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Comments and Critique

Cancer Cachexia Revisited: Old Problems and New Perspectives

DESPITE EVIDENCE that the extent of cancer-associated cachexia correlates with responses to antitumour therapy [1], the mechanisms underlying the progressive host-wasting of cachexia remain elusive. Although previous experimental and clinical studies have extensively described the metabolic parameters associated with cancer cachexia [2], no consensus of opinion regarding the specificity of these parameters to the cancer bearing state has emerged. Recent meta-analysis of prospective clinical trials also suggests that efforts to reverse the cancer cachexia state by nutritional intervention are of little benefit except in the presence of effective antitumour therapy [3]. As a consequence, the predominance of evidence implies that restoration of normal metabolic and functional responses in the cancer patient remains inexorably linked to eradication of the tumour.

The positive relationship between resolution of cachexia and effective disease-specific therapy is not unique to the malignant condition. The progressive erosion of structural protein and energy stores in concert with deterioration of function status is also a manifestation of benign inflammatory and injury processes [4]. Under these circumstances, the reversal of cachexia is often testament to the efficacy of medical or surgical therapy.

The metabolic manifestations of cancer cachexia have been contrasted to those exhibited by normal subjects undergoing starvation [5]. However, cancer patients exhibit only limited capacity to alter energy expenditure and substrate turnover appropriate to the level of nutrient intake [6–11]. The alterations of intermediary metabolism evidenced by the cancer cachexia state more closely resemble those responses elicited by inflammation and traumatic injury rather than those of a starvation-adapted physiology. Given the wealth of previous work in the field of injury metabolism, this recognition could provide productive directions in which to pursue mechanisms.

Two papers appearing in the current issue of this journal are ample evidence of both the progress and pitfalls emerging in recent cancer cachexia research. The clinical studies reported by Hyltander and colleagues from Gothenburg emanate from one of the prominent research groups in the field. The first of these (p.9) addresses the fundamental concept that weight-losing cancer patients exhibit a disproportionately elevated energy expenditure in comparison to their non-tumour-bearing counterparts. Given that cancer patients do not appear to have systemic alterations of energy expenditure during nutrient assimilation (feeding) [12], such an increase in energy expenditure is more readily documented during interdigestive periods. Using indirect calorimetry, the current study again documents that some populations of tumour-bearing patients, in this case those with solid tumours, manifest increased energy expenditure relative to body mass [6]. The authors have further sought to ascribe potential mechanisms to this process by covariate analysis of circulating hormone levels. Taken in concert with their previous observations [13, 14] this analysis leads them to propose that increased catecholamine sensitivity or production may represent the mechanism underlying this relative increase in energy exenditure. This form of retrospective analysis and statistical inference is reminiscent of those previously performed [4] in injured patients. Although a catecholamine influence upon systemic energy expenditure is demonstrable in normal subjects during exogenous administration, the hypothesis that a significant endogenous mechanism underlies the increased energy expenditure observed following injury has been disputed. In fact, recent work has suggested a disassociation of catecholamine responses from energy expenditure in some injury models [15].

To now propose that enhanced adrenergic activity represents the fundamental mediating event in cancer-associated energy expenditure requires a bit of mechanistic retrenchment. While there can be little doubt that cancer patients, like their injured counterparts, do exhibit some elements of altered macroendocrine hormone activity, intuition as well as recent data [16, 17] suggests that this endocrine activity represents a secondarily induced event. The nature of the proximal signal precipitating this response is at the very heart of the cancer cachexia controversy. The search for these signals would likely benefit from examination of cancer cachexia as a component of the inflammation and injury spectrum.

The authors, like others in the field, have previously suggested that inflammatory mediators, such as the cytokines, may be proximal mediators of this cachectic response. The cytokine class of mediators has proven capable *in vivo* of inducing many of the metabolic sequelae of acute injury as well as of the more chronic tissue responses of both inflammation and the tumour-bearing state [18–21]. Among the responses induced by enhanced cytokine production are anaemia and a counter-regulatory hormone response. These are precisely the components observed by the authors to be associated with increased energy expenditure.

Many of the cancer patients included in the current report did not exhibit detectable circulating levels of cytokines (tumour necrosis factor and interleukin-1) [22]. This observation, coupled with the lack of a statistical association between increased energy expenditure, anaemia, or other clinical evidence of inflammation, has led the authors to conclude that such mediators may not be necessary for the altered energy expenditure of cachexia. However, given the evidence that much of the paracrine activity of cytokine mediators occurs beyond the probing eye of current immunoassays [23, 24], such an analysis does little to decry a role for tissue-derived cytokine mediators in the cachexia process.

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The second paper emanating from the Gothenberg group (p. 16) further testifies to the similarities between cancer patients and their injured counterparts. By determination of both regional and systemic metabolic responses during parenteral feeding, these studies have sought to eliminate substrate availability as a major determinant of altered host metabolism. In contrast to post-absorptive conditions, where modest differences in substrate oxidation or utilisation may be demonstrable between cancer and non-cancer subjects, the process of parenteral feeding serves to minimise these differences. Such observations do not support the concept of a cancer-specific metabolic milieu, as regional and body protein responses in tumour and injury patients appear to coalesce during parenteral feeding. These data again suggest the existence of a unifying mechanism underlying both malignant and injury associated metabolic perturbations.

The observation that lean tissues do not respond to parenteral feeding in an anabolic fashion is not unique to these populations, as even normal subjects do not readily exhibit lean tissue nitrogen accrual during parenteral feeding [25–27]. This uniform lack of net tissue nitrogen accrual across the breadth of parenterally fed populations implies a condition of inadequate substrate supply or a deficiency of appropriate anabolic factors. It is likely that both circumstances apply although the ability to dissect nutrient adequacy from other components of hospitilisation, such as activity, is a challenging task [28].

There is a growing body of evidence to suggest that the route by which nutrients are provided may also influence the assimilation and ultimate tissue distribution of substrate. This influence is more clearly evident with regard to systemic substrate utilisation [29] than within regional (muscle) tissues [30]. However, differences in lean tissue metabolic response are demonstrable during stressful conditions such as infection (and possibly antitumour therapy) [31, 32].

In addition to evidence that metabolic responses can be influenced by both the adequacy and route of feeding, it is also likely that a synergy between macroendocrine hormones and the inflammatory mediators discussed above also directs the process of nutrient assimilation. These mediators may also influence the production of essential anabolic agents [33]. These initial observations now suggest that an integrated hypothesis of cancer cachexia, like that evolving in injury research, will require a molecular perspective relating inflammatory mediator and hormone interactions to the adequacy of nutrient intake and the host capacity for growth factor generation.

It is increasingly evident that cachexia, be it associated with malignancy or tissue injury and repair, is initiated and propagated by a complex system of mediators. Thus far, both the specific initiating event(s) as well as those signals serving to sustain the process have proven elusive. Rather than addressing the issue of cancer associated cachexia as a unique state, it will likely prove more rewarding to pursue future efforts in parallel with developments in other fields of metabolic and nutrient biology.

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Radiotherapy in the Elderly

ALTHOUGH there is an obvious need to lay down guidelines for the use of radiotherapy in elderly patients, few books or publications have dealt specifically with this aspect of oncology, usually without providing the detailed information necessary for the development of appropriate routine practice. There is, however, considerable current interest in developing more rational approaches to oncological problems in old age as shown by the organisation in October 1990 of a joint NCI–EORTC consensus meeting by the European School of Oncology on neoplasia in the elderly.

These initiatives complement the efforts directed by oncologists to the treatment of malignant disease in children over the past 20 years. Indeed the considerable volume of data describing tolerance to radiation in childhood contrasts with the paucity of information dealing specifically with comparable problems in the elderly. Oncological approaches directed specifically towards the old age group assume that there are important and relevant biological differences between the elderly and young adults. Clearly in this respect the definition of old age is arbitrary; for example a 60-year-old obese individual with cardiac problems is biologically older than Gandhi in his later years, underlining the fact that the concept of old age is more a combination of chronic pathologies than a straightforward chronological issue.

Epidemiological information, together with medical and ethical factors, underlines the importance of considering geriatric oncology as an integral part of general oncology. In the most common forms of malignant disease (cancers of the lung, prostate and digestive system in men, and of the breast, digestive system and gynaecological organs in women, with lung cancer becoming increasingly important), incidence increases progressively with age. This, taken in conjunction with the trend towards an ageing population in Western countries, explains why the annual incidence of cancer increases regularly with time and suggests that cancer patients will increasingly present at an advanced age. In this department for example 63% of new patients are over the age of 60 and 25% over the age of 70. With current demographic trends it may be anticipated that the proportion of elderly patients will increase in the coming decades particularly in patients over the age of 70.

A further important epidemiological finding is the increasing frequency of isolated or multiple organ insufficiencies associated with old age [1]. We believe that the problem for the use of radiotherapy in old age is the frequency of associated pathologies which may determine the tolerance of older patients' normal tissues to treatment. Thus, it is rather the general condition of the patient than age which conditions the approach to the management of his disease and to the selection of treatment on an individualised basis. Old patients are frequently considered unsuitable for curative surgery because of their general condition which further increases the proportion of elderly patients referred for radiotherapy. The basis for the decision of the radiation oncologist with regard to the selection of a palliative or curative approach includes medical judgement and a humanistic appreciation of the patients' needs and wishes.

Epidemiological information also suggests that as age increases, histological verification of the presence of malignant disease decreases [2]. A presumed diagnosis of cancer may be considered adequate in the elderly patient because life expectation is assumed to be limited. It is important to remind ourselves that a woman of 70 years has a further life expectation of 15 years and a man of 70 can expect to live a further 8–10 years [3]. It is true, however, that with increasing age, cancer becomes a relatively less important cause of death (Table 1) [2].

Information on epidemiological trends is a mandatory basis for the future planning of radiotherapy as has been carried out in the Netherlands in the 1980s [4]. This aspect, however, will not be discussed further.

In considering the use of radiotherapy in elderly patients three major problems need to be addressed: firstly to determine the likely natural course of the disease in relation to age and to assess prognosis; secondly to acquire information on the tolerance to radiotherapy which includes a consideration of technical problems (immobilisation, the feasibility of prolonged supine

Table 1. Mortality from cancer according to age (West of Scotland, 1983–1985) [2]

	Deaths	
	Male	Female
All ages	24	22
>65	id.	id.
>75	20	14
>85	14	10

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