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Cancer cachexia

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Cachexia is a common problem in the clinical management of cancer patients, particularly those with solid tumors. Cachexia is most obviously manifested as weight loss with massive depletion of both adipose tissue and muscle mass, and death is probably due to loss of lean body tissue. Not only is the survival time shorter in patients with cachexia, but the frequency of response to chemotherapy is also significantly reduced. Although anorexia frequently accompanies cachexia, attempts to halt or reverse cachexia by nutritional repletion have not been successful. This suggests that cachexia is due to metabolic abnormalities produced by the tumor in addition to the underlying anorexia. In some patients weight loss is associated with an increased relative energy expenditure possibly through an elevated adrenergic state. Several factors have been postulated as mediators of cancer cachexia and can be divided into two groups. (i) Materials with hormone-like characteristics which result in direct catabolism of host tissues. (ii) Cytokines which cause alterations in host metabolism indirectly. Included in group (i) are the conventional catabolic hormones and a lipid mobilizing factor (LMF) produced by tumors, which causes direct breakdown of adipose tissue. Included in group (ii) are tumor necrosis factor-α, interleukin-6, interferon-γ and leukaemia inhibitory factor. The materials appear to influence adipose tissue indirectly through an inhibition of lipoprotein lipase. Reversal of cachexia has been achieved by two groups of agents. (i) Those stimulating food intake, e.g. megestrol acetate. (ii) Those directly inhibiting the LMF, e.g. eicosapentaenoic acid. While agents in group (i) can cause tumor growth stimulation, those in group (ii) act as tumor growth inhibitors. This latter results suggests that the products of catabolism of host tissues may be important for tumor growth and provides a new avenue for chemotherapeutic intervention.

Key words: Cachexia, cancer, chemotherapy, tumor.

Introduction

The term cachexia is derived from the Greek *kakos* meaning bad and *hexis* meaning condition, and is observed in a number of disease states. In cancer patients cachexia is characterized by anorexia and nausea, weight loss, anemia, and muscle weakness. The most obvious sign of cachexia is loss of adipose tissue and muscle which eventually leads to death of the patient. Although this syndrome is mainly associated with terminal cancer patients with disseminated disease, cachexia may also be present in the early stages of tumor growth, even before other signs and symptoms of malignancy appear.[1,2]

Cachexia is one of the most frequent adverse effects of malignancy. At the time of presentation about one-half of untreated cancer patients were found to have lost some weight and about one-third had lost more than 5% of their usual body weight in the preceding 6 months.[3] The frequency of weight loss varies with the type of tumor ranging from 30% in patients with favorable non-Hodgkin's lymphoma to nearly 90% in patients with gastric or pancreatic cancer.[3] The incidence of severe weight loss (above 10%) also varies with tumor type, being 4–10% in the low frequency group and 26–38% in the high frequency group.[4]

The survival time is also shorter in patients with weight loss than in those without weight loss. For patients with breast cancer, colon cancer, prostatic cancer and unfavorable non-Hodgkin's lymphoma the median survival is approximately twice as long in patients who had not lost weight compared with those that had.[4] Visceral protein and lean body mass depletion (as measured by serum albumin concentration and creatinine: height index) have a worse prognosis than adipose depletion (as measured by triceps skin-fold thickness).[5] The greater the degree of weight loss the shorter the survival time. In a study of the cause of death of 500 autopsied cancer patients, Warren[6] concluded that 22% of these had died of cachexia and that cachexia could be contributed to death from other causes such as infection. It has been suggested[7] that 30% loss in body weight is invariably fatal, although the rare patient may survive up to 50% weight loss. The precise mechanism by which cachexia can cause

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death is not known, although loss of protein is probably the most important factor.

Pretreatment weight loss is also associated with a lower frequency of response to chemotherapy in breast, colon and non-small cell lung cancer as well as in acute lymphocytic leukemia.[4] The impact of weight loss on response was approximately equal to the impact of tumor extent.

Role of anorexia in cancer cachexia

Although anorexia is often associated with cachexia it is difficult to understand if it is a cause or effect since it may develop once weight loss is established. Food intake measurements may be complicated by the fact that most hospital patients will also be receiving radiotherapy or chemotherapy, both of which are known to cause anorexia. However, in a study of Warnold *et al.*[8] in a group of cancer patients with weight loss it was noted that the energy intake, although varying greatly, was not significantly different from that in a group of healthy subjects of the same age range. It was noted that the intake decreased due to nausea as the disease progressed.

Cancer cachexia appears to be distinct from simple starvation and more like the condition produced by major injury or sepsis.[7] Forced feeding, paired feeding and caloric restriction experiments in tumor-bearing animals showed that a decreased food intake alone could not entirely account for the progressive weight loss.[9] Also, although early trials of total parenteral nutrition (TPN) in cachectic cancer patients suggested a clinical benefit,[10] provision of excess calories alone does not appear to change median survival in patients with advanced cancer and many patients either maintain body weight or lose weight while receiving calories which would be predicted to result in weight gain.[11] In a study of a group of patients with small cell lung cancer TPN led to an increase in body weight.[12] However, the rapidity of the weight gain and its subsequent loss suggested that the weight gain was due to accumulation of water. This hypothesis was supported by a transient fall in the concentration of serum albumin, a decrease in hematocrit and signs of peripheral edema. Although patients receiving TPN temporarily maintained body fat stores there was no evidence that lean body mass was preserved. These results suggest that cachexia is due to metabolic abnormalities in addition to the underlying anorexia.

Energy balance in the cancer patient

The energy balance in the cancer patient may be negative because of a decreased caloric intake, an increased expenditure or a combination of the two. As mentioned above a number of studies have been carried out to determine if the caloric intake in cancer patients is adequate for their energy needs. In a study of De Wys *et al.*[13] using 3 day diet diaries to measure energy intake only 30% of cancer patients had a caloric intake that was sufficient to meet the needs for basal energy expenditure. In 40% of patients the caloric intake was greater than calculated for basal energy expenditure, but less than that required for a moderate level of activity, while in 25% of patients the caloric intake was below the calculated basal energy expenditure. Some studies have suggested that cancer patients have a significantly elevated energy expenditure compared with healthy subjects of the same age range.[8] Differences in resting energy expenditure (REE) have been observed in different tumor types. Thus while the REE in patients with non-small cell lung cancer and weight loss was found to be elevated in comparison with healthy controls, no difference was observed with patients with colorectal cancer.[14] No differences in energy intake was observed between the two groups. Thus, whereas weight loss in healthy people leads to an adaptational decrease in energy expenditure (EE), patients with lung cancer have an increased EE. Other studies in mixed groups of cancer patients have observed modest increases in EE in cancer patients with observed values being 20–50% higher than would be expected based on the subjects age, sex, body size and activity levels.[8,15]

In a total population study of 202 (106 cancer patients and 96 non-cancer-subjects) Hyltander *et al.*[16] showed that cancer patients had an elevated REE compared with either weight losing or weight stable controls. This elevated EE was related to an increased heart rate and they postulated that an elevated adrenergic state may be a likely explanation. Many cancer patients have both elevated plasma concentrations of catecholamines and increased urinary excretion of adrenergic substances,[17] in contrast to undernourished patients without cancer who generally show a decrease in the adrenergic tone and catecholamine turnover. Thus increased stress could contribute to weight loss in cachexia.

Other catabolic hormones have also been reported to be elevated in cachectic patients. Knapp

et al.[18] have reported a significant association between fasting plasma glucagon, serum cortisol and immunoreactive tumor necrosis factor (TNF)-α and weight loss in stage IV breast cancer patients suggesting a possible role for these hormonal factors in the development of cancer cachexia. The increased production of glucagon and cortisol could be a consequence either of increased TNF-α synthesis[19] or could be a mediated by increased production of catecholamines associated with stress.[20] However, it is also possible that the increased levels of glucagon and cortisol were a consequence of the weight loss and not the cause of it.

Mechanisms of increased energy expenditure in cancer patients

The most likely explanation for an increased energy expenditure in cancer patients is due to an increased activity of the Cori cycle, whereby circulating lactate is converted into glucose by the liver. Gluconeogenesis from lactate consumes six ATP molecules per lactate–glucose cycle and is particularly energy inefficient for the host. Tumor cells have an increased requirement for glucose as an energy source, either through an altered enzymatic activity,[21] or due to relative hypoxia induced by a poor tumor vascularization. Under such conditions glucose may be the only utilizable metabolic substrate, since glycolysis is the only means of ATP production which does not require oxygen. Also the increased glycolytic activity in tumor cells may be due to an increased activity of lactate dehydrogenase.[22] The increased glycolytic activity leads to an outpouring of lactic acid from the tumor providing an increased substrate availability for Cori cycle activity. A study of the activity of the Cori cycle in a heterogenous group of patients with metastatic carcinoma has shown that patients without progressive weight loss have normal glucose metabolism, but that Cori cycle activity is increased in patients with progressive weight loss, showing that lactate production rates are higher in these patients.[22] Inhibition of phosphoenolpyruvate carboxykinase, a key enzyme in gluconeogenesis, by hydrazine sulfate may decrease the excess Cori cycle activity and improve glucose tolerance in cancer patients, although weight loss is not reversed.[23]

Lipid metabolism in cancer cachexia

Increased mobilization of host lipids may occur early in the development of the tumor.[24] In view of its high calorific value fat is an important fuel source when the metabolic demands of an organism are high. Thus mobilization of lipids may be necessary to sustain the elevated REE observed in cancer cachexia. The increased lipid requirements in the tumor-bearing state is also shown by an increased lipogenesis from glucose in kidney, liver and epididymal fat pads.[25] However, if glucose or other carbohydrate sources are first converted into fat before being used to meet the energy requirements of the host, then there is a reduction in the amount of utilizable energy obtained from the intake of a given amount of carbohydrate. Estimates of the loss of utilizable energy may be between 7[26] and 20–30%[27] of the calorific value of glucose channelled into lipogenic pathways. This energy cost may contribute partly to the increase in REE.

Changes in fuel utilization have been reported in cancer patients with lipid sources predominating.[8] A similar situation is observed in animal models of cachexia.[28] Cancer patients show an increased uptake of infused lipids[29] and this correlates with a decrease in calorie deficit and a gain in body weight. Animal studies using a rat model system have also shown that hyperalimentation using fat as the primary source of calories generated a more favorable host:tumor balance, when measured by the relative rates of growth of each.[30]

In some animal models such as W256 carcinosarcoma in rats plasma levels of both triglycerides (TG) and non-esterified fatty acids (NEFA) have been found to be elevated,[31] while in a mouse model (MAC16) plasma levels of both TG and NEFA were found to be reduced.[32] In humans with cancer plasma levels of NEFA have been reported to be both elevated[33] and normal.[34] The plasma levels of both TG and NEFA are determined not only by the rate of production, but also by the rate of utilization. In view of the increased lipid requirements of cancer patients combined with an increased rate of mobilization it is not surprising that differences have arisen in the measurements of the steady state levels of both TG and NEFA, and that hyperlipidemia is not necessarily a hallmark of cancer cachexia.

Protein metabolism in cancer cachexia

Although loss of adipose tissue constitutes the major proportion of the weight loss in cancer cachexia, skeletal muscle mass depletion is probably more important in the overall survival of the

patient. Studies in tumor-bearing rats show that white or phasic muscle tends to atrophy more rapidly than red or tonic muscle.[35] Peripheral muscle wasting may be due to increased muscle catabolism or decreased protein synthesis or a combination of the two. Rennie *et al.*[36] have suggested that muscle mass in cancer cachexia is regulated primarily by alterations in the protein synthetic rate and that changes in muscle protein degradation are largely secondary. However, Lundholm *et al.*,[37] using 3-methylhistidine release as a marker of muscle catabolism from peripheral muscle in cancer patients, have shown net loss of protein was related to increased breakdown rather than to decreased synthesis of muscle protein. Protein turnover seems not to be related to weight loss, since an elevated rate of protein turnover has also been observed in patients with lung carcinoma with and without weight loss.[38]

The reason(s) for the increased protein turnover in cancer patients must remain speculative. However, tumors have an increased demand for certain amino acids, resulting in an amino acid imbalance in the host. Since protein synthesis requires the full complement of amino acids removal of one, such as leucine,[39] by the tumor would lead to a depression in protein synthesis. Removal of the excess amino acids through the energy inefficient gluconeogenic pathway could contribute to the increased REE and weight loss in cancer patients.[40] However, this does not explain why cancer cachexia is not observed with all large tumors. The degree of cachexia bears no simple correlation to tumor burden, tumor cell type or anatomical site of involvement.[41] This suggests that cachexia is intrinsic to certain tumors, possibly due to the production of circulatory factors by the tumor or host tissues.

Experimental models for the study of cancer cachexia

Evidence for the humoral mediation of cancer-associated cachexia has been demonstrated in a parabiotic pair of rats, one-half of which bore a cachexia-inducing sarcoma.[42] In this case the parabiotic tumor-free half also developed cachexia despite the absence of metastasis. Care must be taken in the selection of appropriate models for the study of cachexia, since large tumors may produce effects on the host due to size alone. Thus Morrison *et al.*[43] have shown that an inert artificial tumor depressed both host weight gain and skeletal muscle mass up to 30% and food intake up to 20% of the depression induced by tumors of comparable size. Most clinical tumors are considered to be large when they comprise less than 1% of the body weight,[41] although few experimental tumors satisfy this criterion. The best experimental models of cachexia are those in mice.

(i) A human hypernephroma xenografted into nude mice produced weight loss of more than 25% when the tumor comprised less than 5% of the body weight.[44] (ii) Murine colon 26 adenocarcinoma which produced 14.5% weight loss when the tumor represented 6% of the body weight.[45] (iii) Another murine colon adenocarcinoma (MAC16) produced 30% loss of host body weight when the tumor comprised just 3% of the total body mass.[46] In contrast rat models of cachexia, e.g. transplantable 3-methylcholanthrene-induced sarcomas, produce substantial weight loss only when the tumor comprises about 30% of the body weight.[47]

Mediators of cachexia

Several factors have been postulated to mediate the process of cancer cachexia. These can be divided into two types of substance. (i) Materials with hormone-like characteristics which result in direct catabolism of host tissues. (ii) Products of host tissues which influence host metabolism indirectly. Predominant among the latter group are the cytokines. A number of studies have suggested that inappropriate release of cytokines might cause changes in host metabolism which accompany tumor growth. In particular the cytokines TNF-α, interleukin (IL)-6 and interferon (IFN)-γ produce in experimental animals some of the features seen in cancer cachexia. Care must be taken in interpreting the effect of potential mediators of cachexia since anorexia and weight loss are common indicators of toxicity in rodents, and many of the materials only produce an effect at near toxic concentrations. In view of the parabiotic transfer of cachexia in rats[42] potential cachectic factors must also be present in the circulation, since cachexia is not due to the local effect of the tumor. In addition, inhibition of the action of the postulated cachectic factor should also reverse the process of cachexia. Not all of the postulated factors fulfill these criteria.

TNF-α

Hypertriglyceridemia in trypanosome-infected rabbits with anorexia/cachexia has been attributed to a

suppression of the clearing enzyme lipoprotein lipase (LPL).[48] Further studies showed that suppression of LPL was due to the production of a 'hormone' by macrophages in response to bacterial lipopolysaccharide (LPS).[49] The macrophage product responsible was termed cachectin and sequence studies on the purified material showed it to be homologous to TNF-α,[50] which had previously been shown as the agent responsible for hemorrhagic necrosis in tumors. These results led to the suggestion that TNF-α was the mediator of other cachexias and, in particular, cancer cachexia.[51]

Administration of TNF-α to experimental animals produces weight loss due to anorexia, although the biochemical changes are often opposite to that found with cachexia inducing tumors.[52] More direct evidence for a role of TNF-α in cancer cachexia was obtained by the transfection of chinese hamster ovary (CHO) cells with the human TNF-α gene where a syndrome was produced in mice resembling cancer cachexia with progressive wasting, anorexia and early death.[53] Rats infused with TNF-α continuously during an 8 day period also lose weight, but have an excess mortality (56%).[54] Thus the concentration of TNF-α required to produce weight loss is very close to the toxic level.

The cachectic effect of TNF-α is thought to arise from an effect on lipid metabolism through inhibition of the enzyme LPL,[51] which would prevent adipocytes from extracting fatty acids from plasma lipoproteins for storage. This would result in a net flux of lipid into the circulation. However, Grunfeld *et al.*[55] have shown that hypertriglyceridemia persists in rats administered TNF-α despite the development of tachyphylaxis to its anorectic/cachectic effect. In fact the acute increase in serum triglyceride seen after TNF-α administration seems to be due to hepatic synthesis and secretion of triglycerides in the form of very low density lipoprotein rather than from adipose tissue.[56]

In order to strengthen the role of TNF-α in the development of cancer cachexia the effect of anti-TNF-α antibodies on weight loss in murine models of cachexia has been studied. In mice bearing a methylcholanthrene-induced sarcoma anti-TNF-α antibodies delayed, but did not prevent the anorexia and had no effect on overall body weight.[57] Treatment slightly reduced the decrease in carcass and lipid content,[57] although this was not confirmed in a second study.[58] The acute phase response measured as an increase in liver weight, hepatic RNA content, increase in plasma concentration of IL-6, serum amyloid P, transferrin, complement (C3) and decrease in plasma albumin were not affected. The effect on body composition was also complicated by the fact that the treatment reduced tumor weight,[58] an interesting observation suggesting that TNF-α may be required for growth of some tumors. In the Lewis lung adenocarcinoma anti-TNF-α antibodies partially reversed the loss in body fat, but had no effect on food intake, change in body weight or final tumor weight.[57] In another model of cachexia the MAC16 colon adenocarcinoma anti-TNF-α antibodies also had no effect on the process of cachexia.[59] In a human squamous cell carcinoma of the maxilla grown as a xenograft in nude mice anti-TNF-α antibodies partially reversed, but did not completely normalize, body weight.[60] These results suggest that if TNF-α is involved in experimental models of cachexia it does not act alone and other factors must be involved.

Although acute administration of TNF-α to humans produces some of the effects associated with cancer cachexia, such as an increase in the efflux of total amino acids,[61] no phase I study of TNF-α has reported weight loss as part of the toxicity. Moreover most studies have failed to measure circulating TNF-α in cachectic cancer patients despite the requirements for high levels of TNF-α to induce cancer cachexia in experimental models. Thus, Socher *et al.*,[62] using a sandwich ELISA capable of measuring TNF-α to 40 pg/ml, failed to detect TNF-α in the serum from 19 patients who had lost 8–40% of their premorbid weight. Another sensitive assay using a double antibody technique capable of detecting TNF-α to 45 pg/ml also failed to detect TNF-α in the serum of 72 cancer patients, 10 of whom had severe cachexia.[63] This data seems to be at variance with that of Balkwill *et al.*[64] who reported elevated levels (0.9–40 ng/ml) of a labile 'TNF-like' activity in the serum of 50% of cancer patients studied using a single antibody technique capable of measuring down to 0.8 ng/ml. Even in this study there was no correlation between weight loss and 'TNF-like' activity. In a study of 32 children with malignancies (ALL, acute non-ALL and solid tumors) the level of TNF-α measured by a double antibody technique (detection limit 10 pg ml) in the serum was found to be elevated in 30 with levels ranging up to 450 pg ml.[65] The serum TNF-α levels decreased when the patients achieved remission, but did not correlate with the degree of weight loss. Thus, while elevated levels of TNF-α may be present in some cancer patients, it does not seem to be correlated with the presence of cachexia. Although local tissue concentrations of TNF-α have been suggested to be more important than

circulatory levels, as mentioned before cachexia is not a local tumor effect. Also mitigating against a local effect of TNF-α are experiments showing that endotoxin-stimulated mice had significantly elevated tissue concentrations of TNF-α mRNA in spleen and livers, but TNF-α mRNA levels were not significantly increased in any host tissue in cachectic tumor-bearing mice, and serum levels of TNF-α were also not elevated.[66] The only serum concentration which was increased was that for IL-6 and recent studies suggest that this cytokine may be more important in the pathogenesis of cancer cachexia than TNF-α.

IL-6

Strassman *et al.*,[67] using a transplantable MC26, which induces cachexia in syngeneic hosts, have shown an increase in the serum concentration of IL-6 with the development of cachexia. Moreover monoclonal antibodies to IL-6, but not TNF-α, were capable of partially reversing the weight loss and significantly increasing the weight of the epididymal fat pad without an effect on tumor weight. Levels of IL-6 but not TNF-α in the serum of cancer patients with weight loss associated with colonic adenocarcinoma and multiple hepatic metastases were also found to be elevated, when compared with patients with cholelithiasis and no weight loss, correlating with hepatic synthesis of acute-phase proteins.[68] It would be interesting to compare levels of circulating IL-6 in cancer patients with and without weight loss since IL-6 production may be related to the tumor-bearing state[69] rather than specifically with cancer cachexia. However, CHO cells transfected with the IL-6 gene have been shown to produce a syndrome of cachexia in nude mice.[70] Like TNF-α, IL-6 reduces adipose tissue LPL activity and this has been suggested as contributing to the loss of body fat stores associated with cancer cachexia.[71] In addition TNF-α increases circulating IL-6 and some of its effects may be mediated or potentiated by IL-6. Further studies are required to evaluate the role of IL-6 in cancer cachexia.

IFN-γ

Administration of repetitive sublethal doses of recombinant murine IFN-γ to non-tumor-bearing rats has been shown to produce a significant decline in both food intake and body weight.[72] Unlike TNF-α, there was no development of resistance to this effect with repeat administration. Passive immunization against recombinant rat IFN-γ partially protected rats bearing a transplantable methylcholanthrene-induced sarcoma from the decline in food intake and decrease in body weight normally associated with this tumor, as well as increasing the survival time.[72] However, elevated serum levels of IFN-γ were not detectable and antisera to TNF-α had no effect on host food intake or body weight change. Using mice bearing Lewis lung tumors it has been shown that tumor development is associated with IFN-γ production and with progressive weight loss.[73] Anti-IFN-γ antibodies counteracted the wasting syndrome, suggesting that IFN-γ production may be directly or indirectly responsible for the tumor-associated cachexia. The interaction between the various cytokines in the pathogenesis of cancer cachexia requires further elucidation.

Leukemia-inhibiting factor (LIF)

A human melanoma cell line, SEKI, which induces severe cachexia in tumor-bearing nude mice produces an inhibitor of LPL in adipocytes.[74] This substance is distinct from the above cytokines, but amino acid sequence analysis revealed that the amino-terminal portion of this material was identical to LIF, a substance capable of inducing differentiation and suppressing proliferation of the MI murine myeloid leukemia cell line.[75] Further studies have shown a relationship between the expression of LIF mRNA in melanoma xenografts and the development of cancer cachexia.[76] In contrast TNF-α mRNA was not associated with xenografts producing cachexia. Medcalf *et al.*[77] have reported that exogenously administered recombinant LIF induced body weight loss in experimental animals, but that this was due to toxicity. Thus care must be taken in attributing weight loss associated with the overexpression of a biological response modifier to cachexia rather than simple toxicity.

Lipid mobilizing substances in cancer cachexia

Fat mobilization by the cytokines is thought to occur indirectly through an inhibition of the enzyme LPL. Suppression of this enzyme activity

may lower the intake of fatty acids by adipocytes resulting in catabolism of lipids in adipose tissue.[78] In addition to this a number of investigations have provided evidence for the presence in cancer cachexia of lipid mobilizing factors (LMF), which cause direct hydrolysis of triglycerides in adipose tissue, with release of NEFA and glycerol, which although similar in mechanism of action appear to differ structurally from the lipolytic hormones.

The initial evidence for the production of LMF in cancer cachexia was provided from studies with Krebs-2 carcinoma cells in mice which showed that weight loss and, in particular, fat depletion could be reproduced with non-viable preparations of this tumor.[79] Further evidence for a circulatory LMF was provided when it was shown that serum from lymphoma-bearing mice when injected into normal mice produced an immediate massive fat mobilization.[80] This effect appeared to be different from mobilizing factors produced in starvation (e.g. adrenaline) since feeding had little or no effect on the ability of serum from tumor-bearing animals to mobilize lipids from adipose tissue. The LMF was also present in tumor extracts and in culture medium from a lymphoma cell line showing that it was a direct product of the tumor rather than being produced by some other tissue. Further studies by the same group suggested that LMF was a heat stable protein of around 5 kDa,[81] although subsequent studies suggested a high molecular weight material as the active species; the low molecular weight species aggregated on standing in the cold to become active.[82] The material was heat stable, but destroyed by trypsin and was not a lipase.

Another LMF, termed toxohormone L, has been isolated from the ascites fluid of patients with hepatoma and mice with sarcoma 180.[83,84] The material of 70–75 kDa, p*I* 4.7–4.8, appeared to be identical in both cases and caused suppression of food and water intake in rats when injected into the lateral ventricle. Trypsin digestion of the active material produced a low molecular weight material which was still active. A similar material of 6 kDa and negatively charged has been isolated from the conditioned medium of the A375 human melanoma cell line.[85] This material was heat stable and resistant to digestion by proteolytic enzymes.

Animals transplanted with the MAC16 murine colon adenocarcinoma also produce a circulatory LMF.[46] This material appears to be composed of three fractions of apparent molecular weight 3, 1.5 and 0.7 kDa as determined by exclusion chromatography.[86] This material is also capable of inducing weight loss in mice without a reduction in food intake, is heat stable and the activity is resistant to digestion by proteolytic enzymes. Again, the material is acidic in character, distinguishing it from the natural polypeptide hormones which are all basic. Material with identical chromatographic and molecular weight characteristics is also present in the serum of patients with clinical cancer cachexia, but is absent from normal serum, even under conditions of starvation. Such material is also absent from patients with Alzheimer's disease and weight loss.[87] The concentration of LMF in the serum of cancer patients correlated with the extent of weight loss up to 20% and the level was reduced with tumor response to therapy.[88]

All of these studies provide evidence for a similar type of molecule which is heat resistant, negatively charged and not degraded by proteolytic enzymes, although there is a wide variation in the estimated molecular weight between the studies. These results suggest either that LMF is a very low molecular weight fraction of a higher molecular weight protein, which is insensitive to trypsin or that it is not a protein molecule.

The availability of certain tumors to elaborate a LMF would explain the variability of cachexia with tumor type rather than with tumor mass[89] since some patients with very large tumors show no sign of cachexia.[40] Since administration of LMF produces loss of host lipids without a drop in food intake it would also correlate with the observation[90] that loss of host lipids is not due to anorexia, since pair-fed animals were found not to lose as much fat as did tumor-bearing animals.

Treatment of cancer cachexia

Treatment of cancer cachexia would be expected to increase the lifespan of the patient but progress has been hampered by the lack of an effective mechanism for the production of the condition. As previously mentioned, TPN is unable to fully reverse the weight loss seen in cancer cachexia and this finding has stimulated attempts to reverse the cachexia by other methods. Treatment can be divided into two groups. (i) Agents which stimulate food intake and alleviate anorexia. (ii) Agents aimed at inhibiting or reversing the metabolic effects of the tumor in the host.

The striking enhancement of appetite and weight

gain seen in breast cancer patients treated with high doses of megestrol acetate has formed the basis for several placebo-controlled, randomized trials in the treatment of cancer cachexia. These trials have demonstrated that megestrol acetate therapy improves appetite and food intake leading to weight gain in a subset of patients.[91] However, care should be exercised in the use of megestrol acetate in the treatment of cancer patients since experimental studies show that host weight gain is associated with the doubling of the weight of the tumor.[92] Also, analysis of body composition showed that the major contribution to the increase in body weight in animals treated with megestrol acetate was an increase in the water content, although patient studies show an increase in both body fat and lean body mass without an alteration in body water content.[93]

The weight enhancing effect of the serotonin antagonist, cyproheptadine, in several clinical situations has led to its evaluation in the treatment of patients with cancer cachexia.[94] However, although it produced a mild enhancement in appetite there was no significant enhancement in body weight.

Food intake and body weight gain has also been shown to be significantly increased by insulin in tumor-bearing rats with cachexia at an early stage.[95] Again care must be exercised in the use of appetite stimulants in patients with cancer cachexia, since insulin-induced body weight gain in an experimental model has been shown to be associated with an increased growth of the tumor.[96] This may explain the observation that provision of excess calories alone does not appear to change median survival in patients with advanced cancer.[11]

Since the mediator of cancer cachexia has not been positively identified fewer studies have concentrated on reversing the metabolic effect of the tumor on the host than on the anorexic effect. However, the polyunsaturated fatty acid (PUFA) eicosapentaenoic acid (EPA) has been shown to inhibit the action of a tumor produced LMF in an *in vitro* assay and to inhibit the development of cachexia in an *in vivo* model (MAC16).[97] The EPA appears to inhibit lipolysis in adipocytes by preventing the rise in cyclic AMP in response to the LMF. In addition to preserving adipose tissue EPA also prevented loss of skeletal muscle by a large reduction in the rate of protein degradation.[98] The anticachectic effect of EPA was exerted without a change in caloric intake. Clinical studies are required to determine the efficacy of EPA in cancer patients.

Cachexia in conditions other than cancer

Cachexia is an important complication in conditions other than cancer, although the mechanism(s) of this state may vary. Severe weight loss is frequently associated with thermal injury and this has been attributed to a combination of hypermetabolism and inadequate caloric intake.[99] Energy expenditures up to twice that of normal have been observed during the first 3 weeks after such injury. The increased energy expenditure may be due to elevated catecholamines.

Acquired immunodeficiency syndrome (AIDS) also produces a progressive and unexplained weight loss.[100] Patients with AIDS lose up to 34% of their ideal body weight during the last 4–5 months prior to death. In addition patients with AIDS typically lose 46% of their potassium by the time of death and this potassium is lost over approximately the last 9 months of life.[101] This will reflect a change in body cell mass, which may be sufficient to cause death. The level of circulating triglyceride has been shown to be elevated in AIDS patients[102] and this may be caused by production of TNF-α in response to infection.

Conclusion

Despite extensive investigations into the mechanism(s) of cancer cachexia no definite mediator of this condition has been identified. More work needs to be done, particularly with respect to the structural elucidation of LMF and its importance in cancer cachexia, as well as the specificity of increases in serum IL-6 to the cachectic state. At first sight cachexia seems an enigma and not advantageous to the tumor, since death of the host results in death of the tumor. However, since tumors are highly dependent upon an exogenous source of both lipids and amino acids, production by tumors of factors capable of causing catabolism of host tissues would secure availability of these substances for tumor metabolism. In this case inhibitors of cancer cachexia, by depleting the tumor of essential nutrients, might also be expected to be effective inhibitors of tumor growth, and indeed one such inhibitor, EPA, is an effective antitumor agent against a colonic adenocarcinoma resistant to conventional cytotoxic drugs.[97,98] This provides hope that a knowledge of the mechanism of cancer cachexia may provide a new locus for therapeutic intervention in the treatment of solid tumors.

References

1. Nathanson L, Hall TC. Lung tumors: how they produce their syndromes. *Ann NY Acad Sci* 1974; **230**: 367–77.
2. Brennan MF. Total parenteral nutrition in the cancer patient. *N Eng J Med* 1981; **305**: 375–82.
3. De Wys WD, Begg C, Lavin PT, *et al.* Prognostic effect of weight loss prior to chemotherapy in cancer patients. *Am J Med* 1980; **69**: 491–7.
4. De Wys WD. Management of cancer cachexia. *Semin Oncol* 1985; **12**: 452–60.
5. Nixon DW, Heymsfield SB, Cohen AE, *et al.* Protein-calorie undernutrition in hospitalized cancer patients. *Am J Med* 1980; **68**: 683–90.
6. Warren S. The immediate causes of death in cancer. *Am J Med Sci* 1932; **184**: 610–5.
7. Brennan MF. Uncomplicated starvation versus cancer cachexia. *Cancer Res* 1977; **37**: 2359–64.
8. Warnold I, Lundholm K, Scherstein T. Energy balance and body composition in cancer patients. *Cancer Res* 1978; **38**: 1801–7.
9. Theologides A. Pathogenesis of cachexia in cancer. A review and a hypothesis. *Cancer* 1972; **29**: 484–8.
10. Copeland EM, Macfayder BV, Dudrick SJ. Effect of hyperalimentation in established delayed hypersensitivity in the cancer patient. *Ann Surg* 1976; **184**: 60–4.
11. Heber D, Byerley LO, Chi J, *et al.* Pathophysiology of malnutrition in the adult cancer patient. *Cancer* 1988; **58**: 1867–73.
12. Evans WK, Makuch R, Clamon GH, *et al.* Limited impact of total parenteral nutrition on nutritional status during treatment for small cell lung cancer. *Cancer Res* 1985; **45**: 3347–53.
13. De Wys WD, Costa G, Aenkin R. Clinical parameters related to anorexia. *Cancer Treat Rep* 1981; **65**: 49–52.
14. Fredrix EWHM, Soeters PB, Wouters EFM, *et al.* Energy balance in relation to cancer cachexia. *Clin Nutr* 1990; **9**: 319–24.
15. Knox LS, Crosby LO, Feurer ID, *et al.* Energy expenditure in malnourished cancer patients. *Ann Surg* 1983; **197**: 152–62.
16. Hyltander A, Drott C, Korner V. Elevated energy expenditure in cancer patients with solid tumors. *Eur J Cancer* 1991; **27**: 9–15.
17. Drott C, Svaninger G, Lundholm K. Increased urinary excretion of cortisol and catecholamines in malnourished cancer patients. *Ann Surg* 1988; **196**: 645–650.
18. Knapp ML, Al-Sheibani S, Riches PG, *et al.* Hormonal factors associated with weight loss in patients with advanced breast cancer. *Ann Clin Biochem* 1991; **28**: 480–6.
19. Warren RS, Donner DB, Starnes HF, *et al.* Modulation of endogenous hormone action by recombinant human tumor necrosis factor. *Proc Natl Acad Sci USA* 1987; **84**: 8619–22.
20. Gerich JE, Karam JH, Forsham PH. Stimulation of glucagon secretion by epinephrine in man. *J Clin Endocrinol Metab* 1973; **37**: 479–81.
21. Weinhouse S. Metabolism and isoenzyme alterations in experimental hepatomas. *Fedn Proc* 1973; **32**: 2162–7.
22. Holroyde CP, Gabuzda TC, Putnam RC, *et al.* Altered glucose metabolism in metastatic carcinoma. *Cancer Res* 1975; **35**: 3710–4.
23. Chlebowski RT, Heber D, Richardson B, *et al.* Influence of hydrazine sulphate on abnormal carbohydrate metabolism in cancer patients with weight loss. *Cancer Res* 1984; **44**: 857–61.
24. Kralovic RC, Zepp EA, Canedella RJ. Studies on the mechanism of carcass fat depletion in experimental cancer. *Eur J Cancer* 1977; **13**: 1071–9.
25. Mulligan HD, Tisdale MJ. Lipogenesis in tumor and host tissues in mice bearing colonic adenocarcinomas. *Br J Cancer* 1991; **63**: 719–22.
26. Krebs HA. Some aspects of the regulation of fuel supply in omnivorous animals. *Adv Enzyme Regul* 1972; **10**: 397–401.
27. Hervey GR, Tobin G. Luxuskonsumption, diet-induced thermogenesis and brown fat. *Clin Sci* 1983; **64**: 7–13.
28. Mulligan HD, Beck SA, Tisdale MJ. Lipid metabolism in cancer cachexia. *Br J Cancer* 1992; **66**: 57–61.
29. Waterhouse C, Nye WHR. Metabolic effects of infused triglyceride. *Metabolism* 1961; **10**: 403–14.
30. Buzby GP, Mullen JL, Stein TP, *et al.* Host-tumor interaction and nutrient supply. *Cancer* 1980; **45**: 2940–5.
31. Siddiqui RA, Williams JF. The regulation of fatty acid and branched-chain amino acid oxidation in cancer cachectic rats: a proposed role for a cytokine, eicosanoid and hormone triology. *Biochem Med Metab Biol* 1989; **42**: 71–86.
32. Mahony SM, Beck SA, Tisdale MJ. Comparison of weight loss induced by recombinant tumor necrosis factor with that produced by a cachexia-inducing tumor. *Br J Cancer* 1988; **57**: 385–9.
33. Mueller PS, Watkin DM. Plasma unesterified fatty acid concentrations in neoplastic disease. *J Lab Clin Med* 1961; **57**: 95–108.
34. Hays ET. Serum lipids in human cancer. *J Surg Res* 1969; **9**: 273–7.
35. Clark CM, Goodlad GAJ. Depletion of proteins of phasic and tonic muscles in tumor-bearing rats. *Eur J Cancer* 1971; **7**: 3–9.
36. Rennie MJ, Edwards RHT, Emergy PW, *et al.* Depressed protein synthesis is the dominant characteristic of muscle wasting and cachexia. *Clin Physiol* 1983; **3**: 387–98.
37. Lundholm K, Bennegard K, Eden E, *et al.* Efflux of 3-methylhistidine from the leg in cancer patients who experience weight loss. *Cancer Res* 1982; **42**: 4807–11.
38. Melville S, McNurlan MA, Calder AG, *et al.* Increased protein turnover despite normal energy metabolism and responses to feeding in patients with lung cancer. *Cancer Res* 1990; **50**: 1125–31.
39. Lazo PA. Tumor–host metabolic interaction and cachexia. *FEBS Lett* 1985; **185**: 189–92.
40. Stein TP. Cachexia, gluconeogenesis and progressive weight loss in cancer patients. *J Theor Biol* 1978; **73**: 51–9.
41. Costa G. Cachexia, the metabolic component of neoplastic disease. *Cancer Res* 1977; **37**: 2327–35.
42. Norton JA, Morley JF, Green MV, *et al.* Parabiotic transfer of cancer anorexia cachexia in male rats. *Cancer Res* 1985; **45**: 5547–52.
43. Morrison SD, Moley JF, Norton JA. Contribution of inert mass to experimental cancer cachexia in rats. *J Natl Cancer Inst* 1984; **73**: 991–8.
44. Strain AJ, Easty GG, Neville AM. An experimental model of cachexia induced by a xenografted human tumor. *J Natl Cancer Inst* 1980; **64**: 217–21.
45. Tanaka Y, Eda H, Tanaka T, *et al.* Experimental cancer cachexia induced by transplantable colon 26 adenocarcinoma in mice. *Cancer Res* 1990; **50**: 2290–5.

46. Beck SA, Tisdale MJ. Production of lipolytic and proteolytic factors by a murine tumor-producing cachexia in the host. *Cancer Res* 1987; **47**: 5919–23.
47. Chance WT, Muggla-Sullam M, Chen M-H, *et al.* Reversal of tumor-induced biochemical abnormalities by insulin treatment in rats. *J Natl Cancer Inst* 1986; **77**: 497–503.
48. Rouzer CA, Cerami A. Hypertriglyceridemia associated with Trypanosoma brucei infection in rabbits: role of defective triglyceride removal. *Mol Biochem Parasitol* 1980; **2**: 31–8.
49. Kawakami M, Cerami A. Studies of endotoxin-induced decrease in lipoprotein lipase activity. *J Exp Med* 1981; **154**: 631–9.
50. Beutler B, Greenwald D, Hulmes JD, *et al.* Indentity of tumor necrosis factor and the macrophage-secreted factor cachectin. *Nature* 1985; **316**: 552–4.
51. Beutler B, Cerami A. Cachectin and tumor necrosis factor as two sides of the same biological coin. *Nature* 1986; **320**: 584–8.
52. Mahony SM, Beck SA, Tisdale MJ. Comparison of weight loss induced by recombinant tumor necrosis factor with that produced by a cachexia-inducing tumor. *Br J Cancer* 1988; **57**: 385–9.
53. Oliff A, Defo-Jones D, Boyer M, *et al.* Tumors secreting human TNF/cachectin induce cachexia in mice. *Cell* 1987; **50**: 555–63.
54. Darling G, Fraker DL, Jensen JC, *et al.* Cachectic effects of recombinant human tumor necrosis factor in rats. *Cancer Res* 1990; **50**: 4008–13.
55. Grunfeld C, Wiking H, Neese R, *et al.* Persistence of the hypertriglyceridemic effect of tumor necrosis factor despite development of tachyphylaxis to its anorectic/cachectic effect in rats. *Cancer Res* 1989; **49**: 2554–60.
56. Grunfeld C, Verdier JA, Neese R, *et al.* Mechanisms by which tumor necrosis factor stimulates hepatic fatty acid synthesis *in vivo*. *J Lipid Res* 1988; **29**: 1327–35.
57. Sherry BA, Gelin G, Fong Y, *et al.* Anticachectin/tumor necrosis factor-α antibodies attenuate development of cachexia in tumor models. *FASEB J* 1989; **3**: 1956–62.
58. Gelin G, Moldawer LL, Lonnroth C, *et al.* Role of endogenous tumor necrosis factor α and interleukin 1 for experimental tumor growth and development of cancer cachexia. *Cancer Res* 1991; **51**: 415–21.
59. Mulligan HD, Mahony SM, Ross JA, *et al.* Weight loss in a murine cachexia model is not associated with the cytokines tumor necrosis factor-alpha or interleukin-6. *Cancer Lett* 1992; **65**: 239–43.
60. Yoneda T, Alsina MA, Chavez JB, *et al.* Evidence that tumor necrosis factor plays a pathogenetic role in the paraneoplastic syndromes of cachexia, hypercalcemia and leukocytosis in a human tumor in nude mice. *J Clin Invest* 1991; **87**: 977–85.
61. Warren RS, Starnes HF, Gabrilove JL, *et al.* The acute metabolic effects of tumor necrosis factor administration in humans. *Arch Surg* 1987; **122**: 1396–400.
62. Socher SH, Martinez D, Craig JB, *et al.* Tumor necrosis factor not detectable in patients with clinical cancer cachexia. *J Natl Cancer Inst* 1988; **80**: 595–8.
63. Selby P, Hobbs S, Viner C, *et al.* Tumor necrosis factor in man: clinical and biological observations. *Br J Cancer* 1987; **56**: 803–8.
64. Balkwill F, Burke F, Talbot D, *et al.* Evidence for tumor necrosis factor/cachectin production in cancer. *Lancet* 1987; **ii**: 1229–32.
65. Saarinen UM, Koskelo E-K, Teppo AM, *et al.* Tumor necrosis factor in children with malignancies. *Cancer Res* 1990; **50**: 592–595.
66. Lonnroth C, Moldawer LL, Gelin J, *et al.* Tumor necrosis factor α and interleukin-1α production in cachectic, tumor bearing mice. *Int J Cancer* 1990; **46**: 889–96.
67. Strassman G, Fong M, Kenney JS, *et al.* Evidence for the involvement of interleukin 6 in experimental cancer cachexia. *J Clin Invest* 1992; **89**: 1681–4.
68. Fearon KCH, McMillan DC, Preston T, *et al.* Elevated circulating interleukin-6 is associated with an acute-phase response but reduced fixed hepatic protein synthesis in patients with cancer. *Ann Surg* 1991; **213**: 26–31.
69. McIntosh JK, Jablons DM, Mule JJ, *et al.* *In vivo* induction of IL-6 by administration of exogenous cytokines and detection of *de novo* serum levels of IL-6 in tumor-bearing mice. *J Immunol* 1989; **143**: 162–7.
70. Black K, Garrett IR, Mundy GR. Chinese hamster ovary cells transfected with the murine IL-6 gene cause hypercalcemia as well as cachexia, leukocytosis and thrombocytosis in tumor bearing nude mice. *Endocrinology* 1991; **128**: 2657–9.
71. Greenberg AS, Nordan RP, McIntosh J, *et al.* Interleukin 6 reduces lipoprotein lipase activity in adipose tissue of mice *in vivo* and in 3T3-LI adipocytes: a possible role for interleukin 6 in cancer cachexia. *Cancer Res* 1992; **52**: 4113–6.
72. Langstein H, Doherty GM, Fraker DL, *et al.* The roles of γ-interferon and tumor necrosis factor α in an experimental rat model of cancer cachexia. *Cancer Res* 1991; **51**: 2302–6.
73. Matthys P, Heremans H, Opdenakker G, *et al.* Anti-interferon-γ antibody treatment, growth of Lewis lung tumors in mice and tumor-associated cachexia. *Eur J Cancer* 1991; **27**: 182–7.
74. Mori M, Yamaguchi K, Abe K. Purification of a lipoprotein lipase-inhibitory protein produced by a melanoma cell line associated with cancer cachexia. *Biochem Biophys Res Commun* 1989; **160**: 1085–92.
75. Tomida M, Yamamoto-Yamiguchi Y, Hozumi M. Purification of a factor inducing differentiation of mouse myeloid leukemic MI cells from conditioned medium of mouse fibroblast L929 cells. *J Biol Chem* 1984; **259**: 10978–85.
76. Mori M, Yamaguchi K, Honda S, *et al.* Cancer cachexia syndrome developed in nude mice bearing melanoma cells producing leukemia-inhibitory factor. *Cancer Res* 1991; **51**: 6656–9.
77. Metcalf D, Nicola NA, Gearing DP. Effects of injected leukemia inhibitory factor on hematopoietic and other tissues in mice. *Blood* 1990; **76**: 50–6.
78. Nilsson-Ehle P, Garfinkel AS, Schotz MC. Lipolytic enzymes and plasma lipoprotein metabilism. *Annu Rev Biochem* 1980; **49**: 667–93.
79. Costa G, Holland JF. Effects of Krebs-2 carcinoma on the lipide metabolism of male Swiss mice. *Cancer Res* 1966; **22**: 1081–3.
80. Kitada S, Hays EF, Mead JF. A lipid mobilizing factor in serum of tumor-bearing mice. *Lipids* 1980; **15**: 168–74.
81. Kitada S, Hays EF, Mead JF. Characterization of a lipid mobilizing factor from tumors. *Progr Lipid Res* 1981; **20**: 823–6.
82. Kitada S, Hays EF, Mead JF, *et al.* Lipolysis induction in adipocytes by a protein from tumor cells. *J Cell Biochem* 1982; **20**: 409–16.

83. Masuno H, Yamaskai N, Okuda H. Purification and characterization of a lipolytic factor (toxohormone-L) from cell free fluid of ascites Sarcoma 180. *Cancer Res* 1981; **41**: 284–8.
84. Masuno H, Yoshimura H, Ogawa N, *et al.* Isolation of a lipolytic factor (toxohormone-L) from ascites fluid of patients with hepatoma and its effect on feeding behavior. *Eur J Cancer Clin Oncol* 1984; **20**: 1177–85.
85. Taylor DD, Gercel-Taylor C, Jenis LG, *et al.* Identification of a human tumor-derived lipolysis promoting factor. *Cancer Res* 1992; **52**: 829–34.
86. Beck SA, Mulligan HD, Tisdale MJ. Lipolytic factors associated with murine and human cancer cachexia. *J Natl Cancer Inst* 1990; **82**: 1922–6.
87. Groundwater P, Beck SA, Barton C, *et al.* Alteration of serum and urinary lipolytic activity with weight loss in cachectic cancer patients. *Br J Cancer* 1990; **62**: 816–21.
88. Beck SA, Groundwater P, Barton C, *et al.* Alterations in serum lipolytic activity of cancer patients with response to therapy. *Br J Cancer* 1990; **62**: 822–5.
89. Hollander DM, Ebert EC, Roberts AI, *et al.* Effects of tumor type and burden on lipid depletion in mice. *Surgery* 1986; **100**: 292–6.
90. Lundholm K, Edstrom S, Karlberg I, *et al.* Relationship of food intake, body composition and tumor growth to host metabilism in non-growing mice with sarcoma. *Cancer Res* 1980; **40**: 2516–22.
91. Tchekmedyian NS, Hickman M, Heber D. Treatment of anorexia and weight loss with megestrol acetate in patients with cancer or acquired immunodeficiency syndrome. *Semin Oncol* 1991; **18**: 35–42.
92. Beck SA, Tisdale MJ. Effect of megestrol acetate on weight loss induced by tumor necrosis factor α and a cachexia-inducing tumor (MAC16) in NMRI mice. *Br J Cancer* 1990; **62**: 420–4.
93. Schmoll E, Wilke H, Thole R, *et al.* Megestrol acetate in cancer cachexia. *Sem Oncol* 1991; **18**: 32–4.
94. Kardinal CG, Loprinzi CL, Schaid DJ, *et al.* A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. *Cancer* 1990; **65**: 2657–62.
95. Moley JF, Morrison SD, Norton JA. Insulin reversal of cancer cachexia in rats. *Cancer Res* 1985; **45**: 4925–31.
96. Beck SA, Tisdale MJ. Effect of insulin on weight loss and tumor growth in a cachexia model. *Br J Cancer* 1989; **59**: 677–81.
97. Tisdale MJ, Beck SA. Inhibition of tumor-induced lipolysis *in vitro* and cachexia and tumor growth *in vivo* by eicosapentaenoic acid. *Biochem Pharmacol* 1991; **41**: 103–7.
98. Beck SA, Smith KL, Tisdale MJ. Anticachectic and antitumor effect of eicosapentaenoic acid and its effect on protein turnover. *Cancer Res* 1991; **51**: 6089–93.
99. Gump FE, Kinney JM. Energy balance and weight loss in burned patients. *Arch Surg* 1971; **103**: 442–8.
100. Kotter DP, Wang J, Pierson RN. Body composition studies in patients with the acquired immunodeficiency syndrome. *Am J Clin Nutr* 1985; **42**: 1255–65.
101. Annon. What do we know about the mechanism of weight loss in AIDS? *Nutr Rev* 1990; **48**: 153–5.
102. Lahdevirta J, Maury CPJ, Teppo A-M, *et al.* Elevated levels of circulating cachectin/tumor necrosis factor in patients with acquired immunodeficiency syndrome. *Am J Med* 1988; **85**: 289–91.

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