Anorexia in Cancer Patients

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Summary

The pathophysiology of anorexia in cancer patients is poorly understood and has been difficult to study because of multiple variables that influence the clinical picture. This essay reviews current understanding of food intake control in normals and attempts to relate this to observations in cancer patients. Hypothalamic centers can either stimulate or suppress feeding behavior, but there is no evidence of alteration of these centers in cancer patients. Sensory input from the mouth may influence feeding behavior. Recent studies have delineated changes in taste sensation in cancer patients that can be correlated with patient symptoms, extent of tumor involvement, and caloric intake. Sensors within the gastrointestinal tract influence the quantity of food eaten; there may be alterations in the function of these sensors in cancer patients, but no direct study of this is available. Thermostatic sensors also influence food intake; it is possible that the heat generated by tumor metabolism may tend to reduce food intake, but this requires further study. Glucosensitive receptors exist in the brain and the liver, and it is possible that the increased metabolic activity in the liver that occurs in cancer may stimulate hepatic receptors to lead to suppression of appetite, but this requires further study. Liposensitive and amino acid-sensitive receptors also influence normal food intake regulation, and alterations in metabolism in the cancer patient such as amino acid imbalances may be anorexigenic. Since eating behavior is controlled by several apparently redundant cues or control mechanisms, there probably is a hierarchy among these cues, and aberration of a cue high on the hierarchical scale may predominate over others. Future research should further delineate the hierarchical ranking of food intake cues and controls in normals and in patients with cancer.

Anorexia is a frequent problem in cancer patients and is a major determinant of cancer cachexia. The pathophysiology of anorexia is poorly understood and has received only limited systematic study. Anorexia in the cancer patient is a difficult problem to study because of its highly variable clinical picture. The clinical picture may be influenced by tumor, host, and treatment variables. Tumor variables include site of the primary tumor, areas of metastatic spread, total tumor size, and tumor growth rate. Host variables include premorbid nutritional status of the patient, host effects of reduced caloric intake, and variable reactions to illness, such as homeostatic and psychological responses to illness. Treatment variables include damage to assimilating organs, to metabolizing systems, and to controlling systems.

A further difficulty is the measurement of anorexia. Patients may deny changes in appetite but may nonetheless have decreased caloric intake (unpublished observations). We are currently evaluating the use of a dietary diary with conversion of data to caloric intake as a measurement of anorexia.

In this essay we will review current understanding of food intake control in normal subjects (5) and relate this to physiological and biochemical observations in cancer patients. This analysis leads to a formulation of a multifactorial basis for anorexia in cancer patients. Current understanding of food intake control in normals involves a model comprised of a controller, a controlled system, and feedback elements. The controller is a complex system within the brain that includes cortical, subcortical, and autonomic components. Feedback elements include plasma glucose, plasma-free fatty acids, plasma glycerol, plasma amino acids, peripheral metabolic state, and signals from the gastrointestinal tract. The controlled system includes caloric intake, distribution, disposal, and storage. Humoral responses (insulin, etc.) to feedback elements also contribute to normal controller function.

Since the system is responsive to multiple feedback stimuli, removal or alteration of only 1 source of stimulation (inhibition) of food intake behavior may not have detectable long-term effects. For example, persons who have undergone surgical vagotomy (loss of gastric and intestinal dis- tention signals) continue to be able to regulate their food intake and maintain a stable body weight. One may therefore speculate that severely anorectic patients may have multiple aberrations in their food intake-regulatory system. Anorexia may be the result of satiety-like signals or may reflect anorectic effects unique to cancer patients that do not usually influence the hunger-satiety state of the organism. This essay will review current understanding of normal food intake control with the goal of identifying satiety-like signals that may contribute to anorexia.

Hypothalamic Centers

Current understanding of hypothalamic function for control of food intake is that there exist 2 central catecholamine mechanisms (22). The 1st is an α-adrenergic mechanism that stimulates feeding behavior. This mechanism is located in the medial hypothalamic region and may be mediated by...
adrenergic pathways that originate in the midbrain and ascend through the periventricular region of the diencephalon. The 2nd system involves β-adrenergic and dopaminergic receptors located in the anterolateral hypothalamic region. This 2nd system suppresses feeding behavior. Mediating pathways include adrenergic pathways that originate in the midbrain and innervate lateral hypothalamic regions. These systems can be influenced by systemic administration of drugs: e.g., amphetamine-induced anorexia is mediated through this 2nd system. One may postulate that the stress of illness may stimulate release of β-adrenergic and dopaminergic substances leading to suppressed appetite in the cancer patient, but no direct studies of this possibility are available.

Sensory Input

The senses of sight, taste, and smell, as well as temperature and proprioception sensations in the mouth, are involved in the encounter with food. These senses contribute to the hedonic value of food and also trigger many physiological reflexes. Stimulation of receptors within the oral cavity is essential for initiation of swallowing (13, 24). Positive taste stimuli such as sweet stimuli result in the flow of saliva and an increase in gastric secretions (19, 33). Positive orogastric stimuli also cause a variety of physiological changes conducive to food intake, including alterations in respiratory quotient and blood glucose (30).

In cancer patients, abnormalities of taste sensation have been reported, and these changes in taste sensation can be correlated with reduced caloric intake (10–12). The detection threshold for sucrose showed an upward skewing in the tumor patient group compared to that in the control population, and this difference between patients and controls was also seen for recognition threshold. Seventeen of 50 tumor patients had sucrose recognition thresholds above 90 mmoles/liter, whereas only 1 of 23 controls had a value this high (χ² = 59.4; p < 0.001). These abnormalities on sucrose testing for cancer patients could be correlated with the symptom of decreased taste sensation. Cancer patients who did not have this symptom had sucrose recognition results quite comparable to the controls, with a similar median (60 mmoles/liter) and a nearly similar range. In the patients with the symptom of decreased taste sensation, 12 of 25 had recognition thresholds above 90 mmoles/liter compared with 5 of 25 with thresholds above 90 mmoles/liter in the asymptomatic patient group (χ² = 3.2; p < 0.08). One patient who had an abnormally low urea threshold had caloric intakes that were significantly lower than were those of the asymptomatic normal taste group (Column 3 versus Column 1; p < 0.02). Patients with an abnormally low urea threshold had caloric intakes that were significantly lower than were those of the group with normal taste (Columns 2 versus Column 1; p < 0.02) and also were lower than those of the total group with normal taste (compare Column 3 with Columns 1 and 2; p < 0.03). In the group with an elevated sucrose threshold, several patients had low caloric intake, but this distribution did not reach statistical significance compared to that of the asymptomatic patient group. One patient who had an abnormally low urea threshold and an abnormally high sucrose threshold had a normal caloric intake. This patient was highly motivated and was apparently able to maintain caloric intake in spite of altered taste sensation. If all the patients with altered taste sensation are considered together, their caloric intake is significantly lower than that in the asymptomatic group (Columns 3, 4).

<table>
<thead>
<tr>
<th>Tumor extent</th>
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<td>9</td>
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The probability of having an abnormality of taste could be correlated with the extent of tumor involvement (12). A group of 9 patients with limited disease had normal recognition thresholds for both sucrose and urea. An intermediate group of 21 patients had slightly more advanced disease, and 3 of these had an abnormality of recognition for either sucrose or urea. Patients with advanced disease had a very high probability of having an abnormality of taste sensation with 15 of 20 having an abnormality of recognition for sucrose or urea or both (Table 1). This correlation of taste abnormality with advanced disease is highly significant (p < 0.001).

In 40 of this series of 50 patients, we obtained data on daily caloric intake. In allowance for differences in body size, caloric intake was expressed as cal per kg body weight per day (Chart 1). Patients whose taste test results were within the normal range were subdivided into 2 groups as to the presence or absence of other factors that might decrease caloric intake. Patients with symptoms of pain, nausea, bowel obstruction, or brain metastases had significant reduction in caloric intake compared with patients without these symptoms (Column 2 versus Column 1 in Chart 1; p < 0.02). Patients with an abnormally low urea threshold had caloric intakes that were significantly lower than were those of the asymptomatic normal taste group (Column 3 versus Column 1; p < 0.02) and also were lower than those of the total group with normal taste (compare Column 3 with Columns 1 and 2; p < 0.03). In the group with an elevated sucrose threshold, several patients had low caloric intake, but this distribution did not reach statistical significance compared to that of the asymptomatic patient group. One patient who had an abnormally low urea threshold and an abnormally high sucrose threshold had a normal caloric intake. This patient was highly motivated and was apparently able to maintain caloric intake in spite of altered taste sensation. If all the patients with altered taste sensation are considered together, their caloric intake is significantly lower than that in the asymptomatic group (Columns 3, 4).

### Table 1

Correlation between tumor extent and incidence of taste abnormality

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and 5 versus Column 1; p < 0.02). The comparison between all patients with abnormal taste sensation and all patients with normal taste sensation approached statistical significance (Columns 1 and 2 versus Columns 3, 4, and 5; p < 0.07). Cancer patients also report symptoms of altered smell sensation; this is currently under study.

**Visceral Sensing Effects**

Visceral receptors exist that are sensitive to osmotic, volumetric, and chemical properties of ingested materials (31). Sensations from the stomach and intestine have a regulatory role in determining the quantity of food eaten (43). In the cancer patient, several changes occur that could lead to reduced eating via this visceral sensing system. The abnormalities in taste noted above could result in decreased production of digestive secretions that could lead to delayed digestion and therefore more prolonged stimulation of gastrointestinal volumetric sensors. Also, the atrophic changes in the intestine noted as a systemic effect of cancer (18) may delay digestion and assimilation of nutrients. These 2 effects may provide an explanation for a commonly observed symptom in cancer patients of decreased eating later in the day. If there were sluggish digestion of the initial meal of the day, satiety from this meal could persist until later in the day.

**Thermosensitive Effects**

The thermostatic hypothesis considers the heat released from the metabolism of food, including the “specific dynamic action” of food, to be a force that regulates food intake (6, 39). It is not clear whether eating responses to changing temperature are related to changes in core temperature or to changes in peripheral temperature sensors. Clinical examples of both altered core temperature and altered peripheral temperature may be considered. The febrile or hypermetabolic patient is often anorectic, which would be consistent with the termination of eating on elevation of central temperature in experimental animals (3). A somewhat opposite picture is seen in the patient who has lost considerable weight and who may become hypothermic on exposure to cold ambient temperature. We have not been able to elicit any evidence for increased appetite in this clinical setting, but Stevenson et al. (38) were able to increase the caloric intake of tumor-bearing experimental animals on exposure to cold. Although this approach may not be feasible in man, Stevenson’s study is of interest as an...
example of a physiological manipulation that had the effect of reversing the anorectic effect of a tumor.

**Glucosensitive Effects**

Feedback from glucose is based on the rate of glucose utilization or the "effective blood sugar" (25). Sensors for changes in blood glucose exist in both the hypothalamus (26, 27) and the liver (36). An increase in glucose utilization (anteriovenous difference) results in satiety. There may be increased glucose utilization by tumor cells (uptake and metabolism to lactate) and by liver cells in the tumor-bearing host (required to provide energy for conversion of lactate to glucose via the Cori cycle), but there is no evidence for enhanced glucose utilization by other host cells. The possibility that glucose utilization by other cells may be decreased is suggested by observations of slower disappearance of i.v.-administered glucose in cancer patients compared with a normal and a decreased level of insulin response to hyperglycemia in cancer patients (A. Theologides, personal communication).

Reduced blood glucose has been noted in tumor-bearing animals (7) but, in our studies of anorectic cancer patients, there were no differences in fasting blood sugar between anorectic patients, nonanorectic cancer patients, or normal controls (12). Thus, it is not clear what role any glucose sensing has in the development of anorexia of cancer. It is possible that the increased metabolic activity of the liver (glucose uptake and Cori cycle activity) and the increased liver weight that occurs in cancer (42) may result in increased firing of hepatic glucoreceptors, which would lead to suppression of appetite. This merits further study with the techniques of Russek (35).

**Liposensitive Effects**

Food intake is also influenced by body lipids (21) with sensors for free fatty acids (32) and glycerol. However, neurons in both the ventromedial hypothalamus and the lateral hypothalamus are sensitive to stimulation by free fatty acids applied locally (32). Increased food intake has been induced in the rat by i.v. injection of free fatty acids (1), but replication of this result has not always been successful (32).

In patients with cancer, fasting free fatty acids may be normal, but there may be a disturbance in the free fatty acid-triglyceride axis, in that high carbohydrate intake does not block the lipolysis of triglyceride or the return of triglyceride fatty acid to free fatty acid (44). It is not clear what effect this alteration in metabolism would have on appetite.

**Amino Acid-sensitive Effects**

The concentration and the pattern of amino acids in the blood and extracellular fluids are important signals for food intake regulation (28, 29). The interrelationships between plasma amino acids and appetite are complex. One mechanism of decreased appetite is through the development of an amino acid imbalance (17, 23) developed experimentally by a diet with either an excess or a deficiency of certain amino acids. Starvation results in a drop of serum levels of amino nitrogen and variations in the concentrations of specific amino acids (2, 15). Amino acids may be increased or decreased overall in the blood of patients with leukemia and solid tumors, and significant imbalances between specific amino acids in the plasma have been observed (4, 20, 35). These amino acid imbalances may be anorexigenic in cancer patients.

**Anorexigenic Peptide Hypothesis**

An anorexigenic peptide was present in the urine of patients with widespread neoplastic disease (8). This observation has led to a hypothesis that tumor-related polypeptides may be important determinants of anorexia (41). It is well known that tumors produce and release polypeptides (14, 40), but further study is needed before one can ascribe anorexia in cancer patients to polypeptides.

**Hormonal Effects**

Many different hormones affect appetite, including insulin (16), glucagon (34), epinephrine (34), enterogastrone (37), and cholecystokinin (9). Increased serum insulin may stimulate appetite, and the decreased insulin production by cancer patients may thus result in less of this positive stimulation of appetite (one could view less stimulation of appetite as an aspect of anorexia). We know of no data on enterogastrone or cholecystokinin levels in anorectic cancer patients and suggest study of hormone levels in anorexia as a worthwhile approach.

**Conclusions**

Many metabolic and physiological factors influence food intake. Simple starvation results in many metabolic changes, some of which depress appetite. Examples of physiological changes that may be common to starvation and cancer patients include atrophic changes of the gastrointestinal tract and amino acid imbalances. Other metabolic and physiological changes occur seemingly as a more specific remote effect of a neoplasm and may depress appetite. Metabolic changes, such as the exothermic effect of tumor metabolism and increased glucose uptake by the liver, may mediate anorectic effects via normal sensing mechanism. Other effects of a neoplasm, such as the development of taste abnormalities and the possible elaboration of anorectic polypeptides by the tumors, may have no counterpart in normal regulation of feeding behavior. The challenge is to identify the metabolic and physiological alterations that are contributing to anorexia in each patient. If these can be adequately delineated, proper metabolic and nutritional corrections may be prescribed.

Eating behavior is controlled by several apparently redundant cues or control mechanisms. There probably is a hierarchy among these cues, and an aberration of a cue high on...
the hierarchical scale may predominate over all others. Furthermore, a cue high on the hierarchical scale may be able to override cues of lower value. In humans, one may speculate that motivation may override factors reducing appetite and may permit adequate caloric intake in spite of cues tending to decrease appetite.

Future research should better delineate the hierarchical ranking of food intake cues and controls in normals. Research should also aim at further delineation of physiological and metabolic changes in cancer patients that may contribute to anorexia. Finally, clinical trials of nutritional and metabolic intervention in cancer patients should include evaluation of effects on appetite and anorexia.

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