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The Eating Disorders
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Chapter 34

Significance of Eating Disorders in Oncologic Diagnosis and Treatment

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INTRODUCTION

Weight loss in patients with advanced cancer has been recognized clinically for many years. More recently the development of weight loss prior to treatment has been shown to be an important factor prognostic of decreased survival in patients with this disease. DeWys and colleagues [1] reported a study involving more than 3,000 patients entered on protocols of the Eastern Cooperative Oncology Group with advanced cancer. In this experience the frequency of significant weight loss varied from 40% in breast cancer patients to more than 80% in patients with pancreatic or gastric cancer. The median survival of patients with weight loss was significantly shorter than that of patients with no weight loss for tumors originating from a variety of sites including lung, colon, prostate, gastric, breast, and sarcomas [1]. The influence of weight loss on survival was independent of tumor extent and performance status as well. In lung cancer, the leading cause of cancer death in the United States, several studies have reported that approximately 50% of patients experience weight loss at the time of their initial presentation [1-3]. In both small cell and nonsmall cell lung cancer, the median survival of patients with weight loss was half that of patients who were within 5% of their usual weight [2]. Even when stage, histologic factors, and treatment were taken into account, weight loss significantly influenced lung cancer patient survival. In one report, anthropometric assessment of nutritional status was an even more sensitive prognostic factor in this population [4]. Thus, accumulating data supports the concept that pretreatment weight loss, representing an alteration in nutritional status, is an important, independent factor prognostic of decreased survival in patients with a variety of cancers.

Taken from a somewhat different perspective, weight loss as a clinical presentation is commonly associated with a diagnosis of cancer. In a series of 91 patients presenting with involuntary weight loss as a major clinical problem, a diagnosis of underlying malignancy was found in 19% [5]. Cancer represented the most common diagnosis in 65% of patients found to have a physical cause for weight loss in this report. However, almost all patients with cancer were detected during initial evaluation, and occult cancer as a cause of weight loss was rare. Thus, weight loss is not only prognostic of a poor outcome in patients with proven cancer but may well be an indicator of the presence of cancer in an adult population as well.

The factors underlying the development of weight loss in the patient with cancer (cancer cachexia) are mul-

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tifactorial [6-9] and incompletely understood at the present time. Simplistically stated, the cause of cancer cachexia may be related to a failure of the patient to ingest sufficient nutrients to meet the host metabolic requirements. In fact, cancer patient populations have been demonstrated to have reduced caloric intakes, an increased energy requirement, and a variety of abnormal metabolic processes [6-9]. Details of such changes seen in the cancer-bearing host are outlined in this chapter.

ANOREXIA

Anorexia leading to a decreased caloric intake has been recognized clinically for many years in patients with cancer [10]. Suggested factors [8,11-14] contributing to anorexia in this situation include: alterations of taste sensation, psychological influence of a cancer diagnosis, metabolic products and hypothetical tumor toxins, as well as direct effects on the appetite center. Once treatment for cancer is under way, anorexia may result from complications of chemotherapy or radiation treatment as well [6,8,15].

The older concept that the weight loss in cancer patients is related to the "tumor feeding on the host" can be severely challenged when one considers that in the usual clinical situation, tumor burdens rarely exceed 1% of a host body mass [16,17]. Thus, the suggestion that changes in tumor metabolism are of sufficient magnitude to alter overall host energy balance cannot be easily supported. Only limited information on the CNS food intake control mechanism in patients with cancer and weight loss is available. In animal models, the hypothalamic components of control of food intake appear not to be affected by the presence of tumor [10,14]. Hypotheses implicating derangements in the serotoninergic system in the regulation of feeding behavior in the cancer-bearing host have been proposed but have undergone limited clinical evaluation [18]. At present then, little direct evidence suggests a major role for central control of weight loss development in the patient with cancer.

TASTE ABNORMALITIES IN CANCER PATIENTS

Alteration in taste perception is one factor that has undergone considerable evaluation in the cancer patient population. Cancer patients have reported a general reduction in the pleasant taste of food and negative taste sensations related to specific foods [19,20]. More quantitative efforts in this area have included determination of taste recognition and detection thresholds for salt, sweet, sour, and bitter taste sensations. Although most trials in this area have been small, involving fewer than 50 patients, several characteristic abnormalities have been described [20-25]. Although some investigators reported the increased taste recognition threshold for bitter taste [20,25,26], the most consistent abnormality seen is an increased taste recognition for sweet substances, occurring in approximately one third of patients tested with a variety of tumors [9,20]. In several of these studies, the presence of abnormal taste sensation has been associated with decreased caloric intake [20,27]. DeWys and Walters [20] reported, in addition, a correlation between tumor extent and sensitivity of taste sensation abnormality in cancer patients. Patients determined to have only a limited tumor burden had no taste threshold abnormalities (in nine cases) compared with patients determined to have extensive tumor involvement where 15 of 20 patients had abnormalities of taste detected. Similar abnormalities of taste can be independently reproduced by radiation therapy as well. Mossman and coworkers [28] serially assessed taste sensation in a series of patients who had received radiation one to seven years previously for tumors of the head and neck. Sixty-nine percent of patients had measurable taste loss. The authors estimated that the maximal tolerance doses resulting in a 50% complication rate five years after treatment was between 50 and 65 gy for taste loss. Such changes may reflect direct damage to taste receptors as well as interference with salivary function, since in another prospective study over 80% of radiation-treated patients with tumors of the oral cavity noted complications of taste loss and/or dry mouth. Of interest was the observation that 25% of patients experienced similar complications before initiation of radiation therapy as a consequence of their tumor [29].

An intriguing but unexplained observation in patients receiving radiation treatment is the relatively common development of appetite perversions and taste changes triggered or abolished by radiotherapy given at sites distant from the oropharynx. Brewin [30] has reported that 147 of 819 oncology patients questioned reported that local tumor radiation, regardless of tumor type, site, or volume radiated, either triggered (in 97 cases) or abolished (in 50 cases) an isolated appetite perversion. These changes occurred early in the treatment course at a time when little if any tumor regression was apparent. The same association with the cravings or aversions for food noted during pregnancy in some cases were reported [31].

Only limited information on the influence of chemotherapy on taste sensation in patients with cancer is available. A combination chemotherapy regimen that included bleomycin, actinomycin-D, vindisine, and

DTIC diminished patients' ability to discriminate between the highest and lowest concentration for sweet, sour, and bitter tastes [32]. In another study, therapy with 5-FU resulted in a decrease in elevated sweet recognition thresholds to the normal range after two weeks of treatment [33].

Changes in cancer-associated taste abnormalities appear to be reversible, at least under some circumstances. Improvement in taste parameters have been noted in patients responding to antineoplastic therapy, parenteral nutritional support, and tumor excision [19,34,35]. In successfully treated patients with laryngeal carcinoma, recovery of taste sensation was noted to occur for up to six months after completion of treatment. It is noteworthy that recurrence of taste abnormalities was seen in patients demonstrating tumor recurrence in this same trial [34].

The true relationship among taste sensation abnormalities, the presence of cancer, and the development of weight loss remains to be clearly defined. That is, are these taste sensation abnormalities a specific and direct consequence of the tumor resulting in a decreased caloric intake and weight loss, or are such taste abnormalities themselves the result of other factors commonly seen in a cancer patient population? A smoking history and/or advancing age have been shown to profoundly influence taste sensation thresholds in cancer-free populations [36-38]. Obviously, these parameters are also associated with the development of a variety of cancers as well. In an attempt to determine the relative importance of such factors influencing taste sensation thresholds in patients with cancer, we have recently evaluated taste recognition thresholds in 93 patients with malignancy, including 18 patients with lung carcinoma, and compared our results with a 61-patient control population free of cancer [24]. Sucrose (sweet) and urea (bitter) taste thresholds were determined by a forced choice technique. Albumin, transferrin, anthropometrics, caloric intake, and protein intake were used to assess nutritional status. Sweet and bitter taste thresholds were significantly higher ($p<0.05$) for smokers compared with nonsmokers. In cancer patients, no cases of decreased threshold of bitter tastes were detected. Thirty-eight percent of cancer patients had an increased threshold for sweet substances, a proportion significantly greater than that seen in control patients without cancer ($p<0.01$). However, when correction using a multivariant analysis was made for smoking history and age of study patients, no differences in taste test parameters were seen between cancer patients and control patients without malignancy. In addition, we did not find an association between caloric intake and taste test abnormalities in our cancer patient population. Therefore, the altered taste sensation threshold found in these cancer patient populations may be related to factors such as age and smoking history rather than cancer per se. In any event, it is possible that the combination of cancer-associated malnutrition and taste sensation abnormalities can set up a vicious cycle, since disturbance of regeneration of chemoreceptors for taste can result from general malnutrition by itself [39].

One possible consequence of malnutrition in cancer populations that may contribute to the development of taste sensation abnormalities is relative zinc deficiency. Early studies suggested that zinc deficiency may be associated with taste sensation threshold elevation [37,40]. However, Bolze and coworkers [21] could not demonstrate a significant correlation between the taste thresholds and plasma zinc levels in 35 patients who were undergoing radiotherapy, nor could Trant and colleagues [33] correlate hair zinc levels with taste perception in 62 patients. In a somewhat larger population reported by Silverman and Thompson [41], 75 patients with oropharyngeal carcinoma were studied to assess the relationship between serum zinc levels and radiation-induced taste loss. Thirty patients who did not experience spontaneous postradiation taste recovery were subsequently supplemented with zinc sulfate daily for at least one month. In 11 cases, improvement in taste sensation was reported with markedly increased serum zinc levels seen in the patients with taste improvement [41]. Thus, further study of zinc sulfate supplementation in treatment of taste sensation abnormalities in other cancer-bearing populations would seem warranted.

The common occurrence of increased thresholds to such tastes in patients with cancer has led to recommendations for adding more highly sweet foods to the cancer patient's diet [9]. However, taste threshold data did not correlate with taste preference data in an anorectic cancer patient population reported by Trant [33]. In fact, preference data suggested a favored reduction of sweet foods in some subsets [33]. Such apparently conflicting information points to the complexity of factors influencing food intake in the cancer population. Taken together the current data suggest that information obtained from individual patients [42] is needed to outline the optimal dietary composition needed to maximize caloric intake in the patient with cancer.

Another factor potentially influencing caloric intake and development of weight loss in cancer patients that has received surprisingly limited evaluation is the influence of psychological factors such as depression. In a population of 72 advanced solid tumor patients receiving chemotherapy, Bruera and coworkers [43] examined for associations among caloric intake, psychological depression, glucose taste threshold, and tumor burden. An equivalent number of malnourished patients and patients with normal nutritional status were

Table 34.1 Factors potentially contributing to the development of anorexia in the patient with cancer

Taste abnormalities
Food aversions
Psychological factors (depression)
Abnormal host metabolism
Effects of treatment:
Radiotherapy
Chemotherapy

included. In the malnourished group, a significantly lower caloric intake and higher incidence of depression (59% versus 20%; $p<0.03$) was seen. Interestingly, although abnormal glucose taste thresholds occurred in over 60% of patients, the percentage showing this abnormality were equivalent in the malnourished and well-nourished cancer patient groups. As in many of the previously described studies, once again the question of association rather than causation must be raised. Prospective studies involving patients either at high risk for cancer development or cancer recurrence following primary treatment of their initial localized disease will be needed to definitively address these problems.

Factors potentially contributing to the development of anorexia in the patient with cancer are outlined in table 1. Regardless of specific etiology, anorexia and decreased caloric intake represent a major problem confronting patients with a diagnosis of cancer.

ENERGY BALANCE AND ABNORMAL METABOLISM

Although, as outlined above, caloric intake is clearly decreased in cancer cachexia, an increasing body of evidence suggests that other factors may play a role in the weight loss seen in the cancer patient population as well. A large study has compared quantitative food intakes of 205 normal individuals with 198 ambulatory cancer patients using a 24-hour recall technique [3]. Although the caloric intake of normal males free of cancer significantly exceeded that of males with lung cancer (2,358 kcal versus 1,778 kcal, p.05), essentially no difference in caloric intake between normal females and females with lung cancer was seen. Furthermore, the caloric intake for cancer patients who had lost body weight compared with those who had been able to maintain their body weight was nearly identical (1,776 kcal versus 1,780 kcal). Thus, anorexia or reduced caloric intake alone could not account for the weight loss experienced by these lung cancer patients. In further support of the concept that factors other than a decreased caloric intake play a major role in the development of weight loss in lung cancer is the failure of the provision of calories via force feeding [44] or hyperalimentation [33] to uniformly increase lean body mass in patients with cancer. Such observations suggest that weight loss may be related to altered host metabolism brought about by the presence of malignancy.

Recent studies involving basal metabolic rate determinations using the technique of indirect calorimetry have reported a relatively consistent pattern of a moderate increase in energy expenditure in patients with various tumor types [45-47]. In some diseases such as gastrointestinal malignancies, only a minority (26%) of patients appear to be hypermetabolic [45]. In other diseases such as small cell carcinoma of the lung, a more consistent increase in resting energy expenditure has been found [47]. Chemotherapeutic administration alone or use of nutritional support [36,45] did not reduce the elevations of resting energy expenditure. However, either tumor resection or complete response to chemotherapy resulted in reduced resting energy expenditure in these reports [47,48]. Such data suggest that in some cases the cancer patient may manifest a characteristically increased energy demand that contributes to the weight loss. The underlying mechanism of such an increase in energy expenditure is poorly understood at the present time. However, a wide range of metabolic changes have been described in the cancer-bearing host including abnormalities of carbohydrate, protein, and lipid metabolism [49-52].

CANCER CACHEXIA: THERAPEUTIC IMPLICATIONS

While the impact of malnutrition on survival in cancer patients is evident, the ability of existing methods of nutritional intervention to influence this adverse clinical outcome is not established. Early trials with forced feeding [44] and enteral supplements [53] achieved only mixed results. The introduction of total parenteral nutrition (TPN) has permitted the physician to provide nutritional support without using the gastrointestinal tract. Early clinical experience in nonrandomized trials have suggested TPN to be beneficial in converting skin tests and decreasing toxic effects associated with chemotherapeutic regimens [54]. However, in a series of investigations supported by the Diet, Nutrition, and Cancer program of the National Cancer Institute, no significant improvement in either response or survival was associated with TPN use in patients with lymphoma, metastatic colon cancer, adenocarcinoma of the lung, or metastatic testicular carcinoma [55]. Similar conclusions have been drawn from randomized TPN trials involving pediatric patients as well [56]. It is worth noting that these studies have not directly tested the hy-

Table 34.2 Metabolic treatment strategies for cancer cachexia under evaluation

Metabolic abnormality seen in cancer cachexia providing rationale	Treatment Approach	References
Abnormal protein metabolism	Prednisolone	Willox et al (61)
	Medroxylprogesterone	Lelli et al (64)
Hypogonadism	Nandrolone decanoate	Chlebowski et al (63)
Abnormal glucose metabolism	Hydrazine sulfate	Gold (67)
		Gershanovich (69)
		Chlebowski et al (65)
	Insulin	Schein et al (84)

pothesis that nutritional repletion of a malnourished patient with cancer will improve clinical outcome, since sequential improvement in lean body mass has not been reported in these trials. As they currently stand, the data from these studies has been recently reviewed and the consensus is that provision of increased calories alone does not significantly alter the clinical course of patients with advanced cancer and weight loss [54,55,57].

Although pre- and perioperative TPN has demonstrated benefit in the cancer patient undergoing curative resection in terms of decreasing operative morbidity and mortality in several reports [58-60], this result may well represent the influence of nutritional status on surgical outcome rather than reversal of a specific cancer-related abnormality.

The failure of increased calories alone to alter the clinical course of patients with cancer and weight loss suggests that consideration of the mechanism underlying the development of cancer cachexia may be needed to develop more successful nutritional strategies in this population. Based on observed metabolic disturbances in the cancer population with weight loss, a number of nutritional-metabolic therapeutic interventions are under investigation (table 2).

The weight gain associated with corticosteroid use in a variety of clinical situations is well established. Based on this rationale, investigators have evaluated the impact of prednisolone in a 5 mg, three-times-a-day dose compared with placebo administration in advanced cancer patients [61]. Study endpoints included subjective parameters of sense of well-being and appetite and objective parameters of caloric intake and weight change. A statistically significant improvement in appetite without change in caloric intake or weight was noted in the prednisolone-treated population, which was associated with an improvement in sense of well-being as well. Thus, prednisolone treatment may be considered to represent a symptomatic approach to the problem of cancer cachexia.

The recent identification of hypogonadism or low testosterone levels in male patient populations with advanced cancer, which was correlated with weight loss and adverse outcome [49,62], has led to a trial of replacement therapy with androgen in this condition. Chlebowski and coworkers [63] have recently conducted a randomized prospective clinical trial in which short-term addition of nandrolone decanoate to chemotherapy treatment in patients with non-small cell lung cancer was evaluated. Patients received a standard platinum-containing combination chemotherapy regimen plus or minus the addition of nandrolone decanoate at 200 mg dose given intramuscularly every week for four doses. This short term androgen therapy was associated with a decreased rate of weight loss, which was of borderline statistical significance. However, since pretreatment androgen levels were not identified in this trial, further prospective studies of such agents using pretreatment testosterone levels to guide administration will be needed to definitively evaluate its role in lung cancer cachexia treatment. The recent report that high-dose medroxyprogesterone acetate had anabolic effect in advanced cancer patients in a small trial represents a similar approach using a currently available agent that bears further evaluation [64].

Finally, abnormal glucose metabolism has been frequently seen in patients with cancer cachexia. The increase in total glucose production [50,65,66] which has likewise been observed, has led to the suggestion that inappropriate activation of such pathways could lead to futile cycling and host energy loss [67]. Since hydrazine sulfate is an inhibitor of gluconeogenesis in animals, this agent has undergone preliminary clinical trials as a potential therapeutic approach to cancer cachexia in humans as well [65,68,69]. Randomized trials have demonstrated an ability of hydrazine sulfate administration in a 60 mg, three-times-a-day dosage to favorably influence abnormal glucose metabolism seen in patients with advanced cancer [65]. More recent studies in Russia [69] and the United States [68] have suggested a role for this agent in weight stabilization as well. Further clinical trials, some of which are under way currently at our institution, will define whether such changes in me-

tabolic parameters and nutritional indices will be associated with any change in clinical outcome.

LEARNED TASTE AVERSION AND BEHAVIORAL INTERVENTION

Another potential factor that may influence the development of anorexia in a cancer patient population is the phenomenon of learned taste aversion [70-72]. In both animal and preliminary clinical observations in pediatric populations, an aversion to specific tastes are learned after even the single pairing of the taste with gastrointestinal symptomatology related to radiation therapy or chemotherapy [70,73,74]. It is interesting that in animal models, learned food aversions may occur apparently as a result of the discomfort induced by tumor growth itself [74]. In these circumstances, it is postulated that tumor growth may suppress appetite indirectly by producing chronic symptoms that act as unconditioned stimuli leading to subsequent food avoidance. In a pediatric population studied by Bernstein [73], foods eaten up to five hours after administration of a chemotherapy regimen that was associated with nausea and vomiting were subsequently identified as disliked foods. This observation may have important therapeutic implications, especially in terms of maintaining caloric intake in patients undergoing chemotherapy administration.

A comprehensive discussion of the treatment of nausea and vomiting in a cancer patient population is beyond the scope of this chapter but has recently been extensively reviewed [75,76]. Two relatively recent developments in this area appear to be related to the phenomenon of learned food aversion. In patients receiving chemotherapy as adjuvant to their primary breast surgery, anticipatory nausea and vomiting (patients developing gastrointestinal toxicity before the actual administration of the emetogenic chemotherapeutic agent) has been observed to be a major problem in several reports [77,78]. An opposite extreme of the same spectrum is the increasing attention given to behavioral intervention for reduction of nausea and vomiting in cancer patient populations receiving chemotherapy [79]. Behavioral intervention strategies have included hypnosis with guided imagery for relaxation [80], electromyographic biofeedback combined with relaxation training imagery [81], and systematic desensitization [81].

In adult patient programs largely aimed at anticipatory nausea and vomiting, some effectiveness has been seen [82]; however, symptoms control has largely been dependent on continuation of the intervention, with symptoms returning after termination [21,74,83]. Recently, however, considerable success has been described in a program involving hypnosis and supportive counseling in a pediatric population in which a favorable impact on gastrointestinal symptomology was maintained after the active behavioral intervention program had been discontinued [79]. These studies are of special interest, since they may help elucidate further the role of psychological factors in cancer-associated anorexia.

In summary, weight loss is commonly seen in patients with cancer and is associated with an adverse prognosis. Anorexia contributes to the relative caloric insufficiency that results in weight loss in this population. The anorexia associated with cancer is almost certainly multifactoral, and precise elucidation of the relative contributions of such factors as taste sensation abnormalities, learned food aversions, psychological factors including depression, and metabolic abnormalities will require further study. Although intensive nutritional support by providing calories via TPN can be safely administered to patients with cancer, only limited therapeutic benefit has been seen with this approach. Consideration of the underlying mechanisms associated with weight loss in this population has led to a variety of new nutritional and metabolic approaches directed at improving the poor prognosis of a cancer patient with anorexia and weight loss. Increasing attention is being directed at behavioral intervention strategies in such populations as well.

REFERENCES

1. DeWys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Am J Med 1980; 69:491-8.
2. Costa G, Bewley P, Aragon M, Siebold J. Anorexia and weight loss in cancer patients. Cancer Treat Rep 1981; 65(5):3-7.
3. Costa G, Lane WW, Vincet RG, Siebold JA, Aragon M, Bewley PT. Weight loss and cachexia in lung cancer. Nutr Cancer 1981; 2:98-103.
4. Freeman M, Frankmann C, Beck J, Valdivieso M. Prognostic nutrition factors in lung cancer patients. J Parent Ent Nutr 1982; 6:122-7.
5. Martin KI, Sox HC, Krupp JR. Involuntary weight loss: diagnostic and prognostic significance. Ann Int Med 1981; 95:568-74.
6. Barry RE. Malignancy, weight loss, and the small intestinal mucosa. Gut 1974; 15:562-70.
7. Cohen A, Heymesfield S, Kuck K, et al. Mechanism of weight loss in hospitalized cancer patients (abst). Clin Res 1978; 26:36.
8. Costa G, Donaldson SS. Effects of cancer and cancer treatment on the nutrition of the host. N Engl J Med 1979; 300:1471-3.
9. DeWys WD, Hoffman FA. Pathophysiology of anorexia and disturbances of taste in cancer patients. In:

Levin B, Riddell RH, eds. Frontiers in gastrointestinal cancer. New York: Elsevier, 1984:81-90.
10. Morrison SD. Control of food intake in cancer cachexia: a challenge and a tool. Physiol Behav 1976; 17:705-8.
11. Chlebowski RT. Effect of nutritional support on the outcome of antineoplastic therapy. Clin Oncol 1986; 5:365-79.
12. Garattini S, Guaitani A. Animal models for the study of cancer-induced anorexia. Cancer Treat Rep 1981; 65(5):23-35.
13. Mordes JP, Rossini AA. Tumor-induced anorexia in the Wistar rat. Science 1981; 213:565-7.
14. Morrison SD. Control of food intake during growth of a Walker 256 carcinosarcoma. Cancer Res 1973; 33:526-8.
15. Kokal WA. The impact of antitumor therapy on nutrition. Cancer 1985; 55:273-8.
16. Schein PS, MacDonald JS, Waters C, et al. Nutritional complications of cancer and its treatment. Semin Oncol 1975; 2:337-47.
17. Young VR. Energy metabolism and requirements in the cancer patient. Cancer Res 1977; 37:2336-41.
18. Krause R, Humphrey C, Von Meyenfeldt M, James H, Fischer JE. A central mechanism for anorexia in cancer: a hypothesis. Cancer Treat Rep 1981; 65:15-21.
19. DeWys WD. Changes in taste sensation and feeding behavior in cancer patients: A review. J Hum Nutr 1978; 32:447-53.
20. DeWys WD, Walters K. Abnormalities of taste sensation in cancer patients. Cancer 1975; 36:1888-96.
21. Bolze MS, Fosmire GJ, Stryker JA, Chung CK, Flipse BG. Taste acuity, plasma zinc levels and weight loss during radiotherapy: a study of relationships. Radiology 1982; 144:163-9.
22. Carson JAS, Gormican A. Taste acuity and food attitudes of related patients with cancer. J Am Diet ASsoc 1977; 70:361-4.
23. Gorshein D. Posthypophysectomy taste abnormalities: their relationship to remote effects of cancer. Cancer 1977; 39:1700-3.
24. Larsen C, Byerley L, Heber D, Chlebowski R. Factors contributing to altered taste sensation in cancer patients. JPEN 1983; 6:575.
25. Williams LR, Cohen MH. Altered taste thresholds in lung cancer. Am J Clin Nutri 1978; 31:122-5.
26. Hall JC, Staniland JR, Giles I. Altered taste thresholds in gastrointestinal cancer. Clin Oncology 1980; 6:137-42.
27. DeWys WD, Costa G, Henkin R. Clinical parameters related to anorexia. Cancer Treat Rep 1981; 65(5):49-52.
28. Mossman K, Shatzman A, Chencharick J. Long term effects of radiotherapy on taste and salivary function in man. Int J Radiat Oncol Biol Phys 1982; 8:991-7.
29. Chencharick JD, Mossman KL. Nutritional consequences of the radiotherapy of head and neck cancer. Cancer 1983; 51:811-5.
30. Brewin TB. Can a tumor cause the same appetite perversion or taste change as a pregnancy. Lancet 1980; 2:907-8.
31. Brewin TB. Appetite perversions and taste changes triggered or abolished by radiotherapy. Clin Radiol 1982; 33:471-5.
32. Mulder NH, Smith JM, Krevmer WM, Bouman J, et al. Effect of chemotherapy on taste sensation in patients with disseminated malignant melanoma. Oncology 1983; 40:36-8.
33. Trant AS, Serin J. Douglass HO. Is taste related to anorexia in cancer patients. Am J Clin Nutr 1982; 36:45-58.
34. Kashima HK, Kalinowski B. Taste impairment following laryngectomy. Ear Nose Throat 1979; 58:88-92.
35. Russ J, DeWys WD. Correction of taste abnormality of malignancy with hyperalimentation. Arch Int Med 1977; 138:799-800.
36. Conger AD, Wells MA. Radiation and aging effects on taste structure and function. Radiation Res 1969; 37:31-8.
37. Henkin R. Taste loss in aging. In: Davis HJ, Neithmeimer R, St. Petersburg R, eds. The biomedical role of trace elements in aging. Echerd College Gerontology Center, 1976:221-36.
38. Kaplan AR. The effect of cigarette smoking on malnutrition and digestion. Gastroenterology 1963; 61:208.
39. Schiffman SS. Taste and smell in disease. N Engl J Med 1983; 308:1337-43.
40. Henkin RI, Schechter PJ, Hoye R, Mattern FCT. Idiopathic hypoguesia with dysguesia, hyposmia and dysosmia: a new syndrome. JAMA 1971; 217:434-40.
41. Silverman S Jr, Thompson JS. Serum zinc and copper in oral/oropharyngeal carcinoma. Oral Surg 1984; 57:34-6.
42. Vickers ZM, Nielsen SS, Theologides A. Food preferences of patients with cancer. J Am Diet Assoc 1981; 79:441-5.
43. Bruera E, Carraro S, Roca E, Cedaro L, Chacon R. Association between malnutrition and caloric intake, emesis, psychological depression, glucose taste and tumor mass. Cancer Treat Rep 1984; 68:873-6.
44. Terepka AR, Waterhouse C. Metabolic observations during forced feeding of patients with cancer. Am J Med 1956; 20:225-38.
45. Dempsey DT, Feurer ID, Knox LS, Corsby LO, Buzby GP, Mullen JL. Energy expenditure in malnourished gastrointestinal cancer patients. Cancer 1984; 53:1265-73.
46. Knox LS, Crosby LO, Fuerer ID, et al. Energy expenditure in malnourished cancer patients. Ann Surg 1983; 197:152-62.
47. Russell DM, Shike M, Marliss EB, et al. Effects of total parenteral nutrition and chemotherapy on the metabolic derangements in small cell lung cancer. Cancer Res 1984; 44:1700-11.
48. Arbeit JM, Lee SDE, Corsey R, Brennen MF. Resting energy expenditure in controls and cancer patients with localized and diffuse disease. Ann Surg 1984; 200:292-

8.
49. Chlebowski RT, Heber D, Block JB. Lung cancer cachexia. In: Greco FA, ed. Biology and Management of Lung Cancer. Boston: Martinus Nijhoff Publishers, 1983:125-42.
50. Holyrode CP, Gabuzda G, Putnam RC, et al. Altered glucose metabolism in metastatic cancer. Cancer Res 1975; 35:3710-4.
51. Heber D, Chlebowski RT, Ishibashi DE, Herrold JN, Block JB. Metabolic abnormalities in lung cancer patients. Cancer Res 1982; 42:2495-8.
52. Jeevanandam M, Horowitz GD, Lowry SF, Brennan M. Cancer cachexia and protein metabolism. Lancet 1984; 1:1423-6.
53. Aker SN. Oral feedings in the cancer patient. Cancer 1979; 43:2103-7.
54. Copeland EM. Intravenous hyperalimentation and chemotherapy: an update. J Parent Ent Nutr 1982; 6:236-9.
55. Nixon DW. Hyperalimentation in the undernourished cancer patient. Cancer Res 1982; 42 (Suppl):727-8.
56. Van Eye J, Copeland EM, Cangin, et al. A randomized controlled clinical trial of hyperalimentation in children with metastatic malignancies. Med Ped Oncol 1980 1980; 8:63-73.
57. Chlebowski RT. Critical evaluation of the role of nutritional support with chemotherapy. Cancer 1985; 35:268-72.
58. Muller JM, Dienst C, Brenner U, Pichlmaier H. Preoperative parenteral feeding in patients with gastrointestinal carcinoma. Lancet 1982; 1:68-71.
59. Silberman H. The role of preoperative parenteral nutrition in cancer patients. Cancer 1985; 55:254-7.
60. Smale BF, Mullen JE, Buzby GP, Rosato EF. The efficacy of nutritional assessment and support in cancer surgery. Cancer 1981; 47:2375-81.
61. Willcox JC, Corr J, Shaw J, Richardson M, Calman KC, Drennan M. Prednisolone as an appetite stimulant in patients with cancer. Brit Med J 1984; 288:27.
62. Chlebowski RT, Heber D. Hypogonadism in male patients with metastatic cancer prior to treatment. Cancer Res 1982; 42:2495-8.
63. Chlebowski RT, Herrold J, Richardson B, Block JB. Effects of decadurabolin in patients with non-small cell lung cancer. Clin Res 1982; 23:541.
64. Lelli G, Angellelli B, Giambasi ME, et al. The anabolic effect of high dose medroxyprogesterone acetate in oncology. Pharm Res Com 1983; 15:561-8.
65. Chlebowski RT, Heber D, Richardson B, Block JB. Influence of hydrazine sulfate in abnormal carbohydrate metabolism in cancer patients with weight loss. Cancer Res 1984; 44:857-61.
66. Eden E, Edstrom S, Bennegard K, Schersten T, Lundhold K. Glucose flux in relation to energy expenditure in malnourished patients with and without cancer during periods of fasting and feeding. Cancer Res 1984; 44:1717-24.
67. Gold J. Cancer cachexia and gluconeogenesis. Ann NY Acad Sci 1979; 230:103-10.
68. Chlebowski RT, Bulcavage L, Grosvenor M et al. Hydrazine sulfate in cancer patients with weight loss: a placebo-controlled clinical experience. Cancer 1987; 59:406-10.
69. Gershanovich ML. Clinical effects of hydrazine sulfate in patients with advanced malignant disease. In: Filov VA, Evin BA, Gershanovich ML, eds. Medical therapy of tumors. Leningrad: USSR Ministry of Health, 1983: 91-138.
70. Bernstein IL. Learned taste aversions in children receiving chemotherapy. Science 1978; 200:1300-3.
71. Smith JC, Blumsack JT. Learned taste aversion as a factor in cancer therapy. Cancer Treat Rep (Suppl) 1981; 65:37-42.
72. Smith JC, Birkle RA. Conditioned aversion to sucrose in rats using xrays. Psychonomic Science 1666; 5:271-2.
73. Bernstein IL, Bernstein ID. Learned food aversions and cancer anorexia. Cancer Treat Rep 1981; 65(5):43-7.
74. Bernstein IL, Fenner DP. Learned food aversions: heterogeneity of animal models of tumor induced anorexia. Appetite: J for Intake Res 1983; 4:79-86.
75. Frytak S, Moertel CG. Management of nausea and vomiting in the cancer patient. JAMA 1981; 245:393-6.
76. Laszlo J, Lucas VS. Emesis as a critical problem in chemotherapy. N Engl J Med 1981; 305:948-9.
77. Morrow GR. Clinical characteristics associated with the development of anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment. J Clin Onc 1984; 2:1170-4.
78. Wilcox PM, Fetting JH, Nettesheim KM, et al. Anticipatory vomiting in women receiving cyclophorphamide, methotrexate, and 5-FU (CMF) adjuvant chemotherapy for breast carcinoma. Cancer Treat Rep 1982; 66:1601-4.
79. Zeltzer L, LeBaron S, Zelter PM. The effectiveness of behavioral intervention for reduction of nausea and vomiting in children and adolescents receiving chemotherapy. J Clin Oncol 1984; 2:683-90.
80. Redd WH, Andersen GV. Conditioned aversion in cancer patients. Behav Res Ther 1981; 4:34.
81. Burish TG, LYles JN. Effectiveness of relaxation training in reducing adverse reactions to cancer chemotherapy. J Behav Med 1981; 4:65-78.
82. Morrow GR, Morrell C. Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. N Engl J Med 1982; 307:1476-80.
83. Redd WH, Andrykowski MA. Behavioral intervention in cancer treatment: controlled aversion reactions to chemotherapy. J Consult Clin Psychol 1982; 50:1018-29.
84. Schein PS, Kisner D, Haller D, Blecher M, Hamosh M. Cachexia of malignancy: potential role of insulin in nutritional management. Cancer 1979; 43:2070-6.