Review

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Metabolic effects of cancer

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The potential causes of deranged metabolism in cancer are discussed with emphasis on changes in energy metabolism of glucose, fat and protein. The implications of these changes for the treatment of cachexia are then considered

Keywords: Cancer, cachexia, metabolism, glucose, fat, protein, parenteral nutrition

Cachexia is commonly the cause of death in cases of advanced malignancy[1], and cancer patients who have lost a significant percentage of their body-weight before surgical treatment are subject to a much greater risk of postoperative mortality and morbidity[2–4]. There is no doubt that reduced oral intake resulting from anorexia or obstruction of the gastrointestinal tract plays a very significant role in the development of the cancer cachexia syndrome. However, whereas the metabolic response to uncomplicated starvation acts to limit the consumption of host reserves, in the cachectic cancer patient there is often an accelerated mobilization and oxidation of energy substrates and loss of nitrogen[5–7]. These changes are a consequence of alterations in intermediary metabolism associated with cancer[8].

Understanding the metabolic response to cancer has become increasingly important over the last two decades with the introduction of effective and safe parenteral nutrition techniques[9]. It is now possible to provide sufficient calories and nitrogen to all cancer patients, but the metabolic milieu associated with advanced cancer may retard the restoration of lean body mass[10]. In the following review the manner in which malignant tumours affect host metabolism will be presented, and the effectiveness of the available therapeutic options will be discussed.

One consistent feature of data from metabolic studies in cancer patients is the range of response between individuals, even when comparing those with the same diagnosis and stage of disease[11]. The interpretative difficulties are compounded by many reports comparing small heterogeneous groups of cancer patients with equally small groups of controls, which may well be poorly matched for age or weight loss. To overcome some of these problems laboratory models have been developed in which malignant cells of identical genotype are transplanted into genetically uniform animals[12]. However, the growth dynamics and tumour-to-host weight ratios frequently do not resemble those observed in patients, and this review will present mainly data from patient studies.

Changes in energy metabolism

The hypothesis that tumour bearing increases energy expenditure and results in a cumulative negative energy balance and progressive weight loss has been exhaustively investigated, and there is now a substantial body of supportive evidence. Bozzetti *et al.*[13] studied a heterogeneous group of patients with advanced tumours and found a highly significant correlation between the resting metabolic expenditure (RME) and the magnitude of weight loss, and other groups of researchers have similarly found elevated RMEs in patients with cancer cachexia[14–18]. There are a few anecdotal reports of cases in which successful antineoplastic therapy has reduced energy expenditure in hypermetabolic patients[14,18], suggesting that the presence of the tumour itself is capable of elevating the RME. However, hypermetabolism is not an invariable finding in cancer patients who have lost weight, with large series having been reported recently which have failed to demonstrate a significant increase in the resting metabolic rate of cachectic cancer patients when compared with patients with weight loss of a similar magnitude due to benign disease or with weight-stable cancer patients[19,20]. In a series consisting of 200 patients with a variety of tumour types 29 per cent had a resting metabolic expenditure that was 10 per cent higher than that predicted by the Harris–Benedict equation, 31 per cent were found to be hypometabolic using the same criterion and no relationship was demonstrated between RME and weight loss or tumour burden[21].

Although some of the disparity in the findings of these studies is no doubt a reflection of differences in experimental material and methodology, it is likely that they are reflecting a true heterogeneity of response to the tumour bearing state. It is now clear that cancers arising from certain tissues, such as sarcomas[22], leukaemias[23] and bronchial carcinomas[24], frequently provoke a hypermetabolic response, whereas patients with pancreatic and hepatobiliary tumours tend to be hypometabolic[25].

Many cancer patients with advanced disease have a reduced caloric intake. In normal people or in patients with benign disease, semistarvation is attended by a reduction in RME[26,27], so in an undernourished cancer patient even a normal metabolic rate represents a failure of this adaptive response[14,28].

The mechanism by which malignant tissue alters the energy expenditure of the host is not clear. It is unlikely that increased energy consumption by the tumour itself is responsible in human tumours as it is rare for tumours to account for more than 5 per cent of body weight[13]. More plausible is the hypothesis that mediators are released by some cancers which alter host metabolism[29,30], and some of the changes that may occur are discussed in subsequent sections.

Changes in glucose metabolism

There are many reports describing an increased rate of endogenous glucose production in cancer patients[11,22,23,31–33] (*Figure 1*), and considerable research effort has been directed towards determining the mechanism and significance of this occurrence. It is clear that the magnitude of the increase in glucose turnover is influenced by tumour stage[6,35] and histology, and that it is associated with cancer cachexia[36]. In this section, some of the observations made in cancer patients of changes in glucose metabolism will be summarized and the implications that these have on energy balance will be discussed.

Gluconeogenesis

Shaw and Wolfe[6] have defined glucose kinetics in a group of

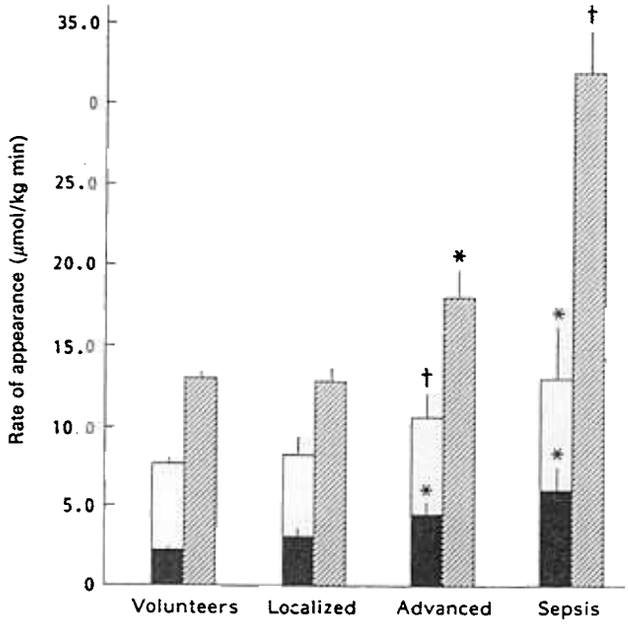

Figure 1 *The influence of localized or non-weight-losing cancer, advanced or weight-losing cancer, and sepsis on the rate of production of glycerol (■), free fatty acids (□), and glucose (▨) compared with rates in healthy volunteers.* *P<0·01, †P<0·05. *(Modified from Shaw and Wolfe[7,34])*

patients with early (limited to the gut wall) and advanced gastrointestinal malignancies. Whereas the rate of glucose turnover in the group of patients with early lesions was indistinguishable from that seen in normal volunteers, glucose production was significantly increased in patients with advanced lesions. Similarly, tumour histology has also been demonstrated to influence the extent of increase of glucose production. The glucose turnover rates in sarcoma[22] and leukaemia[23] patients have been reported to be respectively two and nearly three times the value determined in normal volunteers, whereas the glucose turnover rate in lymphoma patients does not differ significantly from normal[23]. Other researchers have studied the effect of weight loss on glucose turnover. Holroyde *et al.* have reported that weight-stable cancer patients have rates of glucose production similar to those of normal volunteers. However, those with progressive weight loss have markedly elevated rates[37]. This is a particularly significant finding as progressive weight loss secondary to uncomplicated starvation is attended by a reduction in glucose turnover[38].

The hepatic production of glucose becomes less sensitive to the usual homeostatic regulating mechanisms in some patients with cancer. If a normal volunteer is infused with glucose at a rate of 4 mg kg^{-1} h^{-1} (the dose of a typical total parenteral nutrition regimen) the suppression of endogenous glucose production will approach 100 per cent[39]. In patients with advanced gastrointestinal cancer, there is a 70 per cent reduction in endogenous glucose production[6], whereas in sarcoma and leukaemia patients hepatic glucose production is reduced by less than one-third[22–23].

The cause of elevated hepatic gluconeogenesis and its reduced suppressibility in patients with malignant tumours is unclear. The plasma levels of the hormones involved in glucose homeostasis (insulin, cortisol, growth hormone) are not consistently deranged in cancer patients[36] and are unlikely to play a significant role, although insulin receptor insensitivity would be consistent with increased gluconeogenesis. The increased availability of the gluconeogenic substrates lactate, alanine and glycerol presents a plausible mechanism and, of these, lactate is probably the most quantitatively important. More than 50 years ago, Warburn described the dependence of malignant cells on anaerobic glycolysis and the resultant release of lactate[40]. Indeed, lactic acidosis has been reported in some cancer patients, particularly in those with disseminated haematological malignancy[41], and a greater rate of hepatic synthesis of glucose from lactate has been reported by several research groups[31,32]. Increased gluconeogenesis from alanine[42,43] has been described in cancer patients, which would act to accelerate wasting of body protein and which will be discussed in greater detail in a subsequent section. The contribution of glycerol toward encouraging gluconeogenesis is likely to be minor[32]. The balance of available evidence suggests that the increased rate of gluconeogenesis is substrate led; however the isolation of induced gluconeogenic enzymes from hepatocytes of cancer-bearing laboratory animals[44,45] suggests that this may not be exclusively so.

Cori cycling

In the Cori cycle[46], lactate released as a result of glycolysis in peripheral tissues is used as a gluconeogenic substrate by the liver. This process consumes energy, as six ATP (adenosine triphosphate) molecules are required for the resynthesis of glucose from lactate whereas only two are produced by the glycolytic degradation of each glucose molecule. When the anaerobic glycolysis occurs in malignant tissue, the energy cost to the host is compounded by the loss of glucose parasitized by the tumour[47]. Accordingly, there has been considerable interest in determining the extent of Cori cycling in cancer patients as it may be one of the fundamental metabolic changes causing cancer cachexia.

The rate of Cori cycling can be easily measured using ^{14}C- and $6^{3}H$-labelled glucose tracers[48]. Increased rates of cycling have been measured by Holroyde *et al.*[49] in a group of 20 patients with metastatic colorectal cancer when compared with control subjects of comparable age and sex. It was inferred that tumour glycolysis was responsible for the excess lactate production, although this supposition was not confirmed by the lack of correlation between the extent of tumour burden and the increased rate of Cori cycling. Evidence for the cancer *per se* being responsible for increasing the rate of Cori cycling has been provided by the study of Eden *et al.*[50], who compared the rate of Cori cycling in patients with cancer cachexia with a control group of patients who had suffered a similar degree of weight loss but from benign causes. The rate of Cori cycling in both the fasted and enterally fed states was significantly higher in the patients with malignant disease, suggesting that it was the cancer *per se* that was responsible for this increase. However, Burt *et al.*[51] have measured an increased rate of release of lactate from the forearm of a small group of patients with localized carcinoma of the oesophagus, implying that the tumour is capable of effecting a distant influence on the metabolism of carbohydrate in host tissue. It is likely, although still conjectural, that increases in both tumour and host tissue glycolysis are responsible for the observed changes in whole body lactate metabolism.

The role played by such futile cycles in the pathogenesis of cancer cachexia has been the subject of much debate. Gold has performed considerable work in this field and describes the 'fundamental position of tumour glycolysis–host gluconeogenesis in the production of cancer cachexia'[52]. The rate of Cori cycling has been measured by Holroyde *et al.*[37] in two groups of cancer patients, one with progressive weight loss and the other with stable weight. The rate of Cori cycling was considerably elevated in the first group but normal in the second, suggesting that the energy lost by the futile cycling was responsible for the weight loss. However, such findings have not been universally reproduced: Kokal *et al.* were unable to demonstrate any significant differences in glucose cycling rates as a function of pre-illness weight loss[35].

Eden *et al.*, having demonstrated an increase in glucose turnover and glucose cycling in cancer patients, estimated the potential energy cost to the cancer patient[51]. They calculated that, if the incomplete oxidation of glucose were to be substituted by the complete oxidation of fat, this would lead

to an increase in energy expenditure of 250–300 kcal/day and a loss of 0.9 kg fat/month. However, a contrary argument has been forwarded by Young[53], who estimated that if only 15 per cent of the total lactate production is oxidized completely and 85 per cent is converted to glucose then 'there will be maintenance of high energy phosphate balance... and it is difficult to accept therefore that changes in Cori cycle activity are a significant cause of the marked body wasting in patients with progressive neoplasia'. These conflicting but equally well considered viewpoints underscore the great difficulty in accurately determining a long-term energy balance in cancer patients and, accordingly, the influence that changes in metabolic efficiency have on that balance. Nevertheless, the accelerated activity of energy wasting cycles is likely to play some role in the development of cancer cachexia.

Insulin and glucose uptake

Impaired glucose tolerance in patients with leukaemia, lymphoma and a variety of epithelial tumours was described in the 1950s by Marks and Bishop[54] and resistance to both exogenous and endogenous insulin has been subsequently demonstrated in cancer patients[55]. The insulin binding receptors of monocytes extracted from cancer patients are normal, implying that the defect is postreceptor in site[56]. Jasani *et al.* have reported a decrease in the sensitivity of pancreatic β cells to insulinogenic stimuli[57], while others have determined that reductions in both peripheral sensitivity and pancreatic release are responsible for the observed glucose intolerance[58]. However, the cause of the glucose intolerance in the setting of malignancy has undergone some critical reappraisal in recent years, and it has been suggested that it may be due to intercurrent factors such as weight loss, bed rest and sepsis rather than to the cancer *per se*[36,37].

For the plasma glucose concentration to remain constant, the increase in glucose production observed in some cancer patients must be attended by an equal increase in the rate of clearance of glucose from the plasma compartment. This occurs despite the prevailing state of insulin resistance. Results obtained from animal tumour models have suggested that the tumour acts as a 'glucose trap', consuming large quantities of glucose in the process of anaerobic glycolysis[59]. The high tumour–host weight ratio in such models (sometimes exceeding 40 per cent) casts a shadow on their applicability to patients; human tumours rarely exceed 5 per cent of body weight and therefore only very substantial metabolic changes within the tumour itself would be detectable at the whole body level. However, the glucose trap concept is supported by the demonstration of increased glucose uptake across soft tissue sarcoma-bearing limbs compared with the opposite non-tumour-bearing limb[60]. Interestingly, the forearm glucose uptake in patients with oesophageal cancer has been found to be significantly greater than in healthy controls by Burt *et al.*[51]. The plasma insulin levels were lower in the cancer patients so it is unlikely that this hormone mediated the observed changes. The authors speculate that increased non-suppressible insulin like activity (NSILA) may be responsible. NSILA is the likely cause of the hypoglycaemia seen with some non-islet cell tumours in humans[61], and is probably elaborated by the tumour itself[62]. The wider role of tumour-related NSILA remains a matter of conjecture.

Glucose oxidation

Although several studies have reported modest increases in the rate of glucose oxidation in cancer patients[19,37,63], the increases are not commensurate with the greater glucose availability, which implies a reduction in efficiency of the oxidative process[6]. In skeletal muscle isolated from patients with cancer, the activities of enzymes regulating oxidative metabolism have been found to be reduced[64], which is consistent with data gathered from studies of whole body glucose oxidation. It is likely that, in cancer patients in whom glucose production is occurring at an accelerated rate, the extra glucose production is being consumed in Cori cycling[38].

Fat metabolism

In many cases of cancer cachexia the greater proportion of weight loss is caused by depletion of body fat[18,65,66]. Loss of body fat with malignant disease has been confirmed by a variety of anthropometric techniques[14,67,68], and muscle biopsy samples from patients with cancer have been found to have only half the amount of fat present in normal controls[69]. Although the consumption of fat reserves in cancer patients is partly a reflection of reduced caloric intake, several changes in lipid metabolism have been described which probably result from cancer bearing itself, and these will be discussed in the following paragraphs. Fat metabolism in cancer patients has been the subject of far less research effort than carbohydrate metabolism, and correspondingly fewer conclusions can be drawn.

Fat mobilization

Triglyceride in adipocytes, which represents the major storage form of fat, is mobilized by hydrolysis to glycerol and free fatty acids which are released into the plasma. Using stable isotopic tracers Shaw and Wolfe[7] have measured the turnover rates of glycerol and free fatty acids in weight-stable and weight-losing patients with gastrointestinal malignancies and compared these with rates in normal volunteers (*Figure 1*). There were no significant differences in whole body glycerol and fatty acid kinetics between the weight-stable patients and the normal volunteers, but those with weight loss had significantly elevated rates of release into the plasma of both glycerol and free fatty acids. These data, which are in agreement with the work of others[15,70], suggest that the loss of fat reserves seen in patients with cancer cachexia results from increased fat mobilization rather than decreased synthesis. However, definitive studies of the influence of cancer on lipogenesis in human subjects have not been performed, so it is possible that both mechanisms are operating to reduce body fat stores.

Lipid clearance

Lipoprotein lipase is the enzyme responsible for the clearance of triglyceride molecules from the plasma. Although hyperlipidaemia is not a marked finding in cancer patients, it has been found in association with some tumours[71], and the proposed mechanism is a reduction in activity of this enzyme. Support for this hypothesis has recently been provided by Vlassara *et al.*[72] who found that the plasma lipoprotein activity in a group of cancer patients was reduced and that there was a correlation between weight loss and the extent of reduction of enzyme activity. The decreased lipoprotein lipase activity that occurs in uncomplicated starvation is mediated by a reduction in the plasma level of insulin. However, the insulin levels in the patients in Vlassara's study were normal, suggesting that this was not the mechanism responsible for the observed changes.

Fat oxidation

There is a considerable body of data to suggest that fat is oxidized at an increased rate in cancer patients[14,15,50,63,74], although as is common in studies involving small numbers of patients with heterogeneous conditions this finding is not universal[75]. Fat oxidation rates determined in a series of 70 patients with colorectal or gastric cancer by a combination of indirect calorimetry and urinary nitrogen excretion have been recently reported by Hansell *et al.*[19]. They found that the patients with cancer had significantly higher fat oxidation rates (and significantly lower carbohydrate oxidation rates) than control patients with benign disease. Patients with cancer and weight loss oxidized fat more rapidly than either patients with cancer and no weight loss or patients with weight loss caused by benign disease. Similarly, patients with hepatic metastases

had a significantly greater fat oxidation rate than patients with localized malignant disease. Others have reported that in cancer patients a greater percentage of the body's energy requirements is provided by fat than in normal volunteers, and that fat is mobilized and oxidized with at least the same efficiency as in health[15]. It is unlikely that malignant tissue *per se* is responsible for the increased fat oxidation, but rather that the changes induced in the regulation of metabolic pathways occurring in normal host tissues in the cancer-bearing state favour fat oxidation.

Protein metabolism

Loss of body protein in patients with cancer cachexia is manifested clinically as skeletal muscle atrophy and hypoalbuminaemia, and is associated with an impaired tolerance of treatment procedures[2]. Significant protein loss may occur in patients who are maintaining what would be in health an adequate intake of nitrogen and calories, implying that tumour bearing *per se* is able to exert a detrimental influence on whole body nitrogen balance. However, a negative nitrogen balance is not an inevitable accompaniment of malignancy. Nearly 30 years ago, Watkin[76] measured nitrogen balance in a large group of cancer patients and found a range of responses from positive to very negative balances, and he thoughtfully related the more negative nitrogen balances with increased disease 'activity' (reflecting weight loss, increased resting energy expenditure and other factors). This concept concurs with our own observations, in which patients with aggressive metastatic disease[77] or those with histological tumour types frequently associated with a poor prognosis (e.g. sarcoma[22]) tend to lose protein significantly more rapidly than those with less aggressive disease.

Whole body protein kinetics

The rate of whole body protein turnover can be measured using isotopically labelled amino acids as metabolic tracers, and a number of such studies in cancer patients have produced a spectrum of results. A consistent 50–70 per cent increase in turnover rates in large groups of patients with lung and colorectal cancer has been reported[20] and there have been similar findings in patients with small cell cancer[78] and in children with leukaemia[79,80]. Norton *et al.*[81] found an inconsistent response in a diverse group of cancer patients, whereas others have found no difference between patients with cancer and age-matched normal controls[82]. Several investigators have suggested that whole body protein turnover is increased with advancing stage of disease and weight loss[78,83–85].

This accelerated protein turnover seen in many cancer patients contrasts with the reduction in total protein turnover observed in cases of simple starvation[86]. Recently, to distinguish the metabolic effect of pure malnutrition from those of cancer bearing, Jeevanandam *et al.* compared the protein kinetics of malnourished cancer patients with those of patients who were equally malnourished as a result of benign disease and with those of a group of starved normal subjects[87]. Compared with the non-cancer patients and starved normal subjects, whole body protein turnover in the cancer patients was elevated by 32 and 35 per cent respectively. These results confirm the observations made by Brennan nearly a decade earlier that in cancer cachexia there is a maladaptation to the starved state, with a continued mobilization of protein and calorie reserves in the face of a reduced intake[5]. An example of this is the decreased efficiency with which simple substrates limit the rate of gluconeogenesis and protein flux in patients with advanced cancer[31,73,88].

Protein turnover is an energy expensive process which accounts for 10–20 per cent of basal metabolic expenditure[89]. The reduction in protein turnover seen in simple starvation accordingly represents an adaptive response[90], and it has been suggested that its failure to occur in some cases of malignancy is responsible for the development of cancer cachexia[91]. This hypothesis has recently been examined in substantial groups of cancer patients and normal controls[20] and, although the cancer patients had a significantly higher rate of protein turnover, their resting metabolic expenditure was not increased nor was there any correlation between individual rates of protein turnover and energy expenditure. These results suggest that when protein turnover is increased in cancer patients it is unlikely to play a major role in the development of cancer cachexia.

The influence of the cancer *per se* on whole body protein metabolism has been a matter for some conjecture. The concept of the tumour having a 'nitrogen trap' which parasitizes amino acids from healthy tissues was developed by researchers working with rapidly growing transplantable animal tumour models[92,93], but it is unlikely to be applicable to patients in whom tumour bulk is usually a much smaller percentage of body weight. It is more plausible that the tumour is releasing a humoral agent or agents which effect the observed metabolic changes. Glass *et al.*[94] attempted to quantify the influence of tumour bearing on protein dynamics by studying a group of patients with colorectal carcinomas just before and 12 weeks after resection. They were unable to demonstrate a significant difference in whole body protein metabolism after tumour excision, and concluded that the primary tumour does not alter protein kinetics. However, the study group comprised patients with localized lesions whose nitrogen flux was comparable to that of normal controls, and so it is perhaps not surprising that tumour excision caused no change.

Skeletal muscle metabolism

Whole body protein turnover studies reflect the sum total of synthesis and degradation rates in the individual tissues. Accordingly, it is possible for synthesis and/or catabolism to be reduced in one particular tissue while whole body turnover is increased[95]. Several investigators have attempted to determine the manner in which the protein kinetics of individual tissues are affected by cancer. Lundholm *et al.* used the rate of incorporation of [^{14}C]leucine by skeletal muscle biopsies incubated *in vitro* to compare synthesis rates in a heterogeneous group of 43 cancer patients with 55 age- and sex-matched controls[96]. They found that the capacity of the muscle fibres removed from the cancer patients to incorporate the amino acid tracer was significantly impaired, and that having been incorporated the rate of loss of tracer was also greater in the cancer patients. The group concluded that malignant tumours provoke a decrease in protein synthesis and an increase in protein degradation. In a subsequent series of experiments the same group used arteriovenous differences in levels of 3-methylhistidine, an amino acid which is relatively specific to skeletal muscle, and found that there was no significant difference in the rate of appearance of this marker in patients with cancer and controls who were depleted with benign disease[97]. They concluded that the effect of malignant tissue was to reduce the rate of protein synthesis. As skeletal muscle comprises the majority of the body's protein, changes in skeletal muscle protein kinetics are subsequently likely to be manifested at the whole body level. The results of Lundholm's group are therefore at odds with a substantial body of whole body kinetic data which suggests that whole body protein synthesis is either unchanged or increased[20,78–80,83,84]. Recently, Shaw and colleagues have determined *in vivo* fractional synthesis rates (FSR) of muscle in patients with benign disease, weight-stable patients with malignant disease, and patients with cancer cachexia[85]. There were no significant differences in the rate of muscle FSR between patients with benign disease and weight-stable cancer patients, but there was a significant increase in FSR in those patients with cancer cachexia. Given that these patients had lost weight (and presumably protein), this implies the occurrence of an even greater increase in the rate of degradation of muscle protein, and indeed increased activities of lysozymal enzymes isolated from skeletal muscle of cancer patients have been reported[64,96]

Hepatic protein synthesis

There is a paucity of data on the rate of hepatic protein synthesis and catabolism in cancer patients. Using the same *in vitro* methodology employed in their study of skeletal muscle metabolism, Lundholm *et al.* have reported an increase in the rate of protein synthesis in liver biopsies from cancer patients[64]. These results are consistent with those from our own laboratory, in which we have demonstrated *in vivo* a significant increase in the fractional synthetic rate of protein of hepatic tissue in patients with cancer cachexia, but no difference between the hepatic FSR of weight-stable cancer patients and patients with benign disease[85]. There are no data describing the rate of catabolism of structural hepatic proteins in cancer-bearing patients. However, a recent report in which organ imaging techniques were used to determine liver size in a small number of patients with cancer cachexia suggested that there was relative sparing of visceral protein[98], which implies that the observed increase in hepatic protein synthesis is likely to be attended by an equal increase in protein catabolism.

Many patients with advanced malignancy are hypoalbuminaemic, which may result from a reduced rate of synthesis, an increased rate of breakdown or a loss of albumin from the intravascular volume. As albumin degradation rates have been demonstrated to be normal in cancer patients[99,100] and with the exception of cases of malignant effusion the distribution of albumin is relatively unchanged, this implies that the rate of synthesis is decreased. However, this is contrary to some recent data from our laboratory in which we measured the rate of synthesis of albumin using a [^{14}C]leucine marker[101]. A significantly higher rate of albumin synthesis was found in those patients with cancer cachexia compared with rates in cancer patients who were weight stable, and in patients with benign disease. It is clear that the influence of malignancy on hepatic structural and secretory protein synthesis has yet to be clearly resolved.

Treatment of cancer cachexia

Nutritional support

Following the introduction of safe total parenteral nutrition (TPN) techniques nearly 20 years ago, it was hoped that the great majority of cachectic cancer patients could be repleted before surgical treatment, radiotherapy or chemotherapy, and that a reduction in treatment morbidity would be effected. The enthusiasm of the initial reports describing the efficacy of TPN in cancer patients[102] has not always been reaffirmed[103]. It has become clear that providing sufficient nitrogen and calories to a patient with cancer cachexia does not augment lean body mass as efficiently as can be achieved in a malnourished patient with benign disease. The use of TPN in cancer patients raises several questions, such as whether hyperalimentation promotes growth in malignant tissue, how the TPN prescription can be tailored to ameliorate the metabolic defects associated with cancer, and whether the provision of TPN leads to an improved patient outcome.

The concern of clinicians that the protein and energy substrates provided by TPN will be consumed preferentially by the tumour has some support from the results of experiments performed with animal tumour models, in which tumour growth is encouraged more than repletion of host tissues[104–106]. However, to date, stimulation of tumour growth by TPN has not been observed in patients[107]. The most elegant evidence that TPN does not have a deleterious effect has been provided by Mullen *et al.*[108] who used the *in vivo* rate of incorporation of [^{15}N]glycine as a measure of protein synthesis. They found that the tumours of patients who were given TPN for 7–10 days before surgery were synthesizing protein no more rapidly than the tumours of the control patients who were on an *ad libitum* oral diet. Although some caution must be exercised in the interpretation of these results as a net increase in tumour size may have resulted from a reduction in the rate of protein catabolism, it is most likely that malignant tissue is synthesizing protein at a maximal rate and that its rate of growth cannot be significantly affected by the provision of extra nutrients[109].

It is generally agreed that approximately 130 per cent of the RME needs to be provided to cancer patients[110], but there are few data that clearly indicate which is the optimal caloric source. Despite some cancer patients having marked changes in intermediate metabolism, they have been shown to be able to oxidize efficiently both infused glucose and fat[111]. There is some evidence from a laboratory tumour model that the provision of calories as fat retards tumour growth[112], but this has not been duplicated in other animal models[113] and there is no evidence from human studies to support these findings. Shaw and Holdaway have demonstrated that infusion of isocaloric volumes of glucose and fat (administered as Intralipid 20, KabiVitrum Laboratories, Stockholm, Sweden) have an equal ability to spare protein at the whole body level, although lipid infusion fails to suppress endogenous glucose production[114]. Infused glucose is able to suppress gluconeogenesis in cancer patients[42], but it does not do so with the same efficiency as in healthy volunteers[6].

Although it is possible to restore the weight of a cachectic cancer patient with parenteral nutrition, it has been questioned whether the weight gain is primarily as fat[115] or whether it represents a useful replenishment of the lean body mass. There are several reports of positive nitrogen balances being achieved in cancer patients on TPN[43,116], but these studies require meticulous sample collection and may be difficult to interpret in the presence of a growing tumour. However, longitudinal studies of body composition over a 1 month course of TPN have shown no increase in total body nitrogen, despite increases in body fat and total body potassium[10]. These data are compatible with the results of isotopic studies, which have demonstrated an attainment of nitrogen equilibrium with TPN, but not the protein anabolism which is readily achievable in patients depleted by benign disease[117] (*Figure 2*). There is evidence to suggest that leucine is central in the regulation of protein metabolism[118], and leucine-enriched TPN has been provided to cachectic cancer patients in an attempt to improve the nitrogen balance[119,120], with a small improvement in nitrogen balance being demonstrated.

It is likely that the difficulty in achieving restoration of lean body mass with TPN in cachectic cancer patients is partly responsible for the paucity of convincing evidence of its therapeutic efficacy[103]. Prospective randomized trials of less than 1 week of TPN have failed to demonstrate any advantage to the study group over the control group fed *ad libitum*[121,122]. A recently published analysis of the pooled results of 18

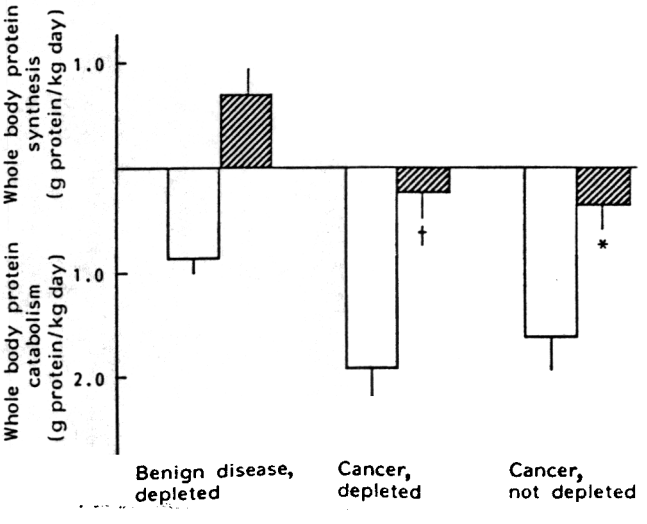

Figure 2 *Response to total parenteral nutrition (■) of depleted patients with benign disease, cancer patients with depletion and cancer patients without depletion compared with basal values (□). *P < 0·01, †P < 0·05. (Modified from Shaw[117])*

randomized trials assessing the effectiveness of perioperative TPN (16 of which consisted of cancer patients) concluded that there was little evidence supporting the routine use of perioperative TPN, but that it may have a role in supporting a subgroup of patients who are at high risk[123]. The authors of this paper were generally critical of the methodology of the trials performed to date, and comment that the effectiveness of TPN may have been underestimated by inclusion of patients who were not malnourished. Certainly, some trials have demonstrated advantages to the patient who received TPN: Heatley *et al.* followed the postoperative course of 70 patients with gastric cancer who were randomized to receive either TPN for 7–10 days or a normal diet, and reported a significant reduction in the occurrence of wound infection in the group who received TPN[124]. A preoperative course of TPN of a similar length in a group of patients with gastrointestinal malignancies reduced the incidence of complications from 19 per cent in the control group to 11 per cent in the treatment group, and the mortality from 11 to 3 per cent[125]. However, any advantage attributed to TPN must be weighed against the risks of pneumothorax and catheter-related septicaemia.

Pharmacological manipulation

As the provision of adequate calories and nitrogen does not ensure protein accretion in cachectic cancer patients, there have been several attempts to counter adverse tumour-associated metabolic changes by administration of pharmacological agents. An example is a trial involving 101 intensively pretreated cancer patients who were randomly assigned to receive either hydrazine sulphate, which inhibits a key enzyme in the gluconeogenic pathway, or a placebo[126]. The treatment group experienced significantly improved weight stabilization and glucose tolerance. Megestrol acetate, an anabolic steroid, has been recently reported to produce enhanced appetite and increased weight in a group of 28 patients with breast cancer[127]. Nearly a decade ago Schein *et al.*[128] argued lucidly that many of the cancer-related metabolic derangements were a result of insulin resistance and suggested that many of these could be ameliorated by the provision of exogenous insulin. This proposal has been supported by the results obtained from animal model experimentation[129–131] but to date no human studies have been published.

Although these and other trials involving anticachectic agents have shed some light on the mechanisms of cancer cachexia, no agent has yet been demonstrated meaningfully to improve the clinical course of cancer patients.

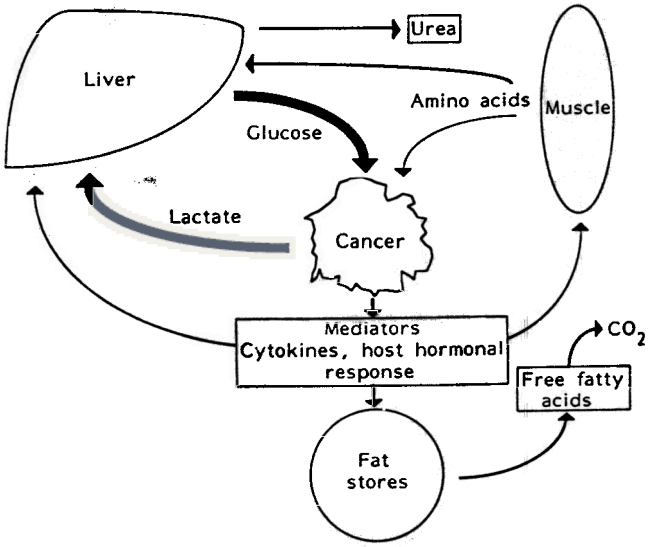

Figure 3 *Overview of the proposed metabolic changes associated with advanced cancer*

Mediators of the metabolic response to cancer

It was long held that the metabolic changes observed in cancer patients at the whole body level were a reflection of the metabolic activity of the malignant tissue *per se*. From this supposition was born the concept of the tumour acting as an internal parasite, trapping nitrogen and energy substrates as the host tissues became progressively more malnourished[132]. Despite the alluring simplicity of this hypothesis it fails to account for the profound metabolic changes that have been documented in some patients with apparently trivial tumour burdens[133], nor does it explain the changes in metabolism detected in host tissue distant from the tumour site[51].

An alternative theory advanced to explain these observations is that tumours release small molecular weight proteins which alter the activities of various host enzymes[30] (*Figure 3*). A large number of polypeptides and other substances secreted by tumour cells have been described, such as toxohormone[134] and lipid mobilizing factor[135], to which have been attributed various roles in the causation of cancer cachexia, largely on the basis of animal experiments. However, there is little evidence that convincingly relates these substances to the metabolic changes seen in cancer patients.

The similarities between the metabolic responses to sepsis and trauma to that provoked by tumours have been clearly described by Brennan[5]. The loss of nitrogen and increased turnover of glucose and mobilization of fat which occur in

Table 1 *Metabolic changes commonly associated with advanced or weight-losing cancer, severe sepsis or multiple trauma, and depletion due to benign disease (or in some cases starvation in normal volunteers)*

	Cancer	Sepsis/trauma	Starvation	Reference
Carbohydrates				
Gluconeogenesis	↑	↑	↓	6, 31, 32, 37, 38, 141, 142
Glucose recycling	↑	↑	–	22, 49, 50, 141, 142
Insulin resistance	↑	↑	–	55, 58, 143
Fat				
Lipolysis	↑	↑	↑	7, 15, 144, 145
Fat oxidation	↑	↑	↑	14, 15, 19, 145, 146
Protein				
Whole body flux	↑	↑	↓	20, 77, 89, 141, 142, 147
Net catabolism (NPC)		↑	↑	6, 22, 141, 142
Responsiveness of NPC to total parenteral nutrition	↓	↓	↑	116, 117
Energy				
Resting metabolic expenditure	↓/N*/↑	↑	↓	13, 16, 18, 21, 25, 26, 27, 146, 148

* No change

severely septic or injured patients result from the combined influences of counter-regulatory hormone secretion and the release of inflammatory mediators from cells of the immune system[136]. It has been suggested that similar mediators released by immunocytes in response to tumour cells are responsible for the metabolic response to cancer. Cachectin, a 17 kDa polypeptide released by macrophages which acts as a mediator of endotoxic shock[137], has recently been found to share strong sequence homology with tumour necrosis factor (TNF)[138], also a macrophage product. It may be that cachectin/TNF is central to the mediation of the metabolic response to both sepsis and cancer[139]. Recently, Wilmore and coworkers have reported a negative nitrogen balance in cancer patients infused over a 5-day period with recombinant TNF, which they attributed to the anorexia induced by the TNF rather than to a cytokine-specific effect on protein metabolism[140]. Kern and Norton have proposed a mechanism explaining the metabolic derangements of cancer cachexia in which the tumour stimulates the host's immune cells to secrete factors such as cachectin/TNF whose primary role is cytotoxic, but which have secondary metabolic effects[8].

Summary

Malignant tumours do not have a consistent effect on the intermediary metabolism of the host. However, patients with advanced disease and/or those demonstrating cancer-related cachexia typically have accelerated rates of energy substrate and protein turnover despite reduced calorie and nitrogen intake. In this manner the metabolic response to cancer cachexia is opposite to that seen in uncomplicated starvation, but rather bears many similarities to the changes described in patients with sepsis and trauma. The rates of gluconeogenesis and Cori cycling, fat mobilization and oxidation, and protein synthesis and degradation tend to be increased, and there is greater difficulty in replenishing lean body mass with methods of nutritional support (*Table 1*). The metabolic response to cancer may be largely effected by mediators released by cells of the immune system, but this matter remains conjectural. Beyond the provision of adequate calories and nitrogen, and removal of malignant tissue, there are presently no metabolic therapies available which have been demonstrated to influence clinical outcome.

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