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CANCER-ASSOCIATED CACHEXIA AND UNDERLYING BIOLOGICAL MECHANISMS

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■ **Abstract** Cancer metastases (spread to distant organs from the primary tumor site) signify systemic, progressive, and essentially incurable malignant disease. Anorexia and wasting develop continuously throughout the course of incurable cancer. Overall, in Westernized countries nearly exactly half of current cancer diagnoses end in cure and the other half end in death; thus, cancer-associated cachexia has a high prevalence. The pathophysiology of cancer-associated cachexia has two principal components: a failure of food intake and a systemic hypermetabolism/hypercatabolism syndrome. The superimposed metabolic changes result in a rate of depletion of physiological reserves of energy and protein that is greater than would be expected based on the prevailing level of food intake. These features indicate a need for nutritional support, metabolic management, and a clear appreciation of the context of life-limiting illness.

CONTENTS

LITERATURE ON CANCER-ASSOCIATED CACHEXIA

A review of current biomedical literature databases using the term "cachexia" and synonym search terms reveals more than 1600 articles since 1999 that addressed some issue related to cachexia (of any disease). About 40% of the 400 citations related to cancer cachexia consist of brief reviews or commentaries; few large, comprehensive, evidence-based reviews of the cancer cachexia literature currently exist. An article on nutrition in bone marrow transplantation is to be found in the Cochrane library (116), as is a review of megestrol acetate in anorexia-cachexia therapy (18). Another systematic review of anorexia-cachexia therapy recently appeared (161).

Of the original scientific investigations represented in the cancer cachexia literature, half were conducted in laboratory animals and the other half in humans. The work in animal models is especially suited to the study of the underlying biological mechanisms and will be important for the rational development and preclinical investigation of cachexia therapy. However, we continue to emphasize (5, 7) that the lack of a consensus set of animal models for investigations into metabolism and nutrition in cancer is an impediment to current understanding. These models must be demonstrated to align with the corresponding cachexia phenotypes evident in humans, and rigorous and standardized monitoring of physical, physiological, metabolic, nutritional, and behavioral paradigms for the various animal models must be developed.

Clinical research on cancer cachexia includes investigations of possible mechanisms and mediators as well as randomized clinical trials of anticachexia therapies. Interestingly, this research emanates largely from oncology teams. Although the nutrition research community possesses a large potential and capacity for research related to cachexia, we found it striking that, for example, less than 5% of articles published by nutrition researchers in our own country (Canada) during the past six years were related to cancer in any context, and the majority of these were related to cancer prevention and not to the nutritional sequelae of cancer. This would

appear to constitute an opportunity for nutrition research, given the degree to which nutrition appears to be implicated in both cancer incidence and cancer progression.

CACHEXIA: DEFINITIONS OF THE TERM

There is no universally accepted definition for cachexia. Features of a "syndrome of cachexia" are often used to evoke a portrait of the problem and its context of advanced malignant disease. Here cachexia is usually expressed as a constellation of factors contributing to the problem (i.e., anorexia, chemosensory distortion, early satiety, and hypermetabolism) or outcomes (i.e., wasting, asthenia, dyspnea, anemia, psychosocial distress, and dependency upon others). This captures the context and conveys a sense of the suffering, but it is not a strict definition.

Cachexia is synonymous with emaciation and is embodied in the apt term "skin and bones." Cachexia may be best defined as a state of depletion; ideally, one would like to quantify this specifically. A classification of underweight using defined age-related cutoff points for body mass index (BMI) might be considered satisfactory; however, the depletion of adipose and lean tissues clearly merit separate consideration. Muscle wasting can coexist with depletion of adipose tissue but may also coexist with obesity. A definition of cachexia would entail the identification of a threshold level of physiological reserves of energy, protein, or both, below which significant impairment or risk occurred. No such explicit definition is currently in use.

In relation to skeletal muscle depletion, researchers on human body composition are attempting to formally define sarcopenia, a generic term for the loss of skeletal muscle mass. It has been suggested that sarcopenia may be defined as values less than two standard deviations below the sex-specific mean for relative skeletal muscle index [muscle mass (kg) divided by stature squared (kg/m^2)] in healthy, younger adults. The limiting levels of skeletal muscle, by these criteria, are $<7.26\ kg/m^2$ for men and $<5.45\ kg/m^2$ in women (13, 14). Another approach used to define sarcopenia has been to test the prognostic significance of different levels of relative skeletal muscle index for clinical outcomes relevant to the patient population in question. Definitions of sarcopenia in the elderly focus on its prognostic significance for functional problems in gait and balance, risk of falls, and inability to complete tasks of daily living (15, 75), whereas definitions of sarcopenia in hospitalized patients focus on outcomes such as length of stay and rates of infectious and noninfectious complications (90). The prognostic significance of skeletal muscle and adipose tissue depletion in relation to cancer-specific outcomes remains to be determined.

The term "cachexia" is sometimes used to describe the dynamic process of involuntary weight loss that leads to depletion of physiological reserves of protein and energy. The process of weight loss is not, per se, cachexia; however, it is important because weight loss is related to the period over which an individual may be expected to become cachectic. The intensity of muscle loss and of negative

energy balance as well as the initial size of adipose tissue reserves and skeletal muscle define the risk of becoming cachectic during a defined period. During weight loss, individuals will pass through the zone conventionally referred to as "healthy" or "ideal" body weight and body composition. However, depending on the intensity of weight loss, severe depletion will be either imminent or will eventually occur; this situation is neither healthy nor ideal. Various perspectives exist on how to classify this involuntary weight loss. At this time, the classifications concern weight and do not separately discriminate rates of muscle and fat loss. The classic work of DeWys et al. (45) defined weight loss >5% prior to the onset of chemotherapy as the defining point for risk of poor response to therapy and shortened survival, independent of stage of malignancy or performance status. The National Cancer Institute's Common Toxicity Criteria (118), used widely for the definition of cancer- and cancer therapy–associated toxicity specific for weight loss, define the total degree of loss relative to prior body weight as follows: Grade 0, <5% loss; Grade 1, 5%–10%; Grade 2, 10%–20%; and Grade 3, >20%. Grade 4 (life-threatening) toxicity is not defined. Taking into account that 5% loss has been clearly demonstrated to be associated with poor outcome and the fact that 20% loss would be fatal in some individuals, these criteria seem considerably underweighted. In another perspective on intensity (loss per time), Blackburn et al. (20) suggest that losses of >2% in one week, >5% in one month, >7.5% in three months, and >10% in six months would be considered severe. That none of the foregoing classifications are commonly agreed upon is an important problem because until there is a widely accepted classification for involuntary tissue loss, there can be no common basis for action.

All of the attempts to classify and to evaluate relative risks of body energy and protein reserves and of rates of weight loss are confounded by a very wide distribution of body compositions in cancer patients. At the comprehensive cancer center where the author is active, the body mass index of newly referred patients at the time of diagnosis of metastatic cancer of the lung or gastrointestinal tract (n = 1500) typically ranges from 13 to 51, with a population mean of 25.5; although 8% of these present with a BMI < 18.5, 18% have a BMI > 30. This distribution increasingly encompasses obese individuals as a result of the overall trend for increased body weight in westernized countries and the fact that certain cancers, such as colorectal, breast, and prostate (56), are up to twice as prevalent in obese as in normal-weight individuals. It seems less likely that fat mass will be an independent predictor of outcome when energy reserves are substantial (139).

THE CONTEXT: NUTRITION IN ADVANCED MALIGNANT DISEASE

A Consideration of Nutritional Aims Across the Disease Trajectory

The nutritionist must appreciate the course of malignant disease and its treatment, and this understanding can be informed by close collaboration with specialists

in oncology and palliative care medicine. In westernized countries, nearly exactly half of current cancer diagnoses end in cure; the other half end in death. Where cure is the outcome, nutritional problems are largely transient and reversible. Incurable disease is the situation in which the most frequent and severe malnutrition and wasting occur, and it is the focus of this review.

Disease and treatment generate a large number of symptoms that affect nutritional status (122). Treatment options for the disease comprise systemic chemotherapy, surgery, and radiation. Nutritional issues related to therapy are considerable, and correction of nutritional status may be considered preoperatively or prior to radiation or chemotherapy. All antineoplastic treatments have nutritional consequences, either because they add a nutritional demand or because they have side effects that limit dietary intake. All of these treatments invoke damage to normal tissues, requiring repair; they also have powerful side effects that limit eating, such as diarrhea, oral mucositis, nausea, and vomiting. Nutritional objectives during treatment may include restoration or prevention of further erosion of body condition and support of physical and physiological function (i.e., immune function, wound healing, activities of daily living), as well as mitigation of the effects of treatment. Nutritional intervention could be early and proactive to prevent malnutrition, emaciation, and starvation from becoming dominating features of the disease trajectory, in the cases where these are preventable.

At later stages, palliation becomes the central theme of care (4). The focus of nutrition support for the patient shifts away from physiological and functional outcomes to improvement of food enjoyment and quality of life as well as assisting the patient and family in accepting the cessation of appetite and feeding. It is appropriate to develop nutritional support within the context of the palliative care overall and of the wishes of the patient and family. The decision to treat symptoms of cancer cachexia should be based on the patient's desires and current medical condition. The choice of the most appropriate agent for this treatment should include consideration of effects on appetite, weight, quality of life, and risk of adverse effects according to current evidence-based medicine, and cost and availability of the agent.

NUTRITION IN THE END OF LIFE

Decline and Cessation of Voluntary Food Intake; Loss of Appetite

Malnutrition from anorexia and reduced nutrient intake is common in patients with cancer. In animal models (see, e.g., 146), spontaneous food intake shows progressive decline on a tumor-specific time scale. A given tumor burden may be associated with varying degrees of anorexia in different models, and such differences may be accounted for by a varying neurohormonal response stimulated by the tumor. Cancer anorexia in humans manifests as a progressively diminishing and eventual total loss of the unconscious impetus to eat. Preparation and consumption

of meals lose most of their pleasurable qualities. In addition, patients rarely crave specific foods and experience little spontaneous food ideation. Cancer-associated anorexia becomes both total and irreversible at some stage of the disease trajectory.

The psychological dimensions of the cancer anorexia experience from the perspective of terminally ill patients and their family members are important. Anorexia is not in itself necessarily distressful to patients; however, its logical, long-term consequences (i.e., weakness and starvation) are distressful, and this is especially pronounced for family members (110). Family members may press the patient to eat, and although this may be done in the sincere belief that it is in the patient's best interest and that it constitutes a means of fighting back or exerting control over the disease, this may become a considerable source of conflict between the patient and family (110). The ability to provide psychosocial support to patients and families requires that caregivers appreciate the psychological effect of cancer anorexia and cachexia on these individuals.

Gastrointestinal Failure: Malignant Bowel Obstruction

Malignant bowel obstruction is a complication that halts food consumption. Obstruction is common in cancers affecting the bowel or abdominal area. The frequency of obstruction has been reported to range from 4% to 24% in colorectal cancer and 5% to 42% in ovarian cancer. This problem was evaluated and reviewed systematically by a working group of the European Association for Palliative Care (132). Surgical therapies are available and can offer good outcomes in selected patients (86). Self-expanding metallic stents are an important addition to the treatment of large bowel obstruction (123). Nonetheless, malignant bowel obstructions remain a challenging problem for surgeons and carry high risks of morbidity and mortality. There are many contraindications to surgical therapy (132), and many patients are poor operative candidates. Treatment of these patients may include palliative medical measures such as analgesics, antisecretory drugs, and antiemetics, used alone or in combination to relieve symptoms (79, 112).

Decision Making About Aggressive Nutritional Support in the End of Life

It is important for any caregiver involved in decisions related to aggressive nutritional intervention in patients with advanced cancer to keep aware of the current state of evidence concerning prognostication in this patient group (105). Some appreciation of life expectancy is required for the nutritionist to negotiate comfortably within the different phases of advanced malignant disease. A case in point may be made for parenteral nutrition, as all available clinical practice guidelines for initiation of parenteral feeding in advanced cancer patients are explicitly based on an expected survival of the order of months (113). The intent is to feed parenterally when the patient would be expected to die of starvation before any other consequences of their disease became life limiting. Many months and even years of life can be supported with parenteral feeding, with excellent quality of life

(25, 49, 70). By contrast, it is undesirable to institute parenteral feeding in patients close to death, as this encumbers them with infusion apparatus and high costs, and exposes them to risks of catheter placement and infection in a context where they have little to gain from nutritional support. This would tend to occur in cases in which the care team overestimated survival, and various reports (36, 61) suggest that the prediction of survival by physicians was inaccurate and tended to be overly optimistic. The difficulty of accurately predicting survival is acknowledged (113) as one of the most difficult aspects of choosing appropriate patients for parenteral nutritional support.

UNDERLYING BIOLOGICAL MECHANISMS OF INVOLUNTARY WEIGHT LOSS IN CANCER PATIENTS

Several dominant themes are evident in our understanding of the mediation of the cachexias of cancer and other diseases. First, it is clear that a trio of influences supports normal anabolic processes: a dietary supply of energy fuels and substrates, an anabolic endocrine environment, and the trophic effects of physical activity are additionally required for skeletal muscle anabolism. In healthy persons, deficits in these elements of anabolic environment cause wasting, and different types of cachexia are generally associated with failure of anabolic competency, with anorexia being a dominant feature, accompanied by endocrine changes and physical inactivity. Second, whereas starvation and chronic malnutrition are associated with adaptive decreases in metabolic rate and increased economy of energy fuel utilization, cancer cachexia is characterized by hypermetabolism (22, 76) and activation of catabolic pathways. The superimposed metabolic changes result in a rate of depletion of physiological reserves of energy and protein that is greater than would be expected based on the prevailing level of food intake.

Factors Inhibiting Consumption of Food

Dietary intakes of patients with advanced malignant disease have been reported (11, 12, 22, 46, 52). Average dietary intakes are close to reported basal metabolic rates (i.e., 22–24 kcal/kg/day), while intakes >35 kcal/kg body weight are required for weight maintenance (46). A significant number of patients consume less energy than required to cover even the basal costs of metabolism. Low intakes are associated with altered perceptions of appetite and satiety as well as a number of symptoms and side effects of treatments that constitute barriers to food intake.

A Dysregulation of Controls of Appetite and Perceived Satiety

Loss of appetite—anorexia—is one of the most frequently reported symptoms associated with cancer. Regulation of appetite is understood to result from a synthesis of orexigenic and anorexigenic factors, comprising peripheral metabolic signals to

the brain (i.e., leptin, insulin, peptide YY, ghrelin, cytokines, and lipid mediators), as well as signaling of the metabolic sensors in the brainstem and hypothalamus [i.e., neuropeptide Y, serotonin, and melanocortin peptides (26, 93, 94, 127, 129, 131)]. These central and peripheral signals have been explored in animal models of cancer cachexia. It is clear from the available evidence that cancer anorexia is multifactorial and involves most of the neuronal signaling pathways modulating energy intake. The influence of anorexigenic factors such as serotonin and α-melanocyte-stimulating hormone is dominant, while the opposing orexigenic action of neuropeptide Y is reduced (104, 111). Cachexia brought about by a variety of illnesses can be attenuated or reversed by blocking these changes (107). The nature of changes in the peripheral metabolic signals that influence appetite regulation in the brain (leptin, insulin, peptide YY, ghrelin, and lipid mediators) is still being evaluated. Experimental evidence suggests that exogenously applied ghrelin increases food intake in tumor-bearing as well as in control laboratory animals (68); however, the clinical efficacy of this factor is presently the subject of only preliminary evidence (60, 72). Dietary omega-3 fatty acids normalize concentrations of several orexigenic and anorexigenic neuropeptides in the brain, including neuropeptide Y, α-melanocyte stimulating hormone, and the neurotransmitters serotonin and dopamine (64). Clinical evidence for changes in these peripheral signals remains preliminary (71, 78, 141).

In healthy individuals, palatable, energy-dense foods retain high incentive value even when immediate physiological energy requirements have been met, and this feature of food intake regulation promotes overeating. The adaptive value of this pathway lies within the consequent development of an energy reserve for potential future food shortages. The brain structures and signaling pathways responsible for the hedonic impact of energy-dense foods are beginning to be appreciated (81). The status of the food reward pathway in cancer cachexia is largely unknown; however, it is possible that it is impaired to some degree. For example, a unique quality of food reward is its strong modulation by palatability cues (73) such as taste. Taste adulteration, particularly by components that are bitter or sour, strongly suppresses food intake and disrupts the normal structure of feeding behavior (73). The higher acuity for and aversion to sour and bitter food elements reported by many cancer patients may be inhibitory to food intake.

Excessive or Early Satiety

Cancer patients suffer varying degrees of early satiety (136). Reduced gastrointestinal motility is one cause, and gastric emptying times may be considerably extended (48). Early satiety may be multifactorial, with low motility associated with autonomic dysfunction or with the suppressive effects of opioid analgesics. Little is known about whether the metabolic signals of satiety (i.e., cholycytokinin) function normally in cancer patients. Although the satiety value of various nutrients and foods have been characterized in healthy humans, there have been essentially

no investigations of the possible uses of foods with relatively low satiety indices in feeding strategies for patients affected by excessive satiety.

More information regarding the regulation of appetite and satiety in relation to the use of dietary supplements is needed. A number of nutritional support products are available, and oral enteral formulae have been the subject of some large, randomized clinical trials (52). Where this has been measured, it is plain that when patients ingest these products there are compliance problems (12, 52), and there is a compensating decrease in oral intake at conventional meals. Stratton & Elia (144, 145) provided a critical and systematic analysis of this compensation in patients with various chronic wasting diseases, including cancer. On average, the net increase in energy intake during supplementation was equal to the ~67% of the energy content of the supplement, with a range of 0% (completely compensated) to 100% in the different studies. Fearon et al. (52) reported that patients with pancreatic cancer showed net retention of only 15% of the energy intake provided by a standard oral liquid supplement (i.e., 85% compensation); however, this feature is not well characterized in malignant disease. Compensating decreases in oral intake at meals of these different magnitudes result in supplementation that may be either completely ineffective or merely inefficient. Clearly, food intake is being closely regulated around a set point that is unfortunately low; however, at present, there is very little way to explain the variable incidence of this compensation effect or to predict which patients will compensate. Finally, Broekhuizen et al. (27) produced some evidence that it is possible to generate an undesirable overall food aversion when anorexic patients are pressed (or force themselves) toward high volumes of supplement intake, producing a net inhibition in total caloric intake at the highest levels of supplementation.

THE NUTRITION IMPACT SYMPTOMS

Typical evaluations (e.g., 85) of the most frequently reported symptoms in patients with advanced cancer suggest 50%–70% incidences of dry mouth, early satiety, taste/smell change, constipation, anorexia, bloating, nausea, abdominal pain, and vomiting, or on average at least four of these symptoms concurrently. Although it is not within the scope of this chapter to address in detail symptom management, it is important to keep in mind that these symptoms present an obstacle course to the patient attempting to maintain oral intake. Many of the nutrition impact symptoms are treatable, and there is a need for an integrated approach to pain and symptom management that would address all treatable causes of malnutrition. Pain management is clearly a central issue, whether or not it primarily affects the gastrointestinal system. Psychological factors, including anxiety, depression, and family and spiritual distress, may contribute, and the patient and family may experience direct distress around the patient's inability to eat and the family's desire for them to do so. Treatment with anxiolytics and antidepressants, social assistance, or counseling may be relevant. Numerous problems can be present with the mouth

and esophagus. Attention must be paid to the condition of teeth and dentures. Mouth sores are common after certain forms of chemotherapy, and sites of mucosal breakdown are susceptible to infections. Dry mouth follows radiation damage to the salivary glands, and this type of damage can potentially be prevented in the first place or palliated in various ways. Swallowing difficulties may result from tumor involvement or after surgical resection of mouth, tongue, or throat, and to some extent these can be compensated through physical therapy and provision of suitable foods. The passage of food may be affected by hypomotility of the gastrointestinal tract, which can be addressed by the use of prokinetic agents. Constipation is a frequent and often severe side effect of the use of opioid analgesics, and meticulous attention must be paid to bowel care.

Chronic Nausea and Chemosensory Abnormalities

Some special attention is due to the problems of chronic nausea and chemosensory abnormalities, as these are frequent, severe, poorly understood, and thus poorly managed. Chronic nausea and chemosensory abnormalities are important problems that are accountable for reduced food intake in the immediate term and are particularly troublesome because they may interact with one another and spawn long-lasting aversions. If the research community in anorexia-cachexia therapy intends to continue to press for the development of appetite stimulants and nutritional supplements, it will be extremely important to get these two important barriers to food intake in hand.

The prevalence of chronic nausea in patients with advanced cancer is high (up to 70%) and leads to significant distress (125, 44). This difficult and complex form of nausea is a different entity compared with chemotherapy-induced nausea. The underlying etiology is often multifactorial. Nausea may be a side effect of certain drugs or may be caused by abdominal disease, intracranial metastases, metabolic derangements (such as hypercalcemia, uremia, and hepatic involvement), as well as gastrointestinal stasis (125). Metoclopramide and domperidone are often used as first-line drugs to treat nausea in patients with advanced cancer because of their antidopamine and gastrointestinal prokinetic effects (106, 125). The efficacy of metoclopramide in patients with advanced cancer has been demonstrated (30, 31); however, generally speaking, there is a conspicuous lack of randomized controlled trials of nausea therapy in advanced cancer patients (30, 31, 39, 62).

Distortion of taste and smell is a frequent problem (85, 158) and encompasses phantom smells, persistent bad tastes, hypersensitivity to odors and flavors (158), and food aversions with nausea (121). These changes, where severe, substantially limit food intake (47, 108, 121) and, not surprisingly, self-perceived quality of life (158). Taste and smell abnormalities are a direct consequence of antineoplastic therapies, which alter or disrupt the renewal cycle of taste and smell receptors (137, 138), but are also reported in up to 90% of advanced cancer patients not undergoing active treatment (47, 85), demonstrating that factors other than active therapy are likely to contribute to chemosensory alterations. Chemosensory

problems are a well-known consequence of certain chronic nutritional deficiencies, and dietary supplementation with nutrients such as zinc may improve abilities to taste and smell (41, 133); however, empirical proof is lacking for these approaches in cancer patient populations. A research opportunity would be to apply the principles of sensory science to this problem to define clearly the clinical features of chemosensory abnormalities and to integrate this knowledge into the development of nutrient-dense foods with features of flavor, odor, texture, and appearance that match the preferences and specifically avoid the aversions experienced by patients with cancer.

Cancer Inflammation-Hypercatabolism Syndrome

Inflammation is the single most important theme consistently emerging from both animal and human studies in cancer cachexia. The presence of a chronic inflammatory state accounts for disparate aberrations, including changes in the hypothalamic-pituitary axis, dysautonomia, hypermetabolism, oxidative stress, decreased muscle protein synthesis, and increased ubiquitin-proteosome-mediated muscle proteolysis together with other metabolic changes such as insulin resistance (2, 6, 17, 38, 42, 51, 55, 57, 92, 100–102, 115, 124, 130, 134, 151). Through its effect on multiple organs and tissues, chronic inflammation leads to the pathophysiologic profile accounting for anorexia-cachexia. It appears that a chronic inflammatory state is also key to anorexia-cachexia across a wide range of disorders, including advanced cardiac failure, chronic obstructive pulmonary disease (COPD) (38, 55, 115, 124, 159), and cachexia in the frail elderly (164).

The role of inflammation in cancer cachexia has been positively established in many animal models. The participation of proinflammatory cytokines including interleukin-1-β, interleukin-6, tumor necrosis factor (TNF)-α, and interferon-γ has been proven by changing cytokine production or activity using experimental approaches such as passive immunization with antibodies to cytokines, cytokine receptor antagonists or receptor knockout mice, animals overexpressing soluble receptor isoforms, and by using agents, such as pentoxyfylline, that suppress cytokine production (2, 37, 50, 59, 97). Eicosanoids are key inflammatory mediators that have also been implicated in cancer cachexia using specific cyclooxygenase inhibitors (69, 109, 134, 146).

Our report that a cytokine, interleukin-1, has a direct action to increase protein catabolism in skeletal muscle (9) created a key link in the understanding of the parallel occurrence of inflammation, infection, injury, and skeletal muscle wasting. It is now well confirmed that skeletal muscle produces cytokines and responds to them through locally expressed receptor proteins (reviewed in 6, 58). TNF-α, interleukin (Il)-1β and Il-6, and interferon (IFN)-γ are currently thought to be the principal catabolic actors in skeletal muscle. Cytokines signal activation of proteolysis (1, 58, 96) as well as inhibit growth hormone and insulin-like growth factor (IGF)-1 signaling (57, 58); they also induce insulin resistance (42). The proinflammatory cytokines show the feature of potentiation of each other's actions, and a

variety of potent synergies among these factors have been noted (i.e., TNF-α + IFN-γ) for protein turnover (1); TNF-α+ IFN-γ + endotoxin (lipopolysaccharide) for cytokine receptor induction (165), and TNF-α + IFN-γ + lipopolysaccharide for nitric oxide synthesis and insulin resistance (17).

Tumor-Derived Catabolic Factors: A Proteolysis-Inducing Glycoprotein

A previously unknown molecule was reported to mediate weight loss and protein catabolism in mice bearing the MAC16 adenocarcinoma. When muscle cells or animals are treated with the purified factor, intense catabolism is elicited (35, 99, 151, 155). This proteolysis-inducing factor of tumor origin has an apparent mass of $\sim$24 Kd and consists of a short polypeptide chain that is phosphorylated and extensively glycosylated (154, 155). An identical factor was reported to be found in humans (153). Preliminary evidence suggested its association with weight loss in cancer patients and its absence in cancer patients who are not losing weight or weight-losing patients with benign disease (trauma or sepsis) (153). The idea that tumors may secrete catabolic factors at random is a highly important concept. If indeed this occurs, then tumors can direct spurious catabolism that does not fall under the usual and known metabolic controls. Although the idea of tumor catabolic factors created a great deal of interest, in the decade that has passed since the original report, there has been essentially no independent confirmation or extension of these results (114). This may be due in part to the fact that neither a laboratory assay for this unusual molecule nor a source of authentic pure proteolysis-inducing factor has been generally available. The idea of tumor-derived catabolic factor(s) as a contributory factor in cancer cachexia in man remains to be definitively ruled in or ruled out.

Proteolysis: Activation of Proteolytic Pathways

Mechanisms common to cancer-associated muscle atrophy are now emerging. In particular, the activation of the ubiquitin proteasome proteolytic system appears to be a common proteolytic pathway of cancer-associated muscle catabolism (3, 83, 95, 152). Most intracellular proteins in skeletal muscle are degraded through the ubiquitin proteasome system, in which proteins are marked for proteasomal degradation by the conjugation of ubiquitin molecules. The first step in this pathway is the covalent attachment of polyubiquitin chains to the targeted protein. Polyubiquitinylated proteins are then recognized and degraded by the 26S proteasome complex. Ubiquitin conjugation involves a series of enzymatic steps including activation of ubiquitin (E1); transfer of activated Ub is relocated to the E2 enzyme that serves as a carrier-protein and interacts with a specific E3 enzyme (ubiquitin ligase). The ubiquitin ligase binds to the protein substrates to be degraded and catalyzes the transfer of ubiquitin to the substrate to generate a ubiquitin chain. A cytokine-inducible ubiquitin ligase has been identified in muscles of tumor-bearing rats (88), and this may provide a plausible link between inflammation and

proteolysis. Polyubiquitinated substrates are targeted to the 26S proteasome and rapidly degraded. A review by Attaix and colleagues (3) summarized evidence from animal models that this comprises a final common pathway of muscle protein catabolism in cancer cachexia, as it also appears to be part of a common program of proteolytic activation across a diverse range of muscle atrophy types (95). Evidence for activation of this pathway is beginning to emerge from studies on cancer patients (23, 24, 43, 82). Further studies are required to better understand the regulation of elements of this system. The importance of the ubiquitin ligase family must be resolved, including identifying the physiological substrates for these enzymes in skeletal muscle, elucidating signaling events that regulate their activity, and analyzing the effects of specific inhibition.

ANTICACHEXIA THERAPIES

Current Standards of Care

The orexigenic progestational agents (megestrol acetate; medroxyprogesterone acetate) have been more extensively evaluated in randomized clinical trials than has any other agent (18, 161). Although progestational agents clearly improve food intake, they have numerous limitations. They are only effective in about 30% of subjects, after the magnitude of the placebo effect is taken into account. The poor overall response rate may be in part due to a large food effect (53), as progestational drugs are very poorly absorbed unless consumed with a lipid-containing meal. Weight gain in response to these agents is invariably composed of fat (98), and because progestational drugs also have significant glucocorticoid character, they are catabolic to skeletal muscle (91). Progestational agents are costly, are contraindicated in patients with hormone-sensitive malignancies, and have consequential side effects, such as impotence in males. These problems underline the need for the development of superior therapeutic approaches and make it easy to understand why this class of drugs is not necessarily valued as a standard of care in many settings.

Principles of Anorexia-Cachexia Therapy

The general approach to the management of wasting syndromes is based on our understanding of contributing mechanisms that form the targets for intervention. It may be generally stated that overall anabolism and muscle anabolism are maximized when:

Contractile work is frequent, especially resistance-type activity (i.e., weightlifting), and

nutrients (amino acids for building muscle protein and necessary cofactors and energy fuels) are not limiting, and

anabolic hormones (i.e., insulin and testosterone) are at optimal levels and muscle is sensitized to their action, and

catabolic factors related to stress (i.e., cortisol) or disease (i.e., proinflammatory cytokines) are minimal.

One of the most important features of cancer cachexia to take into account when designing therapeutic strategies is its various orders of complexity (102, 143). Cancer cachexia is composed, in some degree, of a lack of physical activity, reduced dietary intake, deficits in the anabolic endocrine milieu, and hyperexpression of catabolic factors. Another element of complexity in cancer cachexia is the presence of comorbid conditions contributing to wasting. The median age of cancer diagnosis and death in North America is 64 and 69 years, respectively. Aging is by itself associated with declining body weight, progressive muscle atrophy, limited mobility, risks of malnutrition, and alterations in digestion and metabolism associated with poor nitrogen retention (89, 164). This condition comprises the backdrop of the cancer cachexia experience for many patients. In a similar vein, a distinctive cachexia of COPD is a common comorbid cachexia in lung cancer patients. As COPD is mostly caused by cigarette smoke, as is cancer of the lung, there tends to be a high association between the two diseases. The suggested mechanisms of COPD-cachexia have much in common with cancer cachexia (elevated energy expenditure, reduced dietary intake, and an elevated systemic inflammatory response) (28, 29, 159, 163), although features such as excessive energy expenditure due to increased work of breathing are unique to COPD.

A helpful way to synthesize the foregoing is to consider the challenges of treating malnutrition and wasting in a model patient who:

is age 75 years,

is affected by non-small-cell cancer of the lung and COPD,

has poor mobility due to pulmonary insufficiency and pre-existing sedentary lifestyle,

exhibits a total daily energy intake of 1250 kcal and resting metabolic rate of 1800 kcal,

exhibits chemosensory distortion and food aversions

with evidence of systemic inflammation CRP 70 mg/dL, and

is male, with a testosterone level of 4 nM.

It is obvious from the example above that wasting is multifactorial and that it is unlikely that efficacy of anticachexia treatment will be maximized with any monotherapy. An integrated approach of nutrition, resistance exercise, and hormonal support has been increasingly adopted in the treatment of muscle wasting, and the component therapies are highly developed. Detailed progressive weight-training programs that address specific muscle groups are available. The amino acid requirements for maximal muscle protein deposition are at least partially understood, and elegant work has been done to promote protein synthesis through the appropriate timing of protein feeding relative to the timing and type of exercise bouts (21, 150). The anabolic action on skeletal muscle of synthetic anabolic

steroids derived and developed from the basic structure of testosterone have been intensified, while other outcomes, such as liver damage and masculinizing effects, have been minimized (10). Creatine supplementation in the diet is used as an adjunct in this recipe to support muscle growth and function (102).

This integrated approach has been used for muscle building in otherwise healthy individuals and to treat muscle wasting in the elderly (148). It is encouraging that patients considered too frail and ill to exercise have been shown to benefit and to show robust anabolic potential. Yarasheski (160) provides a pertinent example in frail elderly (76–92 years) who participated in weightlifting. Study participants showed increased biosynthesis of myosin heavy-chain and mixed-muscle proteins, as do younger people. This suggests that the protein synthetic machinery adapts rapidly to increased contractile activity and that the adaptive responses are maintained, even in frail elders. Similarly, a central theme of treatment of COPD cachexia is the trilogy of appetite stimulants and/or nutritional support, physical activity, and anabolic androgenic steroids, as well as various combinations of these factors (66, 140, 142, 162). Collectively, these data suggest a high degree of reversibility of age-related wasting and show considerable potential for an integrated approach in COPD and other cachexias. These approaches have yet to be fully evaluated in cancer patients; however, results from other catabolic conditions may share common mechanisms to cancer cachexia and offer insight into important therapeutic principles.

Some Areas of Cachexia Therapy in Development

Investigational anticachexia therapy is notable in the diversity of agents under consideration (Table 1). Although all of these treatments emanate from current conceptions of the underlying mechanisms of wasting, many more studies are needed to evaluate their efficacy as well as their cost, additional benefits, side effects, and contraindications.

Appetite Stimulants

A group of agents representing a wide range of modes of action has begun to be studied for its positive effects on appetite in cancer cachexia. Kulkarni & Kaur (87) provided a synopsis of a wide variety of drugs that showed weight gain as side effects, and some of these are being explored in anorexia therapy. The review by Yavuzsen et al. (161), however, makes it clear that none of these have been tested in more than one or two trials, and many of these may be described as preliminary in nature. These agents come from diverse drug classes. Appetite is regulated in part by endocannabinoid-mediated pathways, which suggests that this pathway is manipulated to both suppress (149) and activate (16, 161) appetite. Δ-9-tetrahydrocannabinol stimulates appetite in AIDS patients (16) as well as in cancer populations (161), but evidence is not conclusive. The atypical neuroleptic, olanzapine, was noted to have some side effects, including stimulation of appetite, as well as some antinausea activity (119); this drug is in ongoing trials for cancer

TABLE 1 Clinical therapeutic agents for the treatment of cachexia

Action site	Agent	Applications	
		Cancer cachexia	Other cachexia-causing diseases
Appetite stimulants	Progestational agents	√	√
	Cannabinoids	√	√
	Olanzepine	√	√
	Corticosteroids	√	
	Ghrelin	√	√
Nutritional supplements	Amino acids	√	√
	Creatine		√
	Polyunsaturated fatty acids: eicosapentaenoic acid (n-3) (fish oil)	√	√
Anabolic	Steroids	√	√
	Insulin		√
	Insulin-like growth factor, growth hormone	√	√
	β-adrenergic agonists		
Exercise		√	√
Combination therapy	Exercise + oral nutritional supplementation		√
	Anabolic steroids + oral nutritional supplementation		√
Anti-inflammatory	Polyunsaturated fatty acids: eicosapentaenoic acid (n-3) (fish oil)	√	√
	Nonsteroidal anti-inflammatory agents	√	√
	Macrolide antibiotics	√	
	Cytokine inhibitors	√	√
	Statins		√
	Thalidomide	√	
	Pentoxyphylline	√	√

cachexia. Ghrelin, a recently characterized entero-endocrine hormone, is produced by the epithelium of the stomach and is involved in the regulation of appetite in the paraventricular nucleus of the hypothalamus. Ghrelin stimulates hunger and is one of the suspected etiologic agents of Prader Willi syndrome, a disease associated with voracious appetite; thus, it has been proposed as an anorexia therapy (60, 72). Currently, only preliminary evidence is available on the possible efficacy of ghrelin in the treatment of cancer-associated anorexia in mice (68) and in humans with cancer (120) and COPD (117).

Nutritional Supplements

It is notable that the problem of low intake is to date principally approached via pharmacologic interventions directed at appetite. Although one might consider nutritional support as a fundament of anorexia-cachexia therapy, nutrient metabolism and nutrient requirements of cancer patients have not generally been evaluated using current methodology; thus, the extent to which utilization of essential nutrients is altered by cancer progression and therapies is largely unknown. Appropriately formulated nutrient mixtures may be expected to alleviate muscle loss, improve tolerance to treatments, or have immune-stimulatory properties, allowing more effective antitumor immune responses without necessarily stimulating tumor growth (63, 103).

Several amino acids appear to show increased utilization in the tumor-bearing state (reviewed in 103), including aromatic, sulfur-containing, and branched-chain amino acids, as well as several nonessential amino acids that may become conditionally essential (ala, gln, cys, arg). There is not yet an understanding of amino acid utilization that is sufficiently extensive to support the formulation of cancer-specific specialized amino acid formulae for enteral or parenteral nutrition.

There have been a few reports of inhibition of cancer-associated wasting by n-3 polyunsaturated fatty acids eicosapentaneoic acid (20:5n-3) and docosahexaneoic acid (22:6n-3) in animal models and clinical investigations (reviewed in 8). It may be inferred from the results that these compounds are limiting and that dietary needs for them may be elevated. Fish oil feeding reverses anorexia and suppresses wasting, muscle protein catabolism, and muscle protease induction in multiple animal models (8, 64, 80, 128, 129, 156). Clinical evidence on n-3 supplementation remains inconclusive (52, 161).

Anti-Inflammatory Therapy

Given that inflammation is clearly seen to be the leading cause of anorexia and wasting in a wide range of cachexia syndromes, it is disappointing that few randomized clinical trials in this area have been conducted. It is also a concern that these therapies to date have been applied to unselected patient populations without necessarily obtaining any evidence of systemic inflammation, either as an inclusion criterion or as a biochemical marker that could potentially be related to efficacy. More trials are needed to find the most efficacious anti-inflammatory therapy in this application, taking into account costs, side effects, and other features of the agents. The list is long and includes conventional non-steroidal anti-inflammatory agents, COX II inhibitors (100, 101), anticytokine approaches (77), and the n-3 fatty acids (52, 161). There has been some sporadic testing of various compounds with anti-inflammatory properties in clinical research. Macrolide antibiotics (135) and thalidomide (65) have also been suggested as cancer cachexia treatments, in part based upon their anti-inflammatory actions.

Anabolic Agents

It is of interest that muscle is, nonetheless, responsive to a variety of anabolic agents in cancer cachexia, and this has been mostly explored in animal models. For example, β-adrenergic agonists such as formoterol, salbutamol, salmeterol, and clenbuterol (32, 34) preserve muscle mass and activate protein synthesis in tumor models. Thus it may be concluded that anabolic pathways remain competent, which suggests possible therapeutic approaches. Several authors have suggested that cytokines such as Il-15 and Il-4 may make useful treatments because of their myotrophic and anabolic properties and their ability to oppose the actions of catabolic cytokines (6, 126). Il-15 antagonizes muscle atrophy in tumor-bearing rats (33, 54), as does Il-4 (147). It has additionally been suggested that growth hormone or IGF-1 may have therapeutic potential (19, 40, 84, 157), although there is some question as to whether these therapies might spur on tumor growth.

Drug Targets in Downstream Proteolytic Pathways

Activation of the ubiquitin-proteasome system is common in many types of cancer cachexia, regardless of whether one or another hormone, cytokine, or other factor appears to be the humoral signal for the system's activation. The position of ubiquitin ligases in the span of the pathway of muscle protein catabolism that is common to multiple hormones, cytokines, and other factors would allow for a simplification of anticatabolic therapies. Since target proteins bind to the ubiquitin ligase prior to conjugation, it has been suggested that the ubiquitin ligase determines both the specificity and rate of the degradative system (88, 152). This raises the potential of ubiquitin ligase as a therapeutic target (74, 88, 152). Further studies are required to better understand the importance of the ubiquitin ligase family in catabolic disease states. These studies should include identifying the physiological substrates for ubiquitin ligases in skeletal muscle, elucidating various signaling events that regulate their activity, and analyzing the effects of selective blockade, through gene ablation and/or the design of selective small-molecule inhibitors, on response to catabolic challenges. Although therapy at this level is presented as a goal for the far and distant future by some cautious proponents (74), the ubiquitin ligases are nonetheless attractive molecular targets for manipulation of proteolysis since their features potentially allow for local suppression of muscle catabolism without affecting the basal proteolytic processes in other tissues or associated essential functions.

CONCLUSIONS

Cancer cachexia is a syndrome of multifactorial etiology. Many mechanisms have been proposed to underlie anorexia, inability to eat, and tissue wasting, and these seem to be part of a common pattern emerging in a broader family of wasting diseases. This area would benefit from the validation of animal models for the

preclinical investigation of anorexia-cachexia therapy and would be well served by the establishment of a scientific and medical group dedicated to the development of multicenter, randomized clinical trials of anticachexia therapy.

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CONTENTS