al.* 1987; Beck & Tisdale, 1989, 1990; McMillan *et al.* 1994; Nelson *et al.* 1994; Gebbia *et al.* 1996; Simons *et al.* 1996) and many of these agents have significant additional side-effects.

n-3 Polyunsaturated fatty acids

Eicosapentaenoic acid is the major metabolically-active *n*-3 fatty acid in man. It is made by marine algae and is found in the diet as a component of fish oil.

Fish oil supplements rich in *n*-3 fatty acids have been shown to reduce production of the cytokines interleukin-1, interleukin-6 and tumour necrosis factor by mononuclear cells in normal volunteers, and this effect is maintained for some weeks after stopping supplementation (Endres *et al.* 1989; Cooper *et al.* 1993; Meydani *et al.* 1993). Fish oil also

increases T-suppressor : helper cells, decreases T-cell proliferative response to mitogens, decreases the delayed-hypersensitivity skin response and reduces neutrophil chemotaxis (Lee *et al.* 1985; Endres *et al.* 1989; Meydani *et al.* 1993; Calder, 1996).

Eicosapentaenoic acid has also been shown to inhibit fat and protein breakdown in animal models of cancer cachexia (Tisdale, 1996), and it has been suggested that this is due to inhibition of the end-organ effects of tumour-derived lipolytic and proteolytic factors. Furthermore, eicosapentaenoic acid may modify the response of hepatocytes to pro-inflammatory cytokines in terms of acute-phase protein production (Wigmore *et al.* 1997b).

Thus, it would seem that *n*-3 fatty acids can affect not only the production of pro-inflammatory mediators but also their end-organ effects. There are numerous mechanisms by which this may occur. Polyunsaturated fatty acids influence the activity of a number of receptors and enzymes which have a fundamental role in cellular signalling. When agonists stimulate receptors in the cell membrane they may activate adenylate cyclase (EC 4.6.1.1) or a phospholipase, the second messenger products of which (lipids in the case of phospholipases) influence the actions of cAMP-dependent protein kinase and protein kinase C respectively. *n*-3 Fatty acids have been shown to influence the effects of adenylate cyclase (Alam *et al.* 1988; Tisdale, 1993), phospholipase A₂ (EC 3.1.1.4) (Ballou & Cheung, 1985), cAMP-dependent protein kinase (Speizer *et al.* 1991) and protein kinase C (Speizer *et al.* 1991; Holian & Nelson, 1992). Eicosapentaenoic acid also binds to membrane voltage-sensitive Na channels and may alter the conductance of the channel (Kang & Leaf, 1996), and *n*-3 fatty acids bind to the cytoplasmic glucocorticoid receptor at a site different from the hormone-binding site and markedly reduce its affinity for the hormone (Vallette *et al.* 1991; Sumida *et al.* 1993).

Other mechanisms by which *n*-3 fatty acids may modulate inflammation include interaction with peroxisome proliferator-activated receptor- α which is a gene transcription factor that induces the breakdown of leukotrienes and, thus, has a role in limiting the duration and extent of inflammation. A variety of polyunsaturated fatty acids, including eicosapentaenoic acid, and leukotrienes themselves appear to increase the activity of this factor (Keller *et al.* 1993; Devchand *et al.* 1996). Alternatively, the C₂₀ polyunsaturated fatty acids are metabolized by cyclo-oxygenase into the prostanoids, prostaglandins and thromboxanes, and by 5-lipoxygenase (EC 1.13.11.12) into the leukotrienes. The *n*-6 fatty acid arachidonic acid is the major precursor for these substances in man and gives rise to the 2-series prostanoids (e.g. thromboxane A₂ and prostaglandin E₂ and I₂) and the 4-series leukotrienes (leukotriene B₄, C₄ etc.). In contrast, eicosapentaenoic acid is also metabolized by these enzymes, but into the 3-series prostanoids and 5-series leukotrienes. Leukotrienes are involved in regulating inflammatory responses. 5-Series leukotrienes are less active and compete with those of the 4-series for binding sites, resulting in anti-inflammatory effects (Fischer & Weber, 1983; Lee *et al.* 1985; Leaf & Weber, 1988; Fitzgerald *et al.* 1989; Nordøy & Dyerberg, 1989; Schmitt & Dyerberg, 1989).

Clinical studies using eicosapentaenoic acid-based preparations in cancer cachexia

We have hypothesized that there is a block to the accretion of lean body mass in cachectic patients, in part, attributable to enhanced pro-inflammatory cytokine release. By down-regulating cytokine production, fish oil or eicosapentaenoic acid supplementation should modulate this pro-inflammatory state. To test whether supplementation with fish oil could affect the progress of cachexia in patients with advanced pancreatic cancer we have conducted a study using Maxepa (Seven Seas, Hull, UK), a mixed marine triacylglycerol preparation containing (g/kg) 180 eicosapentaenoic acid and 120 docosahexaenoic acid. This was given orally at a median dose of 12 g/d (equivalent to 2 g eicosapentaenoic acid/d) to eighteen patients with unresectable pancreatic cancer. Before treatment, all patients were losing weight at a median rate of 2.9 kg/month. After supplementation for 3 months, patients had a median weight gain of 0.2 kg/month with less than half the patients continuing to lose weight. There was no change in the percentage total body water over the period of the study. This regimen also produced a fall in the serum C-reactive protein level, suggesting that some of the metabolic abnormalities of pancreatic cancer can be reversed, resulting in the stabilization of weight (Wigmore *et al.* 1996b).

Subsequently we have examined the role of eicosapentaenoic acid alone in reversing cachexia. Twenty-seven patients with unresectable pancreatic cancer were given 6 g eicosapentaenoic acid (95 % pure)/d orally after a 4-week dose-escalation period. Patients were losing a median of 2.0 kg/month at baseline. After 4 weeks patients had a median weight gain of 0.75 kg, and this effect remained at 3 months with a median weight gain of 0.25 kg/month. Again, there was no change in the percentage total body water over the course of the study, confirming that the achievement of weight stability was not due to changes in hydration (Barber *et al.* 1997). There were no serious side-effects in these studies and median survival was approximately 7 months.

A subgroup of six patients from the latter study underwent measurement of interleukin-6 and tumour necrosis factor production in peripheral-blood mononuclear cells *ex vivo* and of the acute-phase protein response *in vivo* before and after the administration of eicosapentaenoic acid for the 1-month dose-escalation period. These patients showed a significant fall in their mononuclear cell production of pro-inflammatory cytokines and a fall in the level of the acute-phase response as measured by C-reactive protein (Wigmore *et al.* 1996a, 1997a).

Eicosapentaenoic acid, therefore, would seem capable of arresting the further development of cachexia in patients with advanced pancreatic cancer. This may be related specifically to the down-regulation of pro-inflammatory cytokine-mediated metabolic events. Perhaps more likely, however, is a complex interaction between eicosapentaenoic acid and the production or end-organ effects of (a) protein and lipid mediators of the inflammatory response, (b) tumour-specific catabolic mediators and (c) counter-regulatory neuro-endocrine hormones.

Conclusion

The previously described phase 1 and 2 clinical studies with eicosapentaenoic acid in patients with cancer cachexia point to a potential role for lipids as modulators of the wasting process. The precise contribution from the specific and non-specific components of the immune system to the generation of the inflammatory mediators involved in cancer cachexia in human subjects is poorly understood. However, if current randomized phase 3 studies with eicosapentaenoic acid prove effective, then this should at least provide a model for further study of the interaction between lipids and the role of the immune system in the wasting associated with a variety of human diseases.

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