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The mechanisms and treatment of weight loss in cancer

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It is always a very great pleasure when one meets an individual whose work has been of considerable scientific importance. I was honoured to have met Sir David Cuthbertson on several occasions towards the end of his life and, thus, it gives me particular pleasure to be invited by the Clinical Metabolism and Nutritional Support Group of the Nutrition Society to give this lecture in his memory. Sir David was particularly interested by the metabolic response to trauma and in this lecture I wish to dwell on another part of the spectrum of the response to injury in terms of the metabolic disturbance in patients with cancer.

It goes without saying that the majority of patients with cancer will eventually lose weight and a proportion become emaciated to the extent that they appear to die of starvation. This syndrome is known as cancer cachexia, the term cachexia being derived from the Greek words 'kaxos' and 'hexis' meaning poor condition. The patient with cachexia is characterized by a group of symptoms including anorexia, early satiety, marked weight loss, aesthenia, anaemia and oedema. The importance of weight loss in cancer has long been recognized. As far back as 1932 Warren in a post-mortem study estimated that as many as 22% of patients with cancer die primarily as a result of cachexia (Warren, 1932). More modern studies would put this percentage at perhaps 10 (Inagaki *et al.* 1974). Nevertheless, currently the majority of cancer patients die from sepsis, and there remains the complex inter-relationship between poor nutritional status and a propensity to infection.

Unfortunately, for the majority of patients whose cancer has spread beyond the organ of origin, neither surgery, radiotherapy or chemotherapy is able to offer a cure. With the recognition of the morbidity and mortality associated with cachexia, the past 15 years have seen attempts to use nutritional support to try to reverse the nutritional deficit associated with progressive cancer growth. These studies have, however, not met with great success. Conventional nutritional support does not readily reverse the nutritional deficits associated with progressive tumour growth (Nixon *et al.* 1981; Cohn *et al.* 1982) and not surprisingly nutritional support has failed to reduce overall morbidity and mortality (Brennan, 1981; Chlebowski, 1986). These disappointing results have led investigators back to the drawing board to try to understand the fundamental reasons for

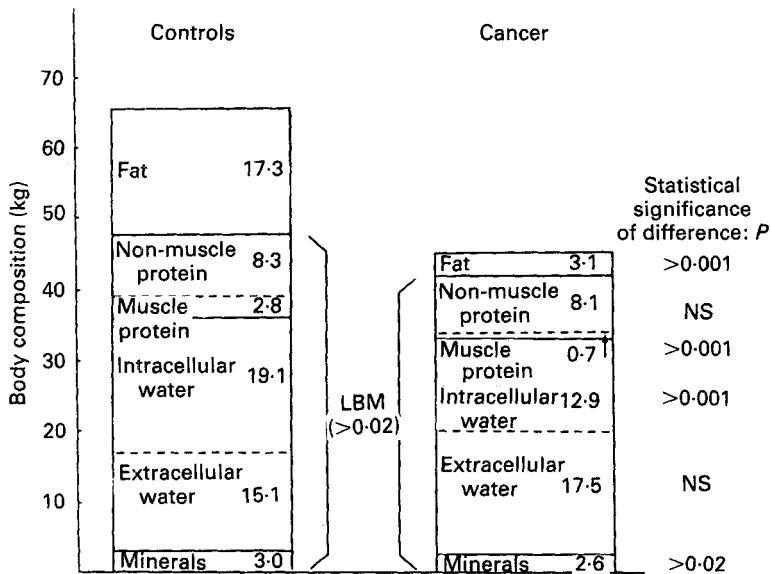


Fig. 1. Body composition of a group of lung cancer patients (n 6) who had lost 30% of their pre-illness stable weight compared with a group of controls matched for age, sex, height and pre-illness stable weight of the cancer patients. NS, not significant; LBM, lean body mass.

weight loss to see if we can design specific forms of nutritional support or metabolic intervention which might influence more favourably the host-tumour relationship.

CHANGES IN BODY COMPOSITION ASSOCIATED WITH CANCER CACHEXIA

In order to understand the mechanisms of weight loss in cancer, perhaps the first step should be to try to quantify the nature and extent of tissue loss. Fig. 1 shows the results of a study undertaken by us on a group of lung cancer patients who had lost 30% of their pre-illness stable weight (Preston *et al.* 1987). The body composition of these patients was compared with a group who were matched for the age, sex, height and pre-illness stable weight of the cancer patients. In the study, body protein was divided into non-muscle and muscle compartments using analysis based on fixed nitrogen:potassium ratios as advocated by Burkinshaw *et al.* (1978). The most dramatic change in body composition was an 85% fall in total body fat. Clearly this reflects a prolonged, severe, negative energy balance. Second, there was marked skeletal muscle wasting with a 75% fall in skeletal muscle protein mass. This certainly reflects the clinical condition of these patients and predicts their mode of death from immobility and hypostatic pneumonia. Interestingly, the non-muscle protein compartment was relatively preserved and this would differentiate cancer cachexia from simple starvation. Several mechanisms have been proposed to account for preservation of the visceral protein compartment in cancer cachexia. First, the mass of the tumour might contribute but since human tumours rarely achieve a size greater than 1 kg, this seems unlikely. Second, it has been proposed that the tumour might produce factors which stimulate protein production by the visceral compartment, a concept I will return to later.

Table 1. *Causes of reduced food intake in cancer patients*

Tumour obstructing gastrointestinal tract
Radiotherapy/chemotherapy-induced nausea and vomiting
Altered taste sensitivity
Depression, stress, anxiety
Oral ulceration or infection
Learned food aversion
Atrophy of the gastrointestinal tract
Altered host metabolism, e.g. lactic acidosis, hypercalcaemia
General debility/weakness
Tumour products

ROLE OF ANOREXIA

Having documented such large negative energy and N deficits how could these have arisen? In terms of energy, a negative energy balance could arise as a result of a rise in energy expenditure, a fall in the energy intake or a combination of the two. The measurement of food intake in human studies is notoriously difficult. However, accepting these limitations it was documented (using a 24 h dietary recall technique) that when compared with predicted values, the food intake of the cachectic cancer patients whose body composition had been studied was markedly reduced both in terms of energy (52% reduction) and protein (25% reduction). It is well recognized that there are numerous factors which may contribute to anorexia in cancer patients and the list shown in Table 1 is by no means exhaustive. From our food intake study it is clear that anorexia can contribute significantly to continuing weight loss. However, the problem is that these patients were already cachectic when studied and, therefore, it is not clear whether the anorexia was giving rise to the cachexia or vice versa. In order to resolve this conundrum, various investigators have looked at food intake during the early phase of weight loss (Costa *et al.* 1981) but due to the difficulties of accurate documentation and substantial inter-individual variation, no clear answer has been achieved. This has led investigators to concentrate on the question of whether a rise in energy expenditure contributes to the negative energy balance of patients and, thus, the considerably important area of anorexia has been left largely unexplored.

ROLE OF ABNORMAL PROTEIN METABOLISM IN HYPERMETABOLISM

Returning to the question of hypermetabolism, we have been particularly interested in the hypothesis that the rate at which protein turns over in the body is increased and that the energy cost of this might lead to a rise in resting energy expenditure and account for accelerated weight loss. Previous investigators have used a variety of labels and tracers to study whole-body protein kinetics and results have been variable. Some have shown no increase (Emery *et al.* 1984a; Glass *et al.* 1983) whilst others have found a marked increase (Heber *et al.* 1982; Eden *et al.* 1984; Jeevanandam *et al.* 1984). We, therefore, decided to look at a large homogeneous group of patients with colon cancer (Fearon *et al.* 1988b). We determined N kinetics using a primed constant infusion of [¹⁵N]glycine with tracer flux estimated from ¹⁵N enrichment in urea and ammonia at the end of the 24 h infusion period. Rates for protein synthesis and degradation were derived

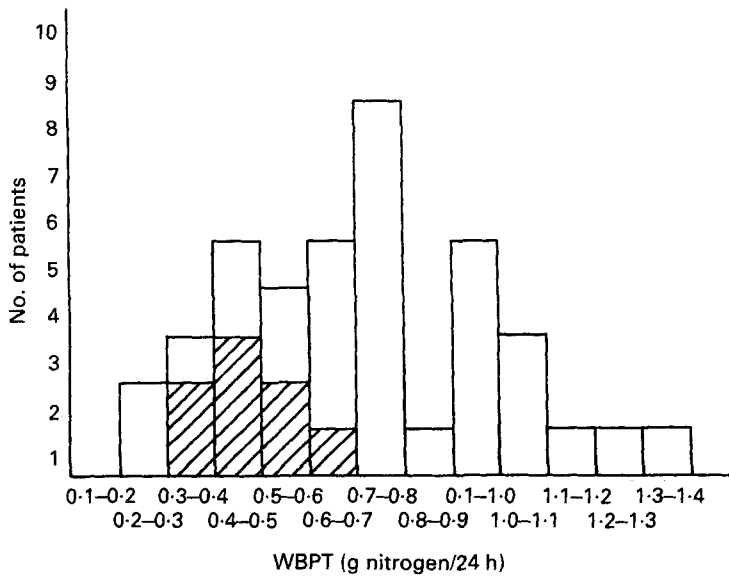


Fig. 2. Whole-body protein turnover (WBPT) measured with a primed, constant 24 h infusion of [^{15}N]glycine in a group of patients with colorectal cancer (\square ; n 38) and in a group of healthy controls (▨ ; n 8).

using a stochastic model and the results for thirty-eight patients and eight healthy controls are shown in Fig. 2. It is clear that within the cancer population there is a substantial number of patients who appear to be normal, but equally there is a group who appear to have a greatly elevated rate of whole-body protein turnover. However, in terms of the influence of protein turnover on energy expenditure there was no correlation between these two variables. A lack of correlation could be due to the energy cost of whole-body protein turnover forming such a small component of resting energy expenditure that with substantial inter-individual variation any relationship between these two variables is lost. Alternatively, it may be that the energy costs of such elevated flux is significant but that other metabolic processes are changed and, thus, energy homeostasis is maintained. Finally, it may be that the elevated rate of tracer flux does not truly reflect the rate of protein turnover in the whole body and that some compartmentation of the tracer may be elevating the derived rate of protein turnover. These questions still have to be resolved. Nevertheless, that this protein kinetic measurement reflects the biology of the patient is indicated by the observation that whole-body protein synthesis increased in a stepwise manner with anatomical stage of disease (Fig. 3).

HEPATIC PROTEIN METABOLISM

With such difficulty in interpreting the results of whole-body tracer flux studies, we decided to look at rates of protein synthesis in individual tissues of the body. It has been suggested that the liver might be one of the principal sites at which protein metabolism is altered in the cancer host (Eden *et al.* 1984). Liver protein synthesis is thought to be divided roughly 50:50 between structural and export proteins. In patients with advanced cancer, production of certain export proteins can be increased, e.g. the acute-phase

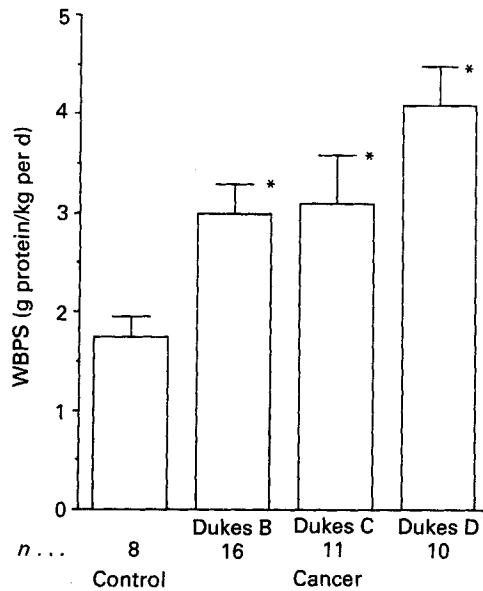


Fig. 3. Rates of whole-body protein synthesis (WBPS) measured with a primed, constant 24 h infusion of [^{15}N]glycine in a group of patients with colorectal cancer (n 38) and in a group of healthy controls. Patients were staged at laparotomy according to Duke's classification (B, spread through bowel wall; C, spread to lymph nodes; D, hepatic metastasis). Values are means with their standard errors represented by vertical bars. Mean values were significantly different from those of healthy controls: * $P < 0.05$.

proteins (Cooper & Stone, 1979; Raynes & Cooper, 1983); however, little is known about hepatic structural protein synthesis. Clearly, the protein mass in an organ is determined by the balance between protein synthesis and degradation. We became particularly interested in the structural (non-export) component of liver protein synthesis with the observation that the organ volume of the liver and other viscera may increase in cancer cachexia (as opposed to a decrease observed in simple starvation (Heymsfield & McManus, 1985)); the obvious question being, could increased synthesis of hepatic non-export proteins contribute to our observed increase in whole-body protein kinetics? We, therefore, attempted to measure fixed hepatic protein synthesis using a primed, constant infusion of [^{15}N]glycine, but coordinated the start of laparotomy with the end of the infusion and at this point obtained a liver biopsy (Fearon *et al.* 1991b). The fractional synthetic rate in the liver was calculated by dividing the amount of [^{15}N]glycine incorporated into tissue protein per unit time, by the ^{15}N enrichment of free glycine obtained from a protein-free homogenate of liver tissue. Six patients undergoing elective cholecystectomy and six patients with colorectal cancer and hepatic metastases were investigated. The patients with cancer had lost approximately 10% of their pre-illness stable weight.

In the advanced cancer patients we confirmed the presence of an elevated rate of whole-body tracer flux but rather surprisingly the non-export hepatic protein synthesis fractional synthetic rate was depressed by about 30%. This draws an interesting parallel between cancer and sepsis where structural liver protein synthesis is also thought to be depressed and goes back to the concept that cancer falls somewhere in the spectrum

Table 2. Summary of changes (%) in tissue protein synthesis rates (skeletal muscle and liver) and energy expenditure in three different murine models of cancer cachexia

Tumour model	Protein synthesis*		Energy expenditure
	Muscle	Liver	
1. XK1 hypernephroma (Emery <i>et al.</i> 1984b)	↓ (70)	↓ (40)	↑ (40)†
2. Ehrlich ascites (Pain <i>et al.</i> 1984)	=	↑ (40)	-
3. MAC-16 (Plumb <i>et al.</i> 1991)	=	=	↑ (23)

* Measured by flooding [³H]phenylalanine method.

† Brooks *et al.* (1981).

between simple starvation and trauma or sepsis (Brennan, 1977). However, to return to our original questions, it would appear that any potential increase in hepatic volume must be due to a reduction in protein degradation rather than an increase in protein synthesis. Furthermore, non-export hepatic protein synthesis cannot be contributing to the observed increase in the rate of whole-body tracer flux. There must be another explanation for this.

ANIMAL MODELS OF CANCER CACHEXIA

While we had been studying these changes in humans a new animal model of cancer cachexia became available; namely, a chemically-induced adenocarcinoma of colon grown subcutaneously in NMRI mice. This model reflects the metabolic component of weight loss in cancer since there is a progressive loss of body-weight yet food intake remains constant. During the period of weight loss tumour volume remains less than 5% of the animal's total body-weight and, thus, it seems an appropriate model of human cancer cachexia. We have investigated this model using indirect calorimetry to measure total energy expenditure and an intravenous flooding dose of tritiated phenylalanine to measure rates of protein synthesis in the tissues (Plumb *et al.* 1991).

The results from three murine models of cancer cachexia (including the MAC-16 model) are summarized in Table 2. Rather uniquely, in each model similar methods have been used to investigate tissue protein synthesis rates (flooding-dose method) and energy metabolism (indirect calorimetry). Brooks *et al.* (1981) using a human XK1 hypernephroma grown in thymectomized/irradiated mice demonstrated a 40% increase in resting energy expenditure. However, Emery *et al.* (1984b) using the same tumour showed a marked reduction in protein synthesis both in skeletal muscle and liver. Clearly, the energy cost of protein synthesis in this model is not the cause of hypermetabolism. In contrast, Pain *et al.* (1984) have shown no change in muscle but an increase in liver protein synthesis in mice bearing the Ehrlich ascites tumour, a dramatically different pattern of change. Energy expenditure was not measured. With our own studies using the MAC-16 tumour (Plumb *et al.* 1991) we were not able to show any alteration in skeletal muscle or liver protein synthesis rates. However, energy expenditure was grossly elevated. It, therefore, becomes apparent that the alterations in energy and tissue protein metabolism which different tumours induce can vary markedly. This is a very important point to appreciate, particularly when trying to interpret the

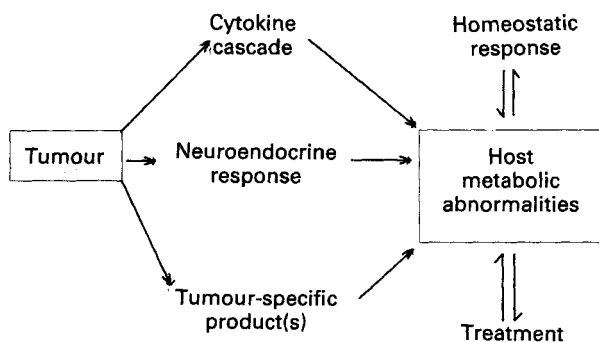


Fig. 4. Pathways by which a tumour may influence host metabolism.

myriad results which have been obtained in human studies. Many investigators have looked at small patient groups containing different types of tumour and not surprisingly results have been quite contradictory.

MEDIATORS OF METABOLIC CHANGES

Having considered the protein and energy metabolism of cancer patients it would be relevant to discuss what might account for the changes, whether they have prognostic significance and whether there are potential methods of correcting such abnormalities of metabolism? When considering how a tumour might influence the host, one has to account for the heterogeneity of the response to cancer. Some patients will remain weight-stable, and some will become profoundly cachectic. For those who lose weight this may be via a series of metabolic changes, through the development of anorexia, or via a combination of the two. Furthermore, there is tremendous heterogeneity in the metabolic response which a host may demonstrate and a whole variety of causes of reduced food intake. In fact, one might almost despair at trying to find one common final pathway to account for all these changes. Nevertheless, I think such heterogeneity gives us a clue. It suggests that for different tumours and even for patients with the same tumour we may be looking at entirely different mechanisms of weight loss. The point may seem obvious but it has been forgotten frequently in the past.

Trying to develop this theme further, at present it is clear that there are three potential pathways whereby a tumour can influence host metabolism (Fig. 4). For the past 50 years people have been searching for a tumour-specific product which might influence the metabolism of host cells. However, although neuroendocrine tumours are well known to produce hormones which have a profound effect on host metabolism, no cachexia-inducing tumour-product has been consistently isolated from human tumours.

The second pathway which might allow a tumour to alter host metabolism would be if the tumour activated the classical neuroendocrine response which so interested Sir David Cuthbertson. I think this area is worthy of much further study and in our own laboratory we have observed marked changes in the insulin:cortisol ratio which would favour the catabolism of host tissues (Selberg *et al.* 1990). However, one problem with this area is that it is very difficult to know whether such changes represent a primary abnormality or whether they may be a homeostatic response to a different change induced by the tumour.

Table 3. Results of a univariate survival analysis using Cox's proportional hazards model on a group of patients with colorectal cancer (n 32)

Variable*	χ^2	Statistical significance:
		P
log CRP:Alb	15.3	0.0001
log CRP	13.3	0.0003
Alb	10.0	0.0016
Duke's stage†	11.1	0.0039
WBPT	4.5	0.0358

CRP, serum C-reactive protein concentration; Alb, serum albumin concentration; WBPT, whole-body protein turnover measured with a primed constant 24 h infusion of [^{15}N]glycine.

* Assessed at time of diagnosis and survival determined 5 years later.

† Anatomical stage of disease.

Finally one comes to consider the area which has seen tremendous advances within the past few years, that being the role of cytokines in the metabolic changes associated with trauma, sepsis or cancer. One reason cytokines may be important is that macrophages and lymphocytes (some of the principal cell types to produce cytokines), are open to a whole variety of influences which might change the amount and type of cytokine produced in response to a given tumour antigen or tumour-induced inflammatory response. Thus, the cytokine cascade may well provide within the same tumour type some of the heterogeneity to which I have repeatedly referred.

THE ACUTE-PHASE PROTEIN RESPONSE IN CANCER

What evidence is there that cytokines are produced in the cancer host and are of importance in determining metabolic change? One of the principal changes that cytokines bring about is a redirecting of body protein metabolism away from peripheral tissues (e.g. skeletal muscle) and towards the liver with the production of acute-phase reactants. These proteins are thought to play a key role in body defences and in the restoration of homeostasis following injury. It has long been recognized that with tumour progression an acute-phase response may develop (Cooper & Stone, 1979). However, it would be important to state that not all patients with metastatic disease have an acute-phase response and neither do all patients with weight loss. The importance of this phenomenon is not that it is the single most important cause of weight loss but that it may be a significant contributor to net of catabolism of peripheral tissues in at least a proportion of individuals.

That the acute-phase response carries biological significance is suggested by our retrospective analysis of thirty-two of the colon cancer patients whose whole-body protein turnover we had studied some 5 years previously (Fearon *et al.* 1991a). By far and away the strongest predictor of shortened survival was the degree of acute-phase response at the time of diagnosis (Table 3). Moreover, this was a much stronger predictor than advanced anatomical stage of disease or the presence of an elevated rate of whole-body protein turnover.

Further evidence to support the significance of the acute-phase response comes from our recent study of the body cell mass (measured by total body K analysis) in patients

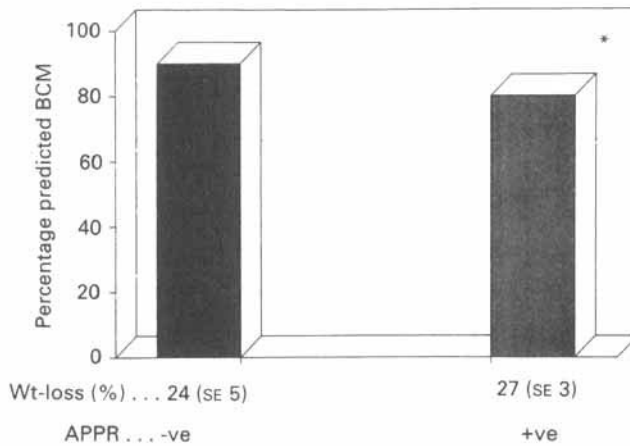


Fig. 5. Body cell mass (BCM; expressed as a percentage of predicted body cell mass) of patients with weight loss and oesophagogastric cancer. Patients are divided into those with (▨; serum C-reactive protein >10 mg/l) and without (■) an acute-phase protein response (APPR). BCM derived from patients' total body potassium. Mean value for subjects without APPR was significantly different from that for subjects with APPR: * $P < 0.05$.

with weight loss and oesophagogastric cancer. In this disease patients lose weight principally through a reduction in food intake. However, from Fig. 5 it can be seen that for equivalent degrees of weight loss (27 (SE 3) v. 24 (SE 5)%; not significant), patients with an acute-phase response had lost 20% of their predicted body cell mass, whereas patients with no acute-phase response had lost only 10%. Thus, in weight-losing cancer patients the presence of an acute-phase response is associated with accelerated loss of the vital body cell mass. Of course, it remains to be seen whether there is a cause and effect relationship between the acute-phase response and our observations on patients' body composition or duration of survival.

THE ROLE OF CYTOKINES IN CANCER CACHEXIA

The next question to consider is which cytokines give rise to the acute-phase response in cancer? Cytokines such as interleukin-1 (IL-1; Dinarello, 1984), interleukin-6 (IL-6; Gaudie *et al.* 1987) and tumour necrosis factor (TNF) (Warren *et al.* 1987) have been shown both *in vitro* and *in vivo* to elicit acute-phase protein production. In the patients with colon cancer whose liver protein metabolism has been studied (Fearon *et al.* 1991a), there was a strong acute-phase protein response as documented by a mean C-reactive protein concentration of 75 mg/l (Table 4). There has been much interest in the role of TNF in cancer cachexia (Balkwill *et al.* 1987; Sherry *et al.* 1989; Langstein *et al.* 1991) and previously it has been demonstrated that infusion of TNF into cancer patients can markedly increase serum C-reactive protein concentration (Selby *et al.* 1987). However, in the present study it was possible to detect circulating TNF in only three of six patients (and in those individuals in whom it was detected it was only observed at very low concentrations). IL-1 could not be detected in patients' serum. In contrast, levels of IL-6 were markedly increased (Table 4).

Table 4. *Acute-phase and serum cytokine concentrations of a group of weight-losing patients with advanced colorectal cancer compared with a group of weight-stable controls*
(Mean values with their standard errors)

	CRP (mg/l)		IL-6 (μ /ml)		TNF (>12 pg/ml)	IL-1 (>20 pg/ml)
	Mean	SE	Mean	SE		
Controls (n 6)	9	1	12	1	0/6	0/6
Cancer (n 6)	75*	19	121**	39	3/6†	0/6

CRP, C-reactive protein; IL-6, interleukin-6; TNF, tumour necrosis factor; IL-1, interleukin-1.

Mean values were significantly different from those of controls (Mann-Whitney U test): * $P < 0.05$, ** $P < 0.01$.

† Range 15–22 pg/ml.

Elevated IL-6 has also been noted in a variety of tumour-bearing mice (McIntosh *et al.* 1989). It is known that IL-6 is one of the main factors controlling hepatic acute-phase protein production in human hepatocytes (Gauldie *et al.* 1987) and, therefore, it is an attractive hypothesis that the acute-phase response in cancer is elicited by IL-6. This observation does not, however, rule out the possibility of localized cytokine production within the liver and either TNF or IL-1 (both of which are capable of inducing the production of IL-6) may be of major significance. Interestingly, it has been shown that administration of recombinant TNF to tumour-bearing mice leads to enhanced IL-6 production compared with controls (McIntosh *et al.* 1989). Thus, cytokines such as TNF may still have a key role in inducing the acute-phase response indirectly via an upregulated IL-6 response. However, in other studies, although anti-TNF antibodies administered to cachectic tumour-bearing mice have been shown to reduce anorexia and some aspects of tissue wasting, there was no change in the acute-phase response (Sherry *et al.* 1989). Such findings bring into question again the role of circulating TNF as a direct inducer of the acute-phase proteins in cancer but give force to the argument that TNF contributes in some part to cachexia independent of this mechanism.

CONTROL OF CYTOKINE PRODUCTION

Lastly, in relation to the acute-phase proteins, I want to consider why some cancer patients develop this response whilst others do not. Clearly, the production of cytokines could be the result of stimulation by a tumour-specific antigen or may simply be the result of a non-specific inflammatory response as a result of tissue destruction. However, further variability might be introduced depending on the ability of the patient's immune system to respond to such stimuli. I have already mentioned the studies by McIntosh *et al.* (1989) showing enhanced IL-6 production by tumour-bearing mice in response to exogenous TNF. We now have preliminary evidence that when cancer patients' isolated peripheral blood mononuclear cells are exposed to endotoxin (another potent stimulus for cytokine production) the more immunosuppressed the patient, as measured by response to the mitogen phytohaemagglutinin, the greater the release of TNF (Gough *et al.* 1992). It is known that lymphocytes can release cytokines (e.g. interleukin-4) which can down-regulate monocyte production of IL-6 and TNF (te Velde *et al.* 1990). Thus,

one explanation for our results is that poor lymphocyte function in the cancer patient may be responsible for the increased release of cytokines. Such inter-individual variability in cytokine production may, thus, contribute to the variable development of an acute-phase response. Furthermore, if this mechanism is important, then improvement of lymphocyte function might provide a method of dampening the production of cytokines in these patients and, thereby, reducing the level of the acute-phase response. Thus, immunoregulation by nutritional or pharmacological means may be an appropriate mode of therapy for the cachectic cancer patient.

TUMOUR ENERGY METABOLISM AS A TARGET FOR ANTI-NEOPLASTIC THERAPY

So far I have concentrated on the nutritional consequences of progressive tumour growth but it is important, when considering nutritional aspects of the host–tumour relationship, not to forget the specific nutritional requirements of the tumour. With knowledge of these requirements it might be possible to develop a selective and, therefore, non-toxic method of reducing tumour growth rate. It goes without saying that the best way to cure cachexia is to cure the cancer!

It was as far back as the 1930s that Warburg (1930) first drew attention to the energy metabolism of tumour cells. With his initial experiments he concluded that in tumours glycolysis is accelerated and is not suppressed in the presence of oxygen. He suggested that respiration was always disturbed in malignant cells and went further to suggest that disturbed energy metabolism was the actual reason for neoplastic transformation (Warburg, 1930). This last part of his hypothesis was certainly not the case. Nonetheless, further investigation has gone on to document a variety of abnormalities in numerous cell lines. In particular, Pederson (1978) has shown that the mitochondria of different tumours have a very wide spectrum of abnormality, including changes in morphology, enzyme content and function. This group has also shown that although glycolysis may be accelerated in certain poorly differentiated tumours, the majority of ATP generation comes from oxidative phosphorylation (Nakashima *et al.* 1984).

PHARMACOLOGICAL MANIPULATION OF TUMOUR GROWTH

Previous investigators who have attempted to use tumour energy metabolism as a target for selective anti-neoplastic therapy have usually concentrated either on glycolysis or on oxidative phosphorylation. We, in contrast, have tried to manipulate both pathways simultaneously to try to obtain a greater degree of selectivity. In terms of inhibiting mitochondrial function, we have been particularly interested in the group of compounds known as the rodamine dyes. Rodamine-6G is a lipophilic, fluorescent, positively-charged dye, which is known to accumulate in the mitochondria of living cells and has been shown to inhibit oxidative phosphorylation (Gear, 1974). The rodamine dyes are of particular interest in anti-cancer therapy because they have been shown to be selective in their inhibition of mitochondrial function when transformed and non-transformed cell lines have been compared *in vitro* (Lampidis *et al.* 1983).

In terms of inhibiting glycolysis the agent most commonly used in anti-cancer therapy has been the glucose analogue 2-deoxy-D-glucose (Ball *et al.* 1957). However, a different approach has been adopted by inducing hypoglycaemia and thereby reducing the amount

of available glucose. For this 3-mercaptopycolinic acid (3MPA) which inhibits gluconeogenesis by inhibiting phosphoenolpyruvate carboxykinase (*EC* 2.7.1.40; Di Tullio *et al.* 1974) has been used. Therefore, a combination of 3MPA and rodamine-6G (R6G) in rats with the Walker 256 carcinosarcoma has been investigated (Fearon *et al.* 1987). Either 3MPA or R6G alone had no significant effect on tumour growth. In contrast, the combination reduced final tumour size by almost 50%. Such results suggest that simultaneous manipulation of both sources of intracellular ATP may be used to achieve a more selective control of tumour growth.

DIETARY MANIPULATION OF TUMOUR GROWTH

Ketone bodies are fat-derived energy substrates which may act to reduce gluconeogenesis by inhibiting muscle protein degradation. Several tumour cell lines have been shown to be deficient in the mitochondrial enzymes which allow the cell to use ketone bodies for energy production (Tisdale & Brennan, 1983; Fearon *et al.* 1985). Moreover, it has been suggested that the *in vitro* growth rate of certain tumour cell lines may be reduced by the presence of 3-hydroxybutyrate at a concentration which is observed in simple starvation (Magee *et al.* 1979). Thus, the induction of systemic ketosis in the cancer-bearing host has been suggested as a method of selectively feeding the host while restricting the supply of glucose to the tumour and reducing tumour growth rate (Conyers *et al.* 1979; Williams & Matthaei, 1981; Tisdale, 1982).

The evidence which supports the hypothesis that ketone bodies reduce protein breakdown in skeletal muscle is controversial. The initial studies by Sherwin *et al.* (1975) suggested that the release of alanine from skeletal muscle may be reduced by ketone bodies, thereby accounting for N conservation in starvation. Subsequently, Pawan & Semple (1983) demonstrated that administration of DL-3-hydroxybutyrate to obese subjects on very-low-energy diets significantly reduced net protein loss and increased the fat:lean ratio of tissue loss. However, the latter study was criticized because the administration of salts of organic acids has a protein-sparing effect by reducing the need for ammonium ion excretion by the kidneys, and the same result can be achieved with an equal amount of sodium bicarbonate (Miles & Hammond, 1983). Thus, the current literature does not support a direct effect of ketone bodies on proteolysis (Miles *et al.* 1983). This has been confirmed in a recent study of cachectic cancer patients (Fearon *et al.* 1988a), where a medium-chain-triacylglycerol diet supplemented with D-3-hydroxybutyrate did not significantly influence N balance or turnover when compared with an isoenergetic, isonitrogenous non-ketogenic diet.

The effect of systemic ketosis on tumour growth rate is similarly controversial. In our own studies the growth rate of the Walker 256 tumour in rats was uninfluenced by the presence of systemic ketosis induced by a medium-chain-triacylglycerol diet (Fearon *et al.* 1985). In contrast, Tisdale *et al.* (1987) have shown that both weight loss and tumour weight are reduced in animals bearing the MAC-16 tumour when they are fed on a ketogenic diet. These contrasting results may simply reflect the different substrate requirements of different tumours. Alternatively, the response of host metabolism to the induction of ketosis may be different, depending on the tumour type involved. Interestingly, it has been suggested that altering the quality (increased *n*-3 fatty acids) of ingested fat rather than the quantity may be a more effective method of favourably altering the host-tumour relationship by dietary means (Beck *et al.* 1991).

SUMMARY

Anorexia and a reduced food intake are probably the major cause of continuing weight loss in the cancer patient. In future much more attention will have to be paid to this area if we are to achieve an improvement in patients' nutritional status. Energy-dependent metabolic cycles such as protein turnover, but including other cycles such as glucose-lactate cycling, probably compromise the adaptation to semi-starvation and account for accelerated weight loss. These abnormalities may be influenced by a variety of factors including tumour specific products, alterations in neuroendocrine activity and mediators of the inflammatory response. Manipulation of cytokine production or the effects of such cytokines provide a new approach to the management of cancer cachexia. It is important not to forget that the altered energy metabolism and substrate requirements of tumour cells may provide a new target for effective anti-neoplastic therapy and there are a host of new approaches available in this area for future investigation.

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