# Understanding and Managing Cancer Cachexia

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## CASE SCENARIO 1

*Mrs MJ is a 56-year-old architect with a husband and two children. You performed a mastectomy and axillary dissection on her after neoadjuvant chemotherapy for locally advanced breast cancer 2 years ago. Unfortunately, she developed widespread disease with metastases to liver, lung, and bone. After several more rounds of chemotherapy, she is currently on antiestrogen therapy. Her disease appears stable. You have continued to follow her and she comes to see you for her routine visit. You notice that she is much thinner than you remember, but otherwise looks well. You ask her about her weight loss. She says: "I don't really know what it is! I can eat, my bowels are working, but I simply don't want to. I force myself to swallow food, but I keep losing weight anyway." On clinical examination, you notice her muscle wasting and recognize the signs of cancer cachexia. You want to know more about how to manage this phenomenon.*

Patients with advanced disease often lose their appetite, lose weight, and become profoundly weak and tired, finding even the most basic activities difficult. These can be manifestations of the cachexia syndrome. Evident in cancer patients, most markedly in lung and upper gastrointestinal cancers, it is also observed in other diseases, including chronic obstructive pulmonary disease, advanced organ failure (heart, liver, kidney), and AIDS. This article is primarily concerned with cancer cachexia, which we define as "a wasting syndrome involving loss of muscle and fat directly caused by tumor factors, or indirectly caused by an aberrant host response to tumor presence."

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Cancer cachexia is a profound metabolic process characterized by breakdown of skeletal muscle and harmful, chaotic abnormalities in fat and carbohydrate metabolism, despite adequate nutritional intake. Although patients often look as if they have been starved, this condition cannot be reversed with short-term nutritional supplementation. A previous article in this series discusses the role of supplemental nutrition in advanced disease.[1] The diagnosis of cachexia is made by a history of substantial weight loss in the context of advanced disease, and a physical examination demonstrating muscle wasting. Causes of potentially reversible weight loss should be assessed and managed as outlined in Table 1. Successful treatment of the underlying disease or tumor may reverse the cachexia syndrome and this issue should be explored and abandoned if futile.

Although a formal classification for cancer cachexia does not exist, we presume that a variable interaction of tumor products, neuroendocrine changes, and host inflammatory molecules leads to wasting in individual patients. Our classification of some of the possible variables contributing to cachexia is outlined in Table 2. As with other illnesses, a targeted therapy can be applied only when we can categorize a patient's wasting in specific pathophysiologic terms. Continued study of the molecular epidemiology of this symptom will result in a better classification system and such studies should be prioritized. Today, we are dependent on an imperfect understanding, based on clinical judgment and a few helpful laboratory studies. Here we focus on some of the exciting advances in our basic understanding of cancer cachexia and the potential clinical interventions that stem from this knowledge.

We begin this discussion by outlining our current and evolving understanding of the basic underlying metabolic changes that occur during cancer cachexia. We will follow with a discussion of past and ongoing clinical endeavors to manage this difficult problem, and finish with a discussion of patient, family, and caregiver con-



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**Abbreviations and Acronyms**

ACE = angiotensin converting enzyme
DHA = docosahexaneoic acid
EPA = eicosapentaenoic acid
IGF = insulin-like growth factor
NSCLC = non-small cell lung cancer
TNF = tumor necrosis factor
Ub = ubiquitin

cerns when the cancer patient reaches a stage of advanced cachexia.

## BASIC MECHANISMS OF CANCER CACHEXIA: AN EVOLVING UNDERSTANDING OF ANABOLIC AND CATABOLIC INFLUENCES

### Loss of skeletal muscle protein

The prognostic significance of weight loss in cancer patients is well established. Weight loss is strongly associated with poor outcomes from the earliest disease stages through to advanced cancer.[2] The negative nitrogen balance underlying cancer cachexia leads to a significant wasting of skeletal muscle. Muscle loss reduces patient mobility, jeopardizes respiratory function, relates to reduced immunity, and is associated with poor performance status and outcomes. So stabilization of muscle losses or regain of lean tissue mass are the targets of interventions that are currently applied.

### Mitigation of catabolic influences and the restoration of anabolism

Reduced nitrogen balance in cancer cachexia results from a fundamental metabolic shift that results in decreased anabolism and increased catabolism;[3-5] the simultaneous presence of both of these defects results in the most rapid muscle atrophy. It is important to appreciate that the mechanisms and regulation of biosynthesis (anabolism) and protein breakdown (catabolism) are functionally distinct. Hypoanabolism implies a deficit in the supply of amino acids or energy or a failure of normal anabolic stimuli required for muscle protein synthesis to proceed. Hypercatabolism involves participation of catabolic mediators and activation of intracellular proteases. Abnormalities of both anabolism and catabolism must be treated. Nutritional support with amino acids and energy may have limited efficacy in the absence of a driver of protein synthesis, and vice versa. Anabolic therapy by itself would be partially effective or

**Table 1.** An Approach to Identify Potentially Correctable Causes of Cancer Cachexia

| Potentially correctable problems | Possible approaches |
|---|---|
| Psychological factors | |
| Anxiety | Anxiolytics |
| Depression | Antidepressants |
| Family distress | Social assistance |
| Spiritual distress | Counseling |
| Eating problems | |
| Appetite | Referral to a nutrition clinic or a dietician |
| Disturbed taste or smell | Zinc supplementation |
| | Multivitamins |
| Oral | |
| Dentures, mouth sores | Antifungal medication |
| Thrush | Oral moisteners |
| Dry mouth | Change medications |
| Swallowing difficulties | Antifungal medication |
| | Esophageal dilation |
| | Regurgitation therapy |
| Stomach | |
| Early satiety | Gastric stimulants |
| Nausea and vomiting | Related to cause |
| Bowel | |
| Obstruction | Related to cause |
| Constipation | Laxatives, especially if on opioids |
| Malabsorption | |
| Pancreas | Pancreatic enzymes |
| Fistulas | Related to cause |
| Fatigue | |
| Inability to sleep | Anxiolytics |
| | Exercise protocol |
| | Sleep protocol |
| Motivation | Exercise protocol |
| | Methylphenidate |
| Function | Exercise protocol |
| | Cause related |
| Pain | Appropriate analgesics |
| | Nerve blocks: surgical, percutaneous |
| | Counseling |
| Metabolic | |
| Diabetes | As indicated |
| Adrenal insufficiency | |
| Hypogonadism | |
| Thyroid insufficiency | |

This assessment is made easier by the routine use of simple patient-completed questionnaires. These allow for ongoing quantitative data that help physicians zero in on specific problem areas. Examples of such scales include the Edmonton Symptom Assessment Scale,[125] the European Organization for Research on the Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ C-30) and its associated disease-specific modules,[126] and the Edmonton Functional Assessment Tool.[127]

**Table 2.** Classification of Potential Variables Contributing to Cancer Cachexia

| Variable | Defect or problem | Intervention |
|---|---|---|
| Human relationship with food | Obstruction | Enteral/parenteral supplementation |
| | Sensory acuity | Sensory enhancement |
| | Appetite | Orexigenic agents |
| | Satiety | Satiety modulation |
| | Psychological | Psychological |
| | Social/environmental | Social/environmental |
| Nutritional deficiency | Essential fatty acids | Referral to a nutrition clinic or dietician or supplements |
| | Essential amino acids | Referral to a nutrition clinic or dietician or supplements |
| | Antioxidant nutrients | Referral to a nutrition clinic or dietician or supplements |
| | Vitamins/minerals | Referral to a nutrition clinic or dietician or supplements |
| Anabolic deficit | Insulin/insulin-like growth factor-1 resistance | Anabolic therapy |
| | Gonadal steroids | Anabolic steroids |
| | Muscle contractile activity | Exercise training |
| Catabolic drivers | Treatment related | Specific anticatabolic interventions |
| | Inflammatory | |
| | Adrenal | |
| | Tumor derived | |

ineffective in the presence of unmitigated hypercatabolism, and it becomes even more apparent that a clear understanding of how to shut off catabolic processes is needed to underpin effective strategies for cancer cachexia. A multimodal strategy that stimulates protein synthesis, provides energy and building blocks for net protein anabolism, and normalizes proteolysis, would be required for effective therapy. Failure to address cancer cachexia at these key levels may explain the failure, to date, to devise consistently effective therapeutic interventions.

### *Identity of circulating anabolic and catabolic factors*

There has been considerable research interest in potential mediators of the process of cachexia, reviewed by a number of authors.[6-9] Although anorexia might be present, the degree of muscle wasting is in excess of that elicited by simple starvation. Factors implicated in cancer-associated muscle wasting include a decreased concentration or responsiveness to various anabolic factors including insulin, insulin-like growth factor (IBF) 1, thyroid hormone, growth hormone, testosterone, and increased presence or activity of various catabolic agents, including glucagon, cortisol, proinflammatory cytokines, eicosanoids, and a proteolysis-inducing glycoprotein of tumor origin. Systematic modulation of the production (or activity) of these factors has been studied in animal models to identify causal factors in cancer-associated muscle wasting. Of these various factors, several dominant themes are evident in current investigations of the humoral mediation of cancer cachexia: inflammation and tumor-derived catabolic factors that provoke unbridled proteolysis and lipolysis.

### *Inflammation and cancer cachexia*

The response of the body to cancer has many parallels with systemic inflammation.[10-13] In this sense, the underlying mechanisms of chronic catabolism in patients with cancer are similar to those associated with acute injury, and agents that have been effective in treating catabolism during acute inflammation may also have relevance to cachexia (Table 3). Cytokines appear to have a significant role in cancer-associated wasting. A range of proinflammatory cytokines play a direct role, including interleukin-1-$\beta$, interleukin-6, tumor necrosis factor (TNF)-$\alpha$, and interferon-$\gamma$.[12] This has been positively established by modulation of cytokine production or activity using experimental approaches such as passive immunization with antibodies to cytokines, cytokine receptor knockout mice, or animals overexpressing soluble receptor isoforms.[6] Such approaches

**Table 3.** Articles Published Since 1999 on the Investigational and Proven Clinical Therapeutic Agents for the Treatment of Cancer Cachexia

| | Reference nos. | |
|---|---|---|
| **Action site/agent** | **Cancer cachexia** | **Other cachexia-causing diseases** |
| Central (CNS) | | |
| Progestational agents | 57,128–131 | 61,132,133 |
| Cannabinoids | 128 | |
| Olanzepine | | 134–136 |
| Corticosteroids | 105 | |
| Cholecystokinin/leptin | 137 | 138,139 |
| Anabolic | | |
| Steroids | 8,38,91–94 | 61,103 |
| Amino acids | 108,109,140,141 | 142,143 |
| Insulin | Review, 144 | |
| Insulin-like growth factor growth hormone | 145,146 | 104,147–149 |
| Creatine | | 83 |
| Exercise | | 61,143,150 |
| Antiinflammatory | | |
| Polyunsaturated fatty acids: Eicosapentaenoic acid (n-3) (fish oil) | 114,117,119,122,151–153 | |
| NSAIDS | Review, 20 | |
| Macrolide antibiotics | 27–29 | |
| Cytokine inhibitors | 154,155 | 156 |
| Statins | | 157–159 |
| Thalidomide | 30,31 | |
| Others | | |
| ACE inhibitors | | 158–161 |
| ATP | 162,163 | |
| Proteasome inhibitor | 164 | |
| Propranolol | 165,166 | 167 |
| Gastric stimulants | | 138,139 |
| Epoeitin-alpha | 168 | |

clearly implicate TNF-$\alpha$ in muscle wasting in animal models, such as with methylcholanthrene fibrosarcoma,[14] Yoshida hepatoma,[15,16] and Lewis lung carcinoma;[17] interleukin-6 appears to play a major role in cachexia induced by the murine C-26 adenocarcinoma.[18] TNF-$\alpha$ has also been proposed to be involved in the development of insulin resistance,[19] which is frequently observed in cancer patients and contributes to tipping the metabolic balance toward catabolism.

Eicosanoids are key inflammatory mediators that have also been implicated in cancer cachexia.[20] Eicosanoids are unsaturated 20-carbon fatty acids that include a host of the lipoxygenase and cyclooxygenase products. These factors are produced by some tumors[21,22] and by the host during immune responses. Some evidence for the involvement of eicosanoids in the inflammatory process that underlies cancer-associated wasting has come from studies examining the action of nonsteroidal antiinflammatory drugs (NSAIDs), including traditional NSAIDs and agents developed to selectively block synthesis of the inducible proinflammatory prostaglandins.[23]

The n-6 and n-3 series of polyunsaturated fatty acids, found in high concentrations in vegetable oils and fish oils, respectively, are known to influence the production of eicosanoids. Eicosapentaenoic acid (EPA) (n-3) and arachidonic acid (n-6) are major substrates for the formation of eicosanoids. Eicosanoids derived from n-3 fatty acids have up to 100-fold less biologic potency in the induction of cellular responses than those derived from arachidonic acid and are usually associated with decreased inflammatory responses.[24] So one clear mech-

anism whereby n-3 fatty acids might influence catabolism would be through modification of the eicosanoid axis, resulting in a reduction in the inflammatory response. Alternatively, they may alter production of eicosanoids involved in the signaling pathways of various catabolic mediators (eg, the proteolysis-inducing factor).[25,26]

It is not clear which form of antiinflammatory therapy might be the most appropriate intervention. The list of possible candidates might include conventional NSAIDs, COX II inhibitors, anticytokine antibodies, cytokine-soluble receptors, and the n-3 fatty acids. Macrolide antibiotics[27-29] and thalidomide[30,31] have also been suggested as cancer cachexia treatments, in part based on their antiinflammatory actions. This question remains to be clarified, and to date no experimental study has made comparisons of the efficacy of these agents, nor have they been systematically compared with regard to their additional benefits, side effects, and contraindications.

### Proteolysis-inducing factor

Tumor-derived proteolysis-inducing factor is a novel molecule that mediates catabolism in mice bearing the MAC16 adenocarcinoma.[32] This proteolysis-inducing glycoprotein of tumor origin consists of a short polypeptide chain that is highly glycosylated. When muscle cells or animals are treated with the purified factor, intense protein catabolism is elicited.[33-35] An identical factor is found in humans,[9,36] and there is provocative preliminary evidence that its presence is associated with weight loss in cancer patients. The proteolysis-inducing glycoprotein was detected in the urine of 80% of patients with unresectable pancreatic cancer.[37] These patients had a greater total weight loss (12.5 kg versus 4.5 kg) and a greater rate of weight loss than patients whose urine did not contain this factor. The factor appears to be present in a broad spectrum of cancer patients (ie, carcinomas of the breast, lung, ovary, melanoma, gastrointestine) with active weight loss, but is absent in cancer patients who are not losing weight or in weight-losing patients with benign disease.[9,36] These results possibly represent discovery of a critical factor responsible for cancer cachexia in man. This discovery is of great interest and deserves confirmation and extension. Until a routine diagnostic test for this factor becomes available, its prevalence remains unknown.

## Targeting convergent catabolic mechanisms

A conclusion arising from experimental studies is that muscle wasting falls into distinct subtypes when considered at the level of humoral mediators.[4,7] For example, in the Yoshida hepatoma, muscle protein catabolism is attributable to a cytokine (TNF-$\alpha$) and the proteolysis-inducing glycoprotein is absent, whereas increased muscle protein catabolism in the MAC16 adenocarcinoma is caused by the proteolysis-inducing glycoprotein and does not appear to involve TNF-$\alpha$.[4] These models may very well be analogous to what occurs in cancer patients, but the full profile of putative catabolic mediators in cancer cachexia has never been detailed in any cancer patient population. Some limited profiles are available. For example, for non-small cell lung cancer, there is evidence that wasting is associated with decreased levels of anabolic mediators including IGF-1 and testosterone paired with a systemic inflammatory response.[38] Subsets of patients may express the proteolysis-inducing glycoprotein.[37] If the catabolic mechanisms in different patients are exclusive, then antiinflammatory or anticytokine therapy would be required in one instance and a different approach, such as antagonism of the proteolysis-inducing factor, would be required in the other. This would also require that patients exhibiting different catabolic mechanisms be discriminated from one another during clinical assessment for appropriate interventions to be applied. It is encouraging that there is building evidence of common elements to catabolic signal transduction in cancer cachexia. A more complete understanding of these common pathways may lead to the development of a single therapy that would be effective regardless of which circulating signal was involved. In particular, activation of the ubiquitin proteasome proteolytic system appears to be a common proteolytic pathway of cancer-associated muscle catabolism.

### Ubiquitin-proteasome proteolytic system

Reversal of catabolic processes has always been a significant challenge related to our incomplete understanding of the mechanisms involved.[39] It has emerged that a nonlysosomal proteolytic system involving ubiquitin and the proteasome is responsible for the bulk of basal proteolysis in skeletal muscle. Glickman and Ciechanover[40] provide an up-to-date review of the biochemistry of the ubiquitin-proteasome pathway and its physiologic functions. Activation of this system is common in muscle atrophy including all rodent models of cancer-

associated muscle wasting tested so far. Muscle biopsy is required to obtain evidence for activation of this system in human subjects, and a few data are becoming available to corroborate animal studies. Bossola and colleagues[41] reported ubiquitin mRNA levels in rectus abdominis muscle biopsies from gastric cancer patients twice those in patients with benign abdominal diseases, and ubiquitin mRNA levels were directly correlated with disease stage.[42]

The ubiquitin-proteasome system is characterized by the concerted action of enzymes that link chains of the polypeptide cofactor, ubiquitin (Ub), onto proteins to tag them for recognition and degradation by the proteasome, a large protease complex.[43] Three enzymes are required to link chains of ubiquitin onto proteins destined for degradation. E1 (Ub-activating enzyme) and E2 (Ub-conjugating enzymes) prepare ubiquitin to be linked to target proteins. E3 (Ub-protein ligase) is a key class of enzyme in the process, coupling ubiquitin and the actions of E1 and E2 to the protein substrate, conferring specificity to the system. Two newly identified muscle-specific ubiquitin-protein ligases (E3s), atrogin-1 (also called MAFbx) and MURF1, have been implicated in the development of muscle atrophy. Multiple ubiquitin ligases may operate in muscle atrophy, possibly to connect protein catabolism to different classes of external stimuli. This is suggested by the reported findings that null mutation of either MAFbx or MURF1 in mice led to resistance to denervation-induced muscle atrophy.[44]

Further studies are required to better understand the importance of the ubiquitin ligase family, including identifying the physiologic substrates for these enzymes in skeletal muscle, elucidating signaling events that regulate their activity, and analyzing the effects of specific inhibition through gene ablation or the design of selective inhibitors. A more complete understanding of this level of regulation may potentially allow for local suppression of muscle catabolism without affecting the degradative processes in nonmuscle tissues.

The degree to which signal transduction from various catabolic mediators is convergent upstream of the ubiquitin-proteasome system remains to be determined. Several potential intracellular signaling molecules are of interest. For example, eicosanoids appear to lie in the catabolic signal transduction pathways of both cytokines and the proteolysis-inducing glycoprotein.[20] Nuclear translocation of the transcription factor NF-$\kappa$B is emerging as a crucial component in catabolic signal transduction.[45] This factor modulates the expression of many genes, including those involved in regulating inflammatory and immune responses, as well as cell proliferation, differentiation, and death. TNF-$\alpha$ is a potent inducer of NF-$\kappa$B,[46] and the proteolysis-inducing factor acts through NF-$\kappa$B.[47]

## Anabolic factors

Low levels of or poor responsiveness to the normal complement of anabolic stimuli is an additional factor contributing to loss of lean body mass in the tumor-bearing state. When appropriately activated, protein synthesis requires the simultaneous provision of energy for peptide bond formation and the correctly balanced mixture of the 20 necessary amino acids.

Recent literature on cancer cachexia in experimental studies has not featured many papers on regulation of protein anabolism. A number of factors that are anabolic to skeletal muscle, such as insulin and IGF-1, are also anabolic to tumors, so are precluded as therapies for cancer cachexia. In the broader literature on muscle anabolism there are a number of contributions relating to the effects of contractile activity, glucocorticoids, and anabolic steroids on muscle protein synthesis, and the interactions among these factors. Glucocorticoids and inactivity act synergistically to activate muscle protein catabolism.[48] Amino acids and anabolic steroids potentiate the anabolic effects of muscular work.[49] Anabolic steroids are emerging as a class of compounds considered in the therapy of wasting diseases.

## Amino acids with anabolic properties

There is not yet sufficient understanding of amino acid use to support cancer-specific specialized amino acid formulae for enteral or parenteral nutrition. Appropriately formulated amino acid mixtures may be expected to alleviate muscle loss, improve tolerance to treatments, or have immune-stimulatory properties, allowing more effective antitumor immune responses.

Current experimental research in this area is based on the concept of manipulating amino acid mixtures to alter the balance between the host and the tumor, in a manner that favors the host overall.[50] For example, glutamine supplementation improved whole body nitrogen retention and increased protein synthesis and glutamine content in muscle and small intestine of tumor-bearing rats, but did not affect size, protein synthesis, or DNA

content of tumors in the same animals.[51-53] An enteral formula containing ornithine and α-ketoglutarate, the metabolic precursors for the formation of glutamine and arginine, did not stimulate growth of two hepatomas.[54] Similar results have been obtained for arginine and ornithine, although at least in some cases, tumor growth is stimulated by the parenteral administration of arginine. The acute phase response, where present, promotes altered amino acid requirements because acute phase proteins contain relatively high levels of sulfur-containing amino acids.[13,55] The branched chain amino acids, leucine, isoleucine, and valine, not only act as substrates for protein synthesis, but also modulate several elements of the protein synthetic machinery involved in initiation of translation.[56] Leucine is the most potent of the three branched chain amino acids in this regard, and leucine supplementation increases skeletal muscle protein synthesis.

## CLINICAL THERAPEUTIC AGENTS FOR THE TREATMENT OF CANCER CACHEXIA

Table 3 provides a summary of clinical studies of cancer cachexia therapy published since 1999. Relevant investigations in other wasting diseases are cited. These diseases may share common pathways to cancer cachexia, offering insight into convergent mechanisms and drug development. It is noteworthy that most trials in cancer represent the only study ever reported for the therapy in question, and these are often limited to a single, highly defined tumor group. The vast majority of the results remain to be corroborated by further work. Apart from corticosteroids and progestational agents, therapies are still at the investigational stages. There is a basis of logic for trials involving polytherapy to simultaneously modulate several axes of the wasting response, but this type of trial remains scarce.

Until recently, therapies concentrated on the anorexia arm of the anorexia-cachexia syndrome. Indeed, the only therapies proved successful in our clinics improve appetite, but do not improve muscle mass. We will not discuss corticosteroids, which are proven appetite stimulants, because they are also catabolic agents that increase muscle breakdown. So they are usually used for anorexia-cachexia late in the disease process and for short time periods. Progestational agents relieve anorexia and reverse weight loss in many patients, but the weight gain is a result of fat accumulation rather than muscle. Cannabinoids also act on central mechanisms controlling appetite, but have no effect on muscle metabolism.

For the first time we may have at hand simple, generally inexpensive compounds that might improve muscle mass and, consequently, patient function and mobility. If the promise of laboratory studies and a few extant clinical trials can be confirmed by large randomized studies, the impact on patient well-being and the healthcare system will be momentous. Anorexia-cachexia removes patient independence, resulting in sharply diminished quality of life and, often, prolonged costly home or institutional care. Moreover, the purposeless inflammatory response noted in cancer patients is also common to other wasting disorders, and measures that correct cancer cachexia may be successfully applied to other chronic illnesses such as congestive failure and chronic obstructive pulmonary disease.

Prior to reviewing agents that might influence lean body mass, a few points must be stressed:

1. With the exception of the progestational agents, all of the compounds we will discuss require further clinical trial corroboration.
2. Patients are subject to multiple problems that can contribute to loss of appetite, weight, and function. The physician must analyze and address the potentially correctable battery of causes before assuming that cachexia stems from tumor factors, neuroendocrine changes, or inflammatory processes. Table 1 outlines a memory aid used by one author (NM) in patient review.
3. One is naturally concerned that relieving patient malnutrition may, in some circumstances, also enhance tumor growth or interfere with chemoradiotherapy. Agents selected for clinical trials must either have a pedigree of safety in animal studies, or act through mechanisms that should not support tumor progression.
4. Nutritional counseling, ideally provided by a dietician, is a necessary platform on which nutraceutical drug therapy can be established. Patients and family members can be taught simply applied stratagies for selecting and preparing tasty foods.

There is an important ethical issue to discuss. Cancer chemotherapy studies are usually based on well-established animal tumor and toxicity models, and proceed in orderly fashion through phase I–III trials. Well funded by pharmaceutical firms, the agents usually carry high potential for profit upon marketing. The provenance of anticachexia agents is more complex. Few animal models are available or used, and preliminary evi-

dence for efficacy arises not from conventional cancer research, but multiple other streams including surgical metabolic laboratories, nutrition programs, AIDS clinics, and geriatric research centers. Because cancer centers have long established links with major pharmaceutical firms, setting up a "pipeline" for cancer cachexia trials may prove problematic if these trials are judged to interfere with traditional cancer chemotherapy studies. At present, a paradox is apparent: cachexia should be managed at onset to prevent its ravages from progressing, yet clinical trials for promising anticachexia agents may not be accessed by patients at risk because the patients will be encouraged to participate in chemotherapy trials, which may exclude participation in other trials because of potential influence on interpretation of the chemotherapy response. In "real time," patients will wish to access all therapies that will help them to control their disease, their symptoms, and their life quality, and to maintain their independence.

An illogical and unethical situation exists if pharmaceutical firm-cancer center–FDA collaboration prevents patients from taking part in nutrition trials at the onset of an illness that predictably will cause them major nutritional problems. New pragmatic clinical trial models that enable patients to access coordinated multiple research programs are necessary, both on scientific and ethical grounds.

## Promising agents

### *Progestational hormones*

Megestrol and medroxyprogesterone acetate are the best established drugs for increasing appetite and reversing weight loss in cancer patients. Indeed, their efficacy has been demonstrated in at least 15 randomized clinical trials.[57] The modus operandi of progestational agents is not certain; they may act through mediation of cytokine production,[58] an effect on hypothalamic systems mediating appetite, or both.[59] The duration of trials is usually short, with few studies extending beyond 12 weeks. Progestational drugs commonly improve appetite,[60] but we don't have evidence that patient function is improved or sustained. In a recent study, geriatric men actually lost muscle mass while on megestrol,[61] consistent with studies reporting the weight gain is primarily fat.[62]

Progestins are patient friendly, with mild and acceptable toxicity, although concerns have been raised about their use in very advanced disease or in combination with chemotherapy.[63,64] At present they are the gold standard for appetite stimulation; their role, if any, in enhancing muscle function or global quality of life in combination with other approaches remains to be established.

### *Cardiovascular agents*

Patients with most forms of cancer tend to be older, and many have been smokers. So a substantial number have evidence of coronary artery disease and other atherosclerotic complications at presentation. Consequently, they may be taking statins (cholesterol lowering agents) or angiotensin converting enzyme inhibitors (ACE inhibitors). It is possible that these drugs may influence the course of cancer-associated wasting.

Statins have antiinflammatory effects independent of their action on cholesterol pathways; they consistently lower C-reactive protein,[65,66] an acute phase protein that is a nonspecific marker for chronic inflammation. High levels of C-reactive protein correlate with the presence of cachexia and tumor progression.[13,67-69] Although statins greatly interest cardiologists, few cancer studies have been carried out. Could their antiinflammatory actions help control tumor cachexia? This issue may first be clarified through epidemiologic studies correlating patients using statins and their subsequent cancer course. For the present, observant clinicians may wish to specially note features of illness in their patients on statins.

ACE inhibitors are commonly used by patients with hypertension, coronary heart disease, and congestive heart failure. Representative agents include lisinopril, captopril, and enalopril. In addition to their control of cardiovascular disorders, ACE inhibitors may have properties that can improve muscle function.

"The renin-angiotensin system is a master regulator of human physiology."[70] Aside from effects on vascular tone and fluid and electrolyte balance, angiotensin-II, activated by an enzyme blocked by ACE inhibitors, increases the production of cytokines linked to the inflammatory response.[71] Reports indicate improved anabolism and function.[72,73] It is noteworthy that ACE inhibitors have a range of potential antitumor effects in animal systems, including modulation of tumor angiogenesis.[74] A number of epidemiologic record linkage reviews have been carried out that report ACE inhibitors have a neutral effect—they neither increase nor decrease the incidence of human tumors.[75,76]

Current evidence indicates that ACE inhibitors may be safely used in patients without fear of stimulating

tumor growth with careful monitoring of blood pressure. It is reasonable to hypothesize that through their ability to interfere with angiotensin stimulation of cytokine activity and their positive effects on energy transfer and ATP availability, muscle function may be improved. At least one trial of an ACE inhibitor in cachectic cancer patients is currently underway. The specific ACE inhibitor under study, imidapril, is highly lipophilic, which may enhance its entry into skeletal muscle, and subsequently affect muscle function.

Recently a study on elderly hypertensive women receiving ACE inhibitors reported superior muscle function, as measured by knee extensor muscle strength and walking speed, in comparison with women whose hypertension was untreated or controlled with other antihypertensives.[72] In an intriguing study on healthy young men, a particular gene polymorphism for ACE correlated with superior muscle performance and anabolic response to exercise.[73] Volunteers with an insertion allele I (a 287 bp fragment) performed better than matched participants lacking the I allele in a series of exercise tests. Followup studies correlating the presence of cachexia with ACE gene polymorphism and response to a variety of therapies will be interesting.

### *Macrolide antibiotics*

Erythromycin and other 14-membered ring macrolide congeners (clarithromycin, roxithromycin) possess antiinflammatory properties independent of their effects on microbes, and this is a potential mode of action for cachexia therapy. Macrolides have been reported to limit TNF-$\alpha$ and interleukin-6 production in vitro [77,78] and in vivo.[79,80] Roxithromycin may be the most antiinflammatory macrolide, followed by clarithromycin and erythromycin; the 15-membered ring macrolide, azithromycin, is less active.[28] Macrolides stimulate gastric motility, an additional anticachexia effect. Additionally, macrolides reduced tumor growth and enhanced chemotherapy tumor kill in animal studies.[81,82]

A small open trial reported that survival of clarithromycin chemotherapy-treated non-small–cell lung cancer (NSCLC) patients was doubled compared with that in patients on chemotherapy alone.[27] A subsequent open label trial involving 33 patients with NSCLC demonstrated that interleukin-6 levels were reduced in patients receiving clarithromycin, a result that correlated with both increased survival and improved body weight.[29] Lung cancer patients are subject to repeated infections and one may argue that effects on survival and weight relate to control of infection. The investigators state that the clarithromycin-treated patients did not have different patterns of infectious illness when compared with other NSCLC patients. The question remains open because of the small study enrollment (49 and 33 patients, respectively).

Laboratory studies and a small patient series reported by a single group have stimulated interest in the study of selected macrolide antibiotics in conjunction with anticancer therapies. Recently, concern has been raised that widespread use of macrolide antibiotics for the management of acute upper respiratory infections, most of which are probably virally induced, is increasing the incidence of resistant bacteria in the community. Should this concern limit macrolide study in cancer patients? When the total numbers of cancer patients who may take part in macrolide clinical trials is contrasted with the vast exposure of the general population to clarithromycin and roxithromycin, we conclude that studying the influence of macrolide agents on the course of cancer and cancer wasting is a worthy objective that will not substantially increase the public health problem associated with reckless use of these antibiotics in medical practice.

### *Creatine*

As one notes browsing in sports and nutrition stores, creatine, offered in large cans hefted by muscular men and women, is a ubiquitous supplement among bodybuilders and athletes, who believe creatine increases muscle energy, enabling them to train longer and perform at a higher level. Indeed it is claimed that well over 50% of athletes at the 1996 Olympic Games were using creatine. Without doubt, creatine is an important metabolite obtained through diet (primarily meat and fish) and synthesized de novo. Creatine phosphate serves as an essential phosphate donor for the synthesis of ATP, a critical energy source for inaugurating muscle activity. Increased lean body mass is generally observed in healthy individuals.[83-87]

If the sports medicine lore on creatine is correct, perhaps creatine can also build up the muscles of weak, malnourished cancer patients. Evidence to date on this straightforward proposition is not available, as few crossover studies from sports medicine to the wasting disorders exist. In some part a dichotomy is present between the mindset of those of us who use treatments to kill

cancer cells; our sports medicine colleagues are more interested in using nutritional supplements to maintain or enhance healthy body functions. Rationally, we should co-opt their knowledge and skills in supporting normal function, an effort that will not detract from and may enhance our primary interest in controlling disease and associated symptoms.

The sports medicine literature is replete with trials demonstrating that healthy individuals taking creatine will achieve a significant increase in lean body mass in comparison with placebo compounds and, less consistently, will also improve muscle function.[83-87] Increase in muscle mass may be secondary to an athlete's ability to maintain a training routine, although it remains possible that creatine may have a direct effect on muscle protein synthesis. A creatine trial in older men concluded that muscle performance improved after a 7-day trial.[88] We are not aware of creatine trials in cancer patients. A recent article reported that nonsmall cell lung cancer patients receiving ATP infusions noted weight and albumin stabilization, and increased function and general quality of life.[89] Because creatine enhances ATP formation, it may be a good clinical trials candidate.

Creatine is regarded as a safe supplement; only minor adverse effects have been reported. Mild abnormalities in renal function may occur.[90] Almost all studies include small numbers of patients and are shortterm, with few of them extending beyond 21 to 28 days. Cancer patients with renal impairment or with fragile fluid-electrolyte balances may be at particular risk and will need careful followup if placed on creatine trials.

### *Anabolic agents*

In 1889 the distinguished French physiologist Brown Sequard reported that an intravenous extract of dog and guinea pig testicles improved his cognition, constipation, and "the arc of his urine" (no doubt a placebo effect—don't try it at home). The predominant male hormone, testosterone, was subsequently identified and characterized in the 1930s and recognized shortly thereafter as a hormone that stimulated muscle growth. Although physicians have been slow to grasp the significance of this finding, athletes around the globe were quick on the pickup and many, either as individuals or as part of state-operated programs, incorporated anabolic agents into their treatment. Many clinical studies report that testosterone and its analogs can facilitate muscle growth,[8,38,54,91-95] yet anabolic steroids have only achieved a tentative hold in medical practice aside from their use in clearly demonstrated hypogonadal states. In part, lack of use stems from the tainted association with widespread illicit use of anabolic steroids. As with opioids, physicians shy away from drugs subject to abuse or that may bring them into contact with sometimes ill-informed punitive regulatory authorities. In addition, the longterm effects of androgens, which include hirsutism in women, liver damage in both genders, and adverse changes in serum lipids, have discouraged their use. Nevertheless, in view of the profound suffering associated with wasting and chronic illness, a reevaluation of the role of anabolic steroids in these conditions is currently underway.

As emphasized throughout this article, muscle mass and function are dependent on a simple triad: adequate nutrients, protein synthesis, and control of proteolysis. Testosterone levels are commonly reduced in patients with severe illness.[93] For example, a hypogonadal state is often present in patients with advanced lung cancer.[38,96,97] The problem may lie at the level of the Leydig cells in the testis because patients with lung cancer and low testosterone often have correspondingly high luteinizing hormone levels.[96]

Testosterone replacement is simply accomplished, but the androgen status of chronically ill patients is rarely assessed, and the results of anabolic therapy in wasting disorders remain somewhat equivocal. Studies on healthy men indicate that supraphysiologic injections of testosterone or its analogs induce muscle synthesis with short-term use.[98,99] Testosterone levels drop in both elderly men and women; testosterone injections that maintain serum testosterone in the middle to high physiologic range (to avoid adverse effects) improved muscle size and function in a group of elderly men.[92] In an acute surgical setting (preparation of older men for knee replacement surgery), physiologic doses of testosterone enanthanate were associated with a nonsignificant decrease in hospitalization and a significant improvement in ability to stand after surgery.[100] Testosterone increases lean body mass, strength, and weight in men with HIV infection and low testosterone,[101-103] and some studies using androgens also report improved function and quality of life.[104] Study differences may relate to a patient's basic hormonal status, anabolic preparation dosage, or route of administration.

To date, studies in cancer patients do not provide a clear vector of support. The North Central Cancer

Treatment Group randomized cancer patients to receive fluoxymesterone (an anabolic agent), dexamethasone, or megestrol. Appetite stimulation and weight gain were significantly less evident in patients on fluoxymesterone; there was no difference in the quality-of-life scores of patients in the three arms.[105] Muscle mass and function were not assessed. Contrast a recently reported trial of oxandrolone (an oral synthetic derivative of testosterone), which concluded that weight-losing cancer patients on this agent not only increased their weight, but weight gain was also associated with improvement in lean body mass, improved Eastern Cooperative Oncology Group performance status and quality-of-life scores, including the functional component.[94] Older studies using other anabolic drugs, nandrolone and danazol, demonstrated stabilization of weight in some cancer patients.[106,107]

It may seem evident that people with associated low testosterone should receive replacement therapy of a hormone that can improve mental function, muscle size, sexual activity, and function. These salubrious results have been noted in hypogonadal but otherwise healthy men. Many questions remain to be clarified in clinical trials. Will chronically ill cancer patients benefit similarly to other populations? How efficacious is testosterone in combination with other drugs and cancer treatments? What is the optimal nutritional support when one is taking steroids? What are some important exclusion criteria from these trials? Given the potential benefits steroids may impart, they should be considered in the context of a multimodal strategy for promoting anabolism in individuals with cachexia. We should prioritize studies on anabolic agents used in combination with amino acids; antiinflammatory agents, such as EPA; and exercise, which enlist participants with early identified anorexia-cachexia with or without chemotherapy- radiotherapy. In view of the widespread evidence of hypogonadism in advanced cancer patients, patient hormonal status should be determined, and testosterone replacement should be offered to patients with abnormal levels and clinical evidence of androgen deficiency, if the patient so desires.

### *Amino acids*

There are a very small number of studies of amino acid supplementation in cancer patients. Supplemental oral N-acetyl-cysteine was reported to improve quality of life, normalize redox state, and increase plasma albumin levels and body cell mass in 50 patients with various forms of inoperable cancer,[108] suggesting that cysteine becomes conditionally essential in cancer. Importantly, the survival curve from the start of treatment to 550 days was not different between the group that received supplementation and the patients who did not, which indirectly suggests that supplemental cysteine did not enhance tumor growth. An amino acid mixture containing glutamine, arginine, and $\beta$-hydroxy $\beta$-methyl butyrate (a metabolite of leucine) promoted deposition of lean body mass in NSCLC patients without any reported side effects.[109] Formal assessments of amino acid requirements using current methods are much needed to formulate amino acid mixtures optimized to support anabolism and function in cancer patients. This represents a large gap in current knowledge, and it seems unlikely that anabolic therapy can be entirely successful without this information. If, as suggested by the few available trials, amino acid supplementation alone can indeed promote net gain of lean body mass, even without a concomitant anabolic therapy, it seems possible that a combination therapy involving both may hold the promise of much more important gains.

### *Omega-3 fatty acids*

EPA and docosahexaneoic acid (DHA) (n-3s) are formed from the conversion of linolenic acid and are found in fish with dark, oily flesh such as salmon, trout, sardines, and mackerel. EPA, in particular, is thought to inhibit the action of the proteolysis-inducing glycoprotein. Dietary fatty acids are incorporated into the cell membrane phospholipids and alter the activity and affinity of receptors, membrane permeability, and transport properties,[110,111] resulting in a profound effect on immune, muscle, and cancer cell function. Both EPA and DHA reduce inflammation by diverting cell membrane prostaglandin metabolism away from eicosanoid mediators of inflammation.[112,113] In addition, EPA decreases inflammatory cytokine production, and can stabilize acute phase protein levels (eg, C-reactive protein).[25,114] These actions, together with EPA's effects in blocking ubiquitin-proteosome-induced muscle proteolysis, probably account for EPA's favorable effect on wasting syndromes. Through mechanisms possibly independent of its effect on wasting, EPA also inhibits animal tumor activity, enhances antitumor effects, and reduces adverse effects of many chemotherapeutic agents.[115,116]

The n-3s are safe compounds. In a phase I trial, participants took up to 0.3 g/kg of EPA, well beyond the 2 to 4 g/day doses used in clinical trials.[117] Even at high doses, toxicity is relatively mild: patients complain of bloating, "a fishy taste," and loose bowel movements. The early phase II trials by the Edinburgh Group that enlisted pancreas tumor patients not otherwise receiving chemotherapy were promising.[114,118] Significant improvements in weight, function, and, to a lesser extent, appetite were reported; of particular interest, in contrast to megestrol acetate lean body mass increased. The n-3 randomized trial conducted by Gogos and associates[119] echoed these results, reporting an improvement in survival and in immune function, with an increase of CD4-CD8 ratios.

In a 14-day study of patients receiving doses of EPA less than 2 g/day, the nutritional parameters of o-3 (EPA plus DHA) showed no significant difference in the selected nutritional parameters measured.[120] Before the supplementation period, plasma and neutrophil content of n-3 fatty acids were markedly lower than those in healthy controls and exhibited further declines after chemotherapy. These levels improved after a short course of EPA-DHA.[121]

Following on their series of phase II trials, the Edinburgh group carried out a phase III double-blind, randomized, placebo-controlled trial, again enlisting weight-losing chemotherapy naïve pancreatic cancer patients. The source of n-3 in this study was a liquid nutrient supplement providing patients with 1.1g EPA and 460 mg DHA, with patients being advised to take two cans each day. The placebo, perhaps not a true placebo because of its nutrient content, was an isocaloric, isonitrogenous supplement without EPA and DHA. An improvement in survival was not demonstrated in the n-3 treated group, but, once again, these authors reported an improvement of lean body mass in patients who were taking more than 1.5 g EPA daily.[122]

A recently completed randomized, double-blind North Central Cancer Treatment Group–National Cancer Institute of Canada study compared the n-3 nutrient supplement used in Edinburgh (and the same placebo) with megestrol and the two agents in combination. In a disparate advanced cancer patient population, a survival advantage was not noted for the n-3 supplemented groups. Megestrol alone remained the superior agent for weight and appetite gain. The trial did not compare changes in lean body mass.[123]

At present, it appears that n-3 fatty acid supplementation can help maintain lean body mass in some cancer patients and a dose of 2 g EPA per day seems to be necessary. Because these compounds are strong oxidants, it is recommended that patients take n-3s in combination with a low dose of vitamin E. Studies on n-3 fatty acids in combination with chemotherapeutic agents are warranted, as are trials that combine these agents with anabolic hormones, amino acid nutrients, and exercise.

We have discussed a number of potential interventional compounds, a few of which should be considered for incorporation into the management of advanced cancer patients, and others that are prime candidates for clinical trials. Reflecting author bias, we have chosen not to discuss other compounds of potential interest, including marketed TNF-$\alpha$ inhibitors, propanalol, growth hormone, thalidomide, melatonin, clentbuterol, or a selective protein synthesis inhibitory substance, myostatin. Among this group, thalidomide and melatonin may be of particular interest. We regard the TNF-$\alpha$ inhibitors as too specific and too expensive, and growth hormone as potentially dangerous in cancer patients in view of the possibility of tumor stimulation. Time may prove us wrong.

## THE TERMINAL PHASE OF CANCER CACHEXIA

### Case scenario 2

*"Oh my God, doctor! He looks like awful!" your office assistant whispers into your ear as you enter the examining room to see "Chuck" on a followup visit. You remember doing a right upper lobectomy on him sometime last year for a non-small cell carcinoma. You are wondering if Chuck, who was never fond of seeking medical attention, was compliant during his followup care with the oncologists. "They have tried a lot of things, but he keeps losing weight. If I could just get him to eat more then he might gain some weight. He's nothing but skin and bones!" says Chuck's wife of 30 years while you take your seat, noting his annoyance at her comment. "She's always going on about my weight. I never did weigh more than 120 pounds soaking wet and now all we ever do is fight about eating! Our son keeps bugging my other doctors to start me on a feeding tube, and my sister keeps showing me all this nutritional supplement stuff from the Internet." The report of last week's CT scan of the abdomen showing interval development of liver metastases does little to increase your own comfort in this encounter. Chuck's wife begins weeping and says, "I just*

*don't want him to starve to death!"*

How does the surgeon respond to this situation, which will arise whenever the wasting syndrome does not respond to treatment or when treatment is declined? Many patients, families, physicians, and nurses are burdened by misinformation regarding the decline in food and water intake at end of life. The association between feeding and caring is so central to our culture, it is little wonder that this emotionally charged scenario presents itself frequently when caring for patients with progressive, chronic illness. Understandably, patients and their loved ones will reach for anything that will distract them from the meaning of the "handwriting on the wall" that accelerating weight loss such as that depicted in the vignette signifies.

As in any other situation with life-limiting implications, surgeons responding to the last stages of the cachexia syndrome will need to balance their fears of taking away hope with their obligation to defend their patients from false and misleading hope. Only a sound understanding of the physiology of the wasting syndrome can provide the cognitive guidance the surgeon will need in this delicate operation. Clearly, the word *starvation* has to be used much more guardedly in discussions about weight loss. Consider the differences in the physiologic and moral contexts of starvation, forced starvation, and cancer-induced cachexia. To imply or allow it to be implied that neglect was the reason for weight loss when it was the result of an irreversible physiologic process is to risk creation of a distress even greater than the illness itself.

Even if the surgeon cannot offer the benefit of a trial of therapy in far advanced cases of cancer-induced cachexia, clarifying the reasons for the weight loss and the implications for feeding can do much to relieve patients and caregivers of an enormous burden. Surgeons have earned a high degree of credibility on matters of nutrition because of their contributions to nutrition research, their familiarity with gastrointestinal illness and its treatment, and their role in establishing routes for nutrition. A surgeon should be able to explain when and why weight loss does not mean hunger. McCann and colleagues[124] demonstrated that hunger and thirst are uncommon complaints in terminally ill cancer patients. When these symptoms occurred, small amounts of food or water were needed for symptom relief. Almost invariably, a patient with far advanced wasting will give a look of relief or thanks when their caregivers are tactfully counseled and gently redirected on this issue.

If the surgeon feels hopeless because nothing more can be done to reverse the physical process, reframing the problem in a larger context will often rekindle the sense of hope and feelings of trust, because reframing a shared disappointment implies nonabandonment. History is replete with examples of "bad" or adverse things that have ultimately served the good such as the promotion of justice by the voluntary self-denial of food. A less lofty but much more common example is the exchange of former eating patterns for diminished eating resulting in greater physical comfort and less psychological, social, and spiritual distraction. As part of the process of redirecting patients toward achievable goals, the surgeon can view this clinical stop in the patient's journey as an opportunity to introduce the necessary elements for future guidance and support, whether it is referral to hospice services, scheduling a home visit with a pastor, or volunteering to call and review the discussion with that pesky son from California.

In summary, based on current views on the anorexia-cachexia syndrome in cancer patients, we put forward the following recommendations:

1. Wasting is a predictable event in many cancer patients, readily diagnosed by assessment of weight, change in appetite, and food intake. Often these patients will also have anemia and low albumin, with a concomitant increase in C-reactive protein. The above simple assessments should form a consistent part of the record of all advanced cancer patients.
2. Use a systematic formal guide to rule out treatable secondary causes of wasting (Table 1).
3. At the onset and throughout the course of illness, offer patients nutritional counseling (they should have access to a nutrition team with a special interest in wasting disorders), encourage them to take part in a rehabilitation program tailor made for their needs and abilities, and consider the use of specific nutraceutical and pharmacologic interventions. Followup visits should not only note careful evaluation of antitumor therapy and tumor volume, but also regular assessment of symptom control, weight, appetite, and function.
4. Take careful note of the full medication profile of patients who are wasting. These might include drugs that could have a favorable effect on anorexia-cachexia (cardiac agents such as the statins, ACE inhibitors) and other agents that may be deleterious (eg, herbal medications laced with corticosteroids). It is reasonable for patients to increase the

amount of EPA-rich omega-3 fatty acids in their diet. This could consist of an increase in the fish content in the diet coupled with EPA supplements in the range of 1.5 to 2.5 g, accompanied by a vitamin supplement containing vitamin E. Oncologists will discourage the use of vitamin E and other antioxidants during the days of chemotherapy treatment.

5. Testosterone status should be established in cancer patients with the anorexia-cachexia syndrome. If clearly reduced, physiologic testosterone supplementation should be considered after discussion with the patient.
6. Patients must be assured of a reasonable intake of amino acids. Protein-containing foods are indicated and rich sources of both essential and nonessential amino acids will support any anabolic potential.
7. Clinical researchers should be more cognizant of the work of their colleagues in sports medicine, AIDS, and geriatrics. Learning from their enterprises, further studies on creatine and supraphysiologic amounts of amino acids with a particular role in protein synthesis should be conducted. Similarly, the role of supraphysiologic doses of anabolic agents, in combination with nutrients and compounds that control muscle proteolysis, should receive a high priority.
8. There are few if any negative exercise trials. Patients should be encouraged to keep active or take part in tailored exercise programs, and studies on nutritional and pharmacologic agents should incorporate the potential additive effects of exercise.
9. Surgeon researchers have led the way in studies on acute stress reactions related to surgery and trauma and the role of nutrients in combating these events. This rich vein of research can guide further anorexia-cachexia trials and should be expanded to encompass studies on wasting associated with chronic disease.

## Appendix

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