Learned Food Aversions in the Progression of Cancer and Its Treatment[a]

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Patients suffering from cancer are exposed to a variety of experiences that can provide the basis for the development of learned aversions, particularly learned aversions to foods. Prominent among these experiences are the severe nausea and vomiting that commonly accompany chemotherapy and radiotherapy.[1] Since drug and radiation treatments are well established as effective unconditioned stimuli in the acquisition of learned taste aversions, foods eaten before such treatments are potential targets for the development of learned aversions.[2,3] Drug side effects are also involved in the phenomenon of conditioned or anticipatory nausea and vomiting.[4-6] This is a form of classical conditioning that occurs in some patients when stimuli associated with repeated drug treatments come to elicit these symptoms before the drugs are actually administered.

Another source of learned aversions is the disease process itself. Animal studies indicate that the aversive physiological consequences of tumor growth may become associated with specific diets, leading to the development of learned aversions to those diets.[7,8] Such aversions have been shown to lead to depressions in food intake and body weight.

The studies discussed in this paper examine the learned food aversions that arise both as a result of antineoplastic drug therapy and as a result of neoplastic disease. Chemotherapy-induced aversions have largely been studied in humans in a clinical setting, although an animal model of chemotherapy-induced aversions has played a role in the development of intervention strategies. Tumor-induced aversions have been examined in animal experiments using rats implanted with experimental tumors. In describing this work I will present the evidence on which I base the conclusion that learned food aversions arise in patients and in animals with cancer and that these aversions contribute to the appetite problems associated with this disease. I will also outline the direction of our current and future work.

DRUG-INDUCED LEARNED FOOD AVERSIONS

Learned Taste Aversions in Patients Receiving Chemotherapy

Our studies in this area were stimulated by the dramatic and compelling nature

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of taste aversion learning in animals. We suspected that humans exposed to pairings of foods and GI toxicity in the course of cancer treatments would develop aversions to those foods. Interview studies[9] suggested that humans often develop profound distastes for foods that were coincidentally associated with gastrointestinal (GI) discomfort. The clinical setting provided an opportunity to examine taste aversion learning in humans experimentally. It was important to determine whether learned food aversions were an inadvertent side effect of cancer chemotherapy and whether ways could be devised to prevent them.

The first study in this series examined learned taste aversions in pediatric cancer patients receiving chemotherapy.[10] We asked whether children receiving drugs that were associated with nausea and vomiting would acquire aversions to a novel food consumed before their drug treatments. We used a novel food as our target stimulus because novel foods are apparently much more susceptible to aversion conditioning than are familiar foods.[11] The "novel food" target in this study was "Mapletoff" ice cream, chosen because children, even anxious and "nondeprived" children, are generally willing to eat ice cream. The novelty was introduced by using unusual flavorings.

Subjects were outpatients, between the ages of two and 16 years, being treated at the Children's Orthopedic Hospital and Medical Center Hematology Clinic in Seattle. Patients scheduled to receive GI toxic chemotherapy were randomly assigned to one of two groups: the Experimental Group, which consumed Mapletoff ice cream shortly before their scheduled drug treatment, or the Drug Control Group, which received similar drug treatments but no exposure to the ice cream. A Taste Control Group composed of patients who either received chemotherapy not associated with GI symptoms (vincristine) or no drug treatment was also included. Patients in this group consumed the same ice cream as the Experimental Group. Approximately two to four weeks later, patients were tested for the development of aversions by being offered a choice between eating Mapletoff ice cream or playing with a game.

Only 21 percent (3/14) of the patients in the Experimental Group chose Mapletoff ice cream during the test session compared to 67 percent (8/12) and 73 percent (11/15) in the two Control Groups. The proportion of subjects selecting ice cream in the Experimental Group was significantly lower than in the combined Control Groups ($p < .01$) suggesting that children will avoid eating a food that has previously been associated with GI toxic chemotherapy.

To evaluate the flavor specificity of these aversions, we offered experimental and control patients a choice between two ice cream flavors: Mapletoff (the flavor previously paired with GI toxic therapy in the experimental condition) and Hawaiian Delight (orange-pineapple). We asked the patients to taste both ice cream flavors, indicate which they preferred, and eat as much of each as they wished. Flavor preference and amount consumed were recorded. Preference for Mapletoff ice cream, whether measured by the amount consumed or the patients' stated preference, was significantly lower in the Experimental Group than in the Control Groups. Thus, aversions appear to be specific to the particular ice cream flavor presented during conditioning.

Although the observation of taste aversion learning in human subjects was not particularly unexpected, there are some interesting features of these results. First, the aversions were acquired in a single conditioning trial even though lengthy delays were likely to have occurred between the tasting of the ice cream and the onset of aversive symptoms. (Symptoms may begin a few minutes to a few hours after drug administration.) Second, many of the patients had received a large number of prior drug treatments. Furthermore, most of the patients were old enough to understand that the cause of their symptoms of nausea and vomiting was their drug therapy and not Mapletoff ice cream. Because factors such as these would be expected to reduce aversion condi-

tioning, the demonstration of significant aversions suggests that humans are relatively susceptible to taste aversion learning.

These studies were subsequently extended to an adult patient population[12] where we found that adults, like children, can acquire learned taste aversions in a single trial. Apparently the cognitive development of adults does not override this conditioning.

Animal Models of Drug-induced Aversions

Since taste aversion studies in the rat originally pointed us to the existence of drug-induced aversions in humans, it seemed particularly appropriate to turn to animal models of these aversions to learn more about the mechanisms involved and to develop intervention strategies.

The vast majority of previous taste aversion studies have employed deprived subjects and novel, flavored solutions. Therefore, our first task was to modify the aversion conditioning paradigm so that it would more closely model the clinical situation. It is obvious that a number of important differences exist between the eating habits of laboratory rats and human patients. Laboratory rats are typically reared on a single, complete food (i.e., commercial laboratory chow). Humans in our society, on the other hand, have a dazzling variety of foods available to them throughout life although the foods they actually consume from day to day are considerably more restricted. In order to provide a target food that was not totally novel, but also was not as familiar as laboratory chow,[13] we exposed rats to a single, complete diet (AIN meal; ICN, Cleveland, OH) for five days before subjecting them to a course of drug (cyclophosphamide) treatments: four i.p. injections of either cyclophosphamide or physiological saline spaced three days apart. The cyclophosphamide dosage used was 20 mg/kg of body weight, which is in the low range of dosages in clinical use. AIN diet was continuously available *ad lib* throughout the 12 days. A 24-hr two food preference test, which offered rats a choice between AIN and a novel diet of comparable palatability, was used to evaluate food aversion learning. Preference scores were calculated for each animal by dividing the amount of AIN diet consumed by total food intake during the test. Drug-treated animals displayed significantly lower preferences than saline-treated controls for the AIN target diet, a strong indication that the drug-treated animals developed learned aversions to the AIN diet. These findings are interesting because the animals were not deprived, and in fact had received five days of "safe" pre-exposure to the AIN diet prior to the first drug treatment. Furthermore the diet was present continuously during the 17-day experiment—i.e. exposure was not linked temporally to the drug treatments in any narrow sense.

Since this treatment model was capable of producing significant diet aversions, we tested a variety of intervention methods for reducing or eliminating the aversions. We rated the success of these interventions by the degree to which they reduced aversions to the AIN diet. The approaches evaluated were: (1) depriving animals of food for six hours before and after each drug treatment; (2) introducing a novel flavor in the animals' water around the time of each treatment; (3) exposing animals to a combination of food deprivation and novelly flavored water; and (4) replacing the animals' standard AIN diet with a novel food on treatment days. As can be seen in FIGURE 1, only the introduction of a novel diet on treatment days was effective in preventing diet aversions. In spite of the fact that the animals in the Novel Diet group consumed very little of the novel food (and therefore would appear to be similar to the Deprivation group), aversions to the AIN diet were completely eliminated. Food deprivation and novel liquid interference stimuli did not reliably reduce the magnitude of AIN

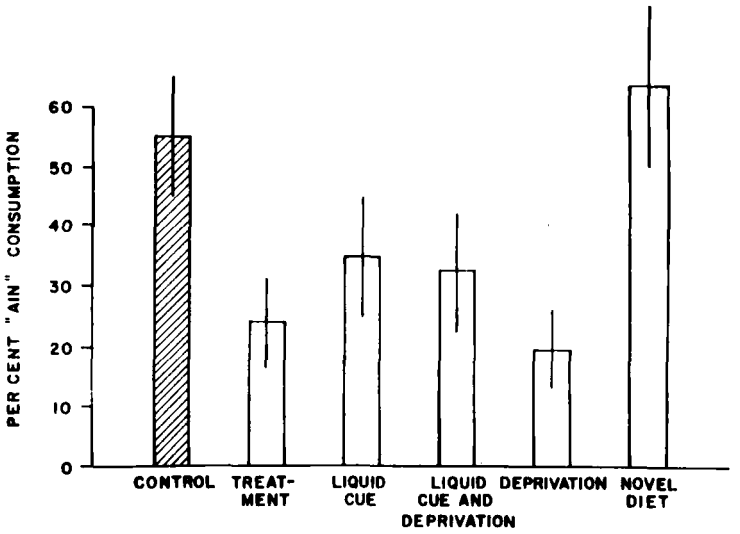

FIGURE 1. Average preference (± SE) for AIN meal in the 24-hour two-food choice test [AIN meal vs. chocolate chow (a novel diet)]. (Reprinted with permission from Bernstein *et al.*[13] Copyright 1980 by the American Psychological Association.)

aversions. The lack of interference by flavored solutions was not due to a failure of these solutions to become conditioned aversive stimuli since strong aversions were acquired to the liquid flavor cues as well as to the target diet. These results suggest that exposure to a novel food interference stimulus might be effective in preventing or reducing learned food aversions to standard diet items in cancer patients receiving chemotherapy. These findings also suggest that asymmetries exist between the potency of foods and drinks as targets in aversion conditioning.[14]

While documenting chemotherapy-induced food aversions in the clinic (using questionnaires described in the next section) as well as food aversions that spontaneously arose in healthy University of Washington undergraduates, we were intrigued to note that a substantial proportion of aversions appeared to be directed at foods that were protein sources (e.g. fish, eggs, meat). Aversions to carbohydrate sources appeared far less frequently. This observation, although interesting and potentially important, is difficult to evaluate critically using survey methods. To date the experimental literature on taste aversions does not provide much information on this topic. Although numerous animal studies have looked at the novelty and intensity of the CS as determinants of conditioning strength, the issue of the salience of specific macronutrients has been largely neglected.

Determining whether protein sources are more likely targets for conditioned aversions than are other macronutrients is of practical as well as theoretical interest. Although examination of this question is complicated by difficulties in equating certain features of these nutrients, such as their flavor intensity and postingestive consequences, it is possible that these features contribute to the salience of proteins as targets in aversion conditioning. We addressed this question by allowing rats to self-select from separate protein and carbohydrate macronutrient sources during a sequence of cyclophosphamide injections. We found that significant aversions developed to the protein but not the carbohydrate source in three studies that varied the composition of both protein and carbohydrate diets. These results suggest that animals on a dietary self-

selection regimen are more likely to develop conditioned aversions to the protein source than the carbohydrate source. A final study in this series examined the generality of the above findings by determining whether aversions would selectively arise to protein but not carbohydrate when nutrients were conditioned in a single trial, using a meal feeding paradigm. Proteins again proved to be more salient targets for aversions than carbohydrates. These findings suggest that the tendency to associate proteins with drug-induced illness more readily than carbohydrates is not limited to a self-selection regimen.[15] Although the specific properties of proteins that contribute to their associability in a taste aversion paradigm have yet to be identified, two possibilities are differences in postingestive and/or taste properties of proteins and carbohydrates.

These findings could lead one to speculate that the propensity to avoid proteins rather than carbohydrates has some adaptive value, particularly if potential sources of toxicosis in the natural diet of rat or human are more likely to be proteins. Our results also imply that the nutritional consequences of learned food aversions, particularly those arising in cancer patients, may involve dietary quality rather than total energy intake.

Learned Aversions to Familiar Foods

We now ask whether aversions affect patients' preference for familiar foods in their routine diets, and not just novel target foods.[16] This study used diet inventories or questionnaires to assess changes in food preferences and food choices as a result of GI toxic chemotherapy. Pediatric patients completed diet inventories during an initial treatment session and again at a subsequent evaluation session that occurred at least a week later. These forms were completed at the same time that some subjects were participating in the previously described "ice cream" study. Children (with the help of their parents) listed their favorite foods, foods they were reluctant to eat, and typical breakfast, lunch, and dinner menus. During the initial session, they also indicated specific food items they had consumed in the four to five hour period before coming to the clinic. Patients receiving GI toxic chemotherapy composed the Experimental Group and the specific foods they had eaten before their drug therapy were considered the targets for the formation of aversions. To assess aversions the two questionnaires from each patient were compared and scored by a rater blind to the group membership of subjects; an aversion was scored when a specific food eaten before therapy was no longer preferred, became actively disliked, or was no longer listed in usual menus. We determined the number of patients whose inventories showed at least one such aversion. Patients receiving vincristine or no drug provided a Control Group that allowed us to compare inventory changes in the Experimental Group to a comparable patient population not currently receiving GI toxic therapy. Control Group changes from Session 1 to Session 2 provided an estimate of the rate such changes occur due to chance, forgetting, or some other factor.

A multiple regression analysis showed that the number of food items consumed before therapy made the greatest contribution to the variance in incidence of aversions. However, when we controlled for the number of "pretherapy items" in the analysis, and classified patients in the Experimental Group with regard to whether they had consumed Mapletoff ice cream before treatment (Group 1) or not (Group 2), an interesting finding emerged. We found that GI toxic drug treatment was significantly associated with the incidence of aversions in Group 2, where nausea symptoms were experienced without ice cream exposure (TABLE 1). In contrast, the incidence of aversions in Group 1 was intermediate between controls (Group 3) and Group 2 and did not differ significantly from either. Thus Group 1 patients exposed to a novel taste

TABLE 1. Aversions to Food in the Diet

	Number of Patients Showing Aversions
Group 1	
GI toxic drugs/ice cream	14/25 (56%)
Group 2	
GI toxic drugs/no ice cream	16/23 (70%)
Group 3	
Controls	11/31 (36%)

Difference between two proportions: Groups 1 and 2 (combined) versus Group 3 = $p < 0.02$. (After Bernstein *et al.*[16])

(Mapletoff ice cream) before treatments did not show a significantly higher incidence of aversions than controls. Since patients scheduled for GI toxic therapy were randomly assigned to Groups 1 and 2 the observation that drug treatment was significantly associated with the formation of diet aversions only in the group not exposed to ice cream suggests that the ice cream may have blocked the development of aversions to foods in the diet. It should be noted that this study was not designed to examine interference effects; but was rather a serendipitous outcome of looking at diet aversions in the same patients that had been in the "ice cream study." The findings are suggestive of an interference effect that clearly needs to be examined further. However, these observations are consistent with some of the results of our animal studies; namely that a novel food presented in association with toxic drug treatment can interfere with aversions to a target food. Perhaps deliberate exposure in the clinic to novel, "scapegoat" tastes prior to chemotherapy treatments would protect normal diet items from becoming the targets for learned food aversions.

The prevalence of aversions to familiar diet items in our pediatric population is somewhat surprising in view of the emphasis placed on stimulus novelty in the taste aversion literature. Possible explanations of our findings include the following: (1)

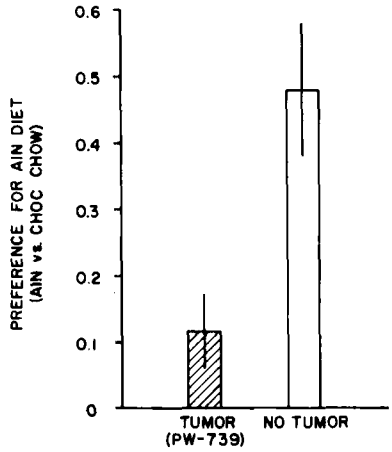

FIGURE 2. Average preference (± SE) for AIN meal in the 24-hour two-food choice test [AIN meal versus chocolate chow (a novel diet)]. Average total consumption: tumor, 18.3 g; control, 17.4 g. (Reprinted with permission from Bernstein & Sigmundi.[7] Copyright 1980 by the AAAS.)

Foods appear to be far more potent stimuli for taste aversion conditioning than are flavored solutions, and conclusions based largely on studies using flavored solutions may not apply. (2) Repeated trials increase the likelihood of aversions to familiar foods.[17] If children tend to consume particular foods repeatedly for breakfast or lunch, when they receive multiple chemotherapy treatments, then one or more of those foods may receive multiple conditioning trials. (3) Familiar foods may taste "novel" to cancer patients since cancer and cancer therapy can induce changes in taste bud function.[18,19]

TUMOR-INDUCED LEARNED FOOD AVERSIONS

In the course of developing an animal model for drug-induced food aversions we began to ask questions regarding the causes of tumor anorexia, i.e., the decline in food intake that frequently accompanies tumor growth. We speculated that aversions could arise in response to the association of a diet with the aversive physiological effects of the tumor itself. Thus, tumor-induced appetite loss could result, at least in part, from the development of learned aversions, with the US being some chronic symptom of tumor growth rather than the acute effects of a drug injection.[7]

To investigate this hypothesis, we implanted transplantable, polyoma virus-induced sarcomas (PW-739) subcutaneously in the flanks of syngeneic Wistar-Furth rats. Control animals received an incision and suture but no tumors. The growth of this tumor is associated with significant depressions in food intake and body weight that typically begin approximately five to six weeks after the tumor is implanted. To determine whether learned aversions would also develop, tumor-bearing and control animals were exposed to a distinctive target diet (AIN meal) for ten days. At the end of the diet exposure period the food intake of tumor-bearing animals had declined significantly below that of controls. Aversions were assessed as previously described.

Mean AIN preference scores are depicted in FIGURE 2. Tumor-bearing animals exhibited conspicuously lower preferences than controls for the AIN diet, the diet that had been available during recent tumor growth. Furthermore, when an alternate diet was available during the preference test, we saw striking elevations of 24-hr food intake in tumor-bearing animals but not in controls. These findings indicate that tumor-bearing animals had developed a pronounced aversion to the AIN target diet by the day of the preference test.

In additional studies, aversions were shown to be specific to the particular diet available during tumor growth, thus excluding the possibility that our original findings were a nonspecific effect of tumor growth on taste preference. We have concluded that tumor-induced aversions are based on learning, that is, the association of a specific food with some symptom(s) of tumor growth. We are currently seeking answers to three questions: (1) What is the overall contribution of learned food aversions to tumor anorexia? (2) How general are tumor-induced aversions? and (3) What are the physiological mechanisms responsible for the development of tumor-induced aversions?

ASSESSING THE CONTRIBUTION OF LEARNED FOOD AVERSIONS TO ANOREXIA

Continuous LiCl Infusions: Conditioned Effects on Food Intake and Preference

Since there is clear evidence that learned food aversions arise in tumor-bearing

animals, an important question is whether the preference shifts that characterize "learned aversions" can actually lead to hypophagia and weight loss. In this regard it is necessary to distinguish between depressions in food intake that are the direct result of tumor-induced physiological changes and those that are secondary to the development of learned aversions. We began these investigations by modeling the effects of a tumor in undiseased animals.[20] We used osmotic minipumps (Alza, Palo Alto, CA), which are small, implantable capsules, to infuse a concentrated solution of lithium chloride (LiCl) over a seven day period. This provided a controlled chemical simulation of the presumed chronic US exposure experienced by tumor-bearing animals. To separate learned from direct effects, we compared the response to LiCl infusions of animals consuming their familiar maintenance diet to those consuming a novel diet. As noted earlier, familiar tastes are relatively resistant to the development of learned food aversions whereas novel tastes rapidly become the target of such aversions.[11] Thus, even though drug infusions were the same in both groups, the likelihood of forming strong aversions was quite different, because the group with a novel diet had a more salient target. Differences in food intake would be a reflection of greater learned aversions in the novel food group.

Rats were assigned either to Novel diet groups (which were given *ad lib* access to C-21, a novel diet in place of their usual diet) or to Familiar diet groups (which received their usual brand of commercial laboratory chow). The next day, an osmotic minipump was implanted in the peritoneal cavity of each subject. We gave half the animals in each diet condition (Drug-Novel and Drug-Familiar groups) minipumps containing a saturated aqueous solution of LiCl. The pumps deliver a relatively constant i.p. infusion of solution (one μl per hour) for approximately seven days. Control animals (Control-Novel and Control-Familiar groups) received nonfunctional pumps. Animals had free access to their assigned diet for six days of LiCl infusion. Food intake was measured daily. On Day 7 we tested for the presence of aversions in a 24-hour two-food preference test. The two foods provided in the test were the target diet, (either ground laboratory chow for familiar diet groups or C-21 for novel diet groups) and AIN meal (a diet novel to both groups).

Food intake over the drug infusion period can be seen in FIGURE 3. Striking differences between Novel and Familiar drug-treated animals are evident, with chronic drug infusions lowering food intake substantially in animals consuming a novel food while those consuming familiar laboratory chow are only slightly different from controls. Furthermore, significant food aversions developed in animals with a novel diet-drug association but not in animals with a familiar diet-drug association.

Two factors were likely to contribute to the decline of food intake associated with minipump infusions. One factor, the direct or unconditioned effect of drug-induced malaise on appetite, presumably afflicts novel and familiar groups equally. On the other hand, the conditioned effect would be based on a diet-illness association. As expected, the novel diet proved much more susceptible to conditioned effects. Since diet aversions arose in the novel but not the familiar diet group the considerable difference in appetite suppression between animals on familiar and novel diets may largely be attributed to the contribution of learned food aversions.

A second study confirmed that it was novelty of the C-21 diet and not some intrinsic difference between the C-21 and the laboratory chow that was responsible for differences in intake suppression. In this study, novel and familiar groups consumed the same diet (C-21) during the infusion period but differed in their prior experience with it. Significant anorexia appeared in animals unfamiliar with the diet but not in those familiar with it, which supports the hypothesis that differential intakes were not due to nutritional or taste properties of the diets but to novelty and differential aversion conditioning.

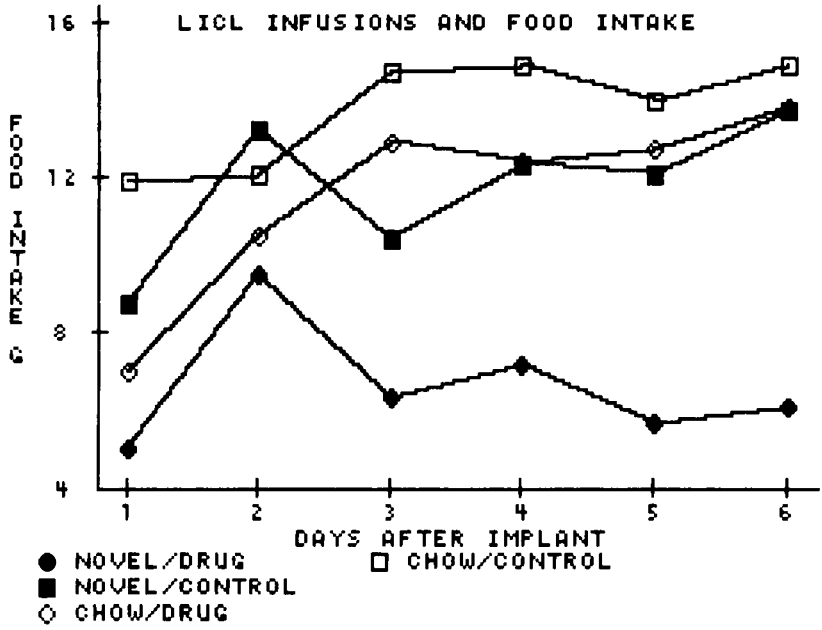

FIGURE 3. Mean daily food intake during LiCl infusions (drug) or no infusions (control). Groups were consuming either C-21 diet (novel) or familiar Wayne lab chow (chow).

Diet Novelty and Tumor Anorexia

The striking effects of diet novelty on food intake in the previous study led us to examine whether parallel effects would be found in tumor-bearing animals. Similar findings would provide strong evidence that learned aversions play a major role in tumor anorexia. Specifically, the hypothesis that tumors suppress appetite directly would not predict a differential effect of diet novelty on severity of appetite depression; whereas the hypothesis that learned aversions contribute substantially to tumor-induced anorexia would predict that animals eating a familiar diet would display less intake depression than those eating a novel diet. When we compared the food intake and preferences of tumor-bearing rats consuming a novel diet to those of rats consuming a familiar diet, we found that animals that consumed familiar laboratory chow did not develop aversions to it and had relatively mild transient anorexia. In contrast, tumor-bearing animals consuming a novel diet (C-21) developed strong aversions to that diet and displayed severe anorexia.[21] These results are consistent with the hypothesis that differential food aversion conditioning led to the striking differences in severity of anorexia seen in tumor-bearing animals consuming familiar and novel diets.

Another prediction from our hypothesis that learned food aversions can make a substantial contribution to anorexia is that frequent changes in diet should attenuate anorexia either by preventing the formation of learned aversions or by repeatedly replacing aversive foods with new ones. In a test of this prediction we fed one group of tumor-bearing animals a variety of diets while maintaining a second group on a single diet. Two control groups were exposed to the comparable diet exposure. Three of the diets were commercially available dog or cat foods; the remaining three were semisynthetic rodent diets. Animals assigned to the Varied Diet groups participated

in initial preference testing, during which each diet was paired with every other diet for a 24 hr period. Preference ratios for these diets over the numerous preference tests were averaged and ranked providing an estimate of relative preference for these diets. In ascending order of palatability the six diets were Safeway Puppy Chow; Friskies Cat Food; Blue Mountain Dog Food; Soy meal diet; AIN meal; and C-21. The diet that was preferred relative to all others (C-21) was used as the single diet offered to the animals in the Same Diet groups. Animals in the Varied Diet group received each diet for three days. The diets were presented in ascending order of palatability. At the end of 18 days a preference test was run to evaluate the development of aversions to C-21, which was the single food source of the Same Diet groups and the last food presented to the Varied Diet groups.

Food intake in both tumor-bearing groups declined during the first few days of observation. However, the tumor-bearing animals receiving a different diet every three days showed average food intakes that were often more than twice what was eaten by the tumor-bearing group with access to the same (initially highly preferred) food (FIGURE 4). Although both tumor groups had significantly lower food intakes than their respective control groups, food intake in the Varied/Tumor group was significantly higher than in the C-21/Tumor group.

The results of the preference test indicated that the rats in the Same Diet-Tumor Group had significant aversion to C-21 relative to their controls. In the Varied Diet-Tumor Group preference for C-21 was lower than in the Varied Diet-Control group, but the differences were not significant. Thus, providing a continually varying menu to tumor-bearing animals significantly elevated their food intake over the amount consumed when a single food was present. This supports the notion that the prevention of learned food aversions, or the presentation of non-aversive foods, can attenuate anorexia in tumor-bearing animals.

Contribution of Learned Food Aversions to Anorexia Syndromes

Although the studies presented in this section had the specific focus of assessing the contribution of learned food aversions to tumor anorexia, there is a more general focus to these studies as well. The general issue is that the symptoms of hypophagia and weight loss, which can be produced by any of a number of experimental treatments, may to a lesser or greater extent be the product of specific learned aversions acquired via the association of treatment symptoms with a specific diet. This suggests that some of the anorexia syndromes that result from brain lesions or other surgical modifications may actually be, partly or wholly, based on learned food aversions. For example, renewed interest in the role of the vagus nerve has been generated by reports that subdiaphragmatic vagotomy produces hypophagia and weight loss in normal rats[22,23] and can reverse the hyperphagia and obesity of rats with ventromedial hypothalamic lesions.[24] Vagotomy can also produce symptoms of nausea and discomfort, symptoms that are highly effective USs in food aversion conditioning. We recently asked whether some of the depression in food intake observed in rats with vagotomy could be due to the development of aversions to the foods eaten after surgery.[26] Significant aversions developed to a novel diet consumed after surgery, but not to familiar laboratory chow. Likewise, hypophagia was more long lasting and severe in animals with a novel diet. We concluded that learned food aversions can contribute to the appetite and weight loss exhibited by vagotomized animals and that the magnitude of this contribution depends on procedural details such as diet exposure and recovery time, which are often unspecified. Similarly, intestinal bypass surgery in rats apparently produces strong conditioned taste aversions to a novel solution presented

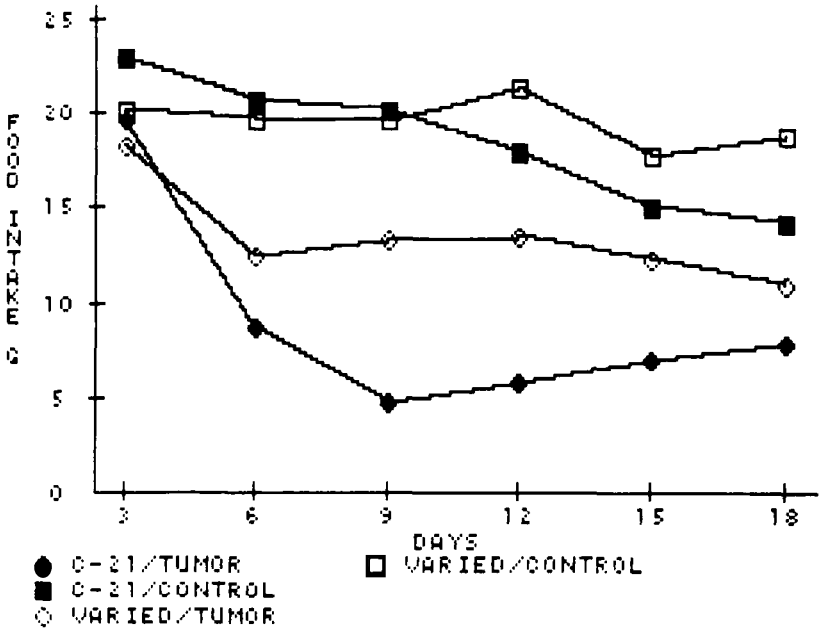

FIGURE 4. Mean daily food intake in three-day blocks for tumor-bearing and control animals. Animals received either C-21 throughout the 18-day period or a succession of diets (Varied) presented for three days each. For the varied group each three-day block represents a different diet. Diets are described in the text.

after surgery.[27] These few studies provide clear evidence supporting the idea that learned food aversions can contribute to anorexia. However, because experimenters typically do not test for learned aversions when their treatments reduce food intake we do not yet have a clear picture of the actual contribution of learned aversions to the total "anorexia" picture.

ASSESSING THE GENERALITY OF TUMOR-INDUCED AVERSIONS

Other experimental tumors besides the PW-739 have been used in recent years to study the physiological bases of tumor-induced anorexia. These include the Walker 256 carcinosarcoma[28,29] and a Leydig cell tumor (LTW(m)).[30] Although growth of all three transplantable tumors is associated with significant declines of food intake and body weight, the mechanisms by which they induce anorexia may be different. The Walker tumor is a rapidly growing tumor that constitutes a substantial proportion (30%) of the animal's body weight at the time significant declines in food intake become apparent.[28,31] The LTW(m) tumor, on the other hand, produces symptoms of appetite loss when the tumor itself weighs less than a gram.[30] The PW-739 tumor is intermediate in its growth rate and effects on food intake and body weight. We were interested in examining the effects of the Walker 256 and LTW(m) tumors on food intake and diet preference and comparing their effects to those of PW-739 tumors.

TABLE 2. Preference Test Scores:[a] Leydig-LTW(m) Tumors

AIN Target	
Tumor	0.13 (± .05)
Control	0.40 (± .08)
C-21 Target	
Tumor	0.14 (± .08)
Control	0.69 (± .07)

[a] Preference test scores = grams of target diet consumed divided by total food consumption during the test.

In studies patterned after our original work,[8] animals were implanted with either LTW(m) or Walker tumors and exposed to target diets. We measured food intake daily and administered a preference test after anorexia was evident. Significant declines in food intake were seen with LTW(m) tumors at 17 days post-implant and with Walker tumor at four weeks post-implant. Results of the preference tests can be seen in TABLES 2 and 3. Animals with LTW(m) tumors, like those with PW-739 tumors, developed strong aversions to the specific diet they had been eating after tumor implant. On the other hand, animals with Walker tumors did not develop diet aversions, displaying instead preferences for the target diet that were indistinguishable from those of healthy controls.

Thus although both tumors produced clear declines in food intake, their effects on target diet preference were different. These results suggest that learned food aversions contribute to anorexia in animals with LTW(m) but not Walker tumors. Such findings emphasize that there are multiple factors contributing to the decline in food intake accompanying tumor growth and that "tumor anorexia" is not a unitary phenomenon with a single cause. It is likely that the clinical picture is at least as heterogeneous.

The presence of learned aversions in animals with certain tumors indicates that physiological consequences of tumor growth can act as USs in aversion conditioning. The finding that the induction of food aversions is not common to all experimental rat tumors indicates that illness and tumor growth per se are not sufficient conditions for the development of aversions. This suggests that tumor-induced aversions are caused by specific physiological changes, not merely by general malaise, and that these changes may prove identifiable.

ASSESSING THE PHYSIOLOGICAL BASIS OF TUMOR-INDUCED AVERSIONS

In considering potential candidates for the physiological USs responsible for tumor-

TABLE 3. Preference Test Scores:[a] Walker 256 Tumor

AIN Target	
Tumor	0.01 (± .01)
Control	0.07 (± .03)
C-21 Target	
Tumor	0.81 (± .03)
Control	0.78 (± .03)

[a] Preference test scores = grams of target diet consumed divided by total food consumption during the test.

induced aversions, two categories of stimuli come to mind. One is substances secreted abnormally or in unusually large amounts by the tumor; it is possible that such substances could have toxic effects that would act as USs in food aversion conditioning. The other possibility is that the tumor-bearing animals' striking similarity to animals on nutrient-deficient diets[32] may be more than coincidental. That is, the tumor may actually produce a state of nutrient deficiency in the host organism by its excessive and preferential utilization of some essential nutrient(s).[33] Both the toxin and nutrient deficiency hypotheses are attractive and, at this point, we cannot favor one over the other. In fact, given the heterogeneity evident in experimental tumors it remains possible that both types of mechanisms are triggering tumor-induced aversions and the one involved may depend on the specific tumor being studied.

One approach to defining the physiological mechanisms responsible for tumor-induced aversions is to identify the neural circuitry mediating the effect. Early efforts to assess the involvement of particular brain regions in tumor anorexia were directed at effects of lesions in the lateral or ventromedial areas of the hypothalamus because of the overwhelming evidence implicating the hypothalamus in the regulation of feeding behavior. These lesions did not prevent or attenuate the appearance of tumor-induced anorexia, and the apparently independent effects of lesions and tumor manipulations on food intake strongly suggested that they are unlikely to involve the same control mechanisms.[34,35] A region of the brain that has received considerable recent attention for its presumed role in taste aversion learning and regulation of food intake is the area postrema (AP).[36-38] Located in the brain stem, the area postrema has also been identified as the chemoreceptor trigger zone for nausea and emesis.[39] Lesioning of the area postrema and the nearby caudal medial nucleus of the solitary tract (AP/cmNTS) is a potentially useful technique for us in our search for the physiological US for tumor-induced food aversions. If the AP is involved in detection of a blood-borne US produced by the tumor, then animals with lesions in this region might be expected to show attenuation or elimination of tumor-induced aversions as well as milder anorexia.[40] However, since AP lesions are themselves associated with substantial reductions in food intake and body weight, effects of a tumor would necessarily be superimposed on the AP syndrome.

In the following experiment thermal lesions were produced in the AP/cmNTS.[41] Half the animals were given AP lesions, the other half were sham operated. Six weeks were allowed for recovery from the acute effects of the lesions. Half the animals with AP lesions and half the sham-operated animals were then implanted with Leydig LTW(m) tumors. Two weeks elapsed after tumor implant before animals were exposed to AIN meal as their sole diet for eight days with intake measured daily. On the ninth day they received a two hour preference test in which they chose between AIN and C-21.

Mean body weights of AP-lesioned animals at the time of tumor implant was approximately 230 g as compared to the weights of unlesioned controls, which were 320 g. The weight differences were statistically significant and reflect the substantial weight loss associated with lesions of the AP. However, sufficient time elapsed between lesioning and tumor implant to allow for stabilization of weights at a new lower level.

Average food intake over the diet exposure period: AP-Tumor = 14.9g; AP-Control = 16.0g; Sham-Tumor = 11.5g; and Sham-Control = 19.9g. It is evident that AP-Control animals eat less than Sham-Control animals, although intake is not different if expressed relative to the animals' body weights. Effects of tumor implant on food intake are dramatically different in lesioned and unlesioned animals. Sham-operated animals develop tumor anorexia as manifested by food intake which declines to levels that are half those seen in controls, a finding consistent with the numerous studies we have already reported. In contrast, AP-lesioned animals show little or no tumor anorexia. A repeated measures analysis of variance yielded a significant main

TABLE 4. Area Postrema Lesions and Tumor-induced Food Aversions

Groups	Preference for AIN[a] (±SE)
AP-tumor	.67 (±.08)
AP-control	.81 (±.09)
Sham-tumor	.02 (±.00)
Sham-control	.92 (±.04)

[a] Preference for AIN = grams of AIN consumed divided by total food consumption during the test.

effect of tumor and a significant interaction. Planned comparisons indicated that food intake of the Sham-Tumor group is significantly lower than the Sham-Control group and the AP-Tumor group. The AP-Tumor group is not significantly different from the AP-Control group. Tumor growth was also associated with considerably less weight loss in AP-lesioned animals than in sham-operated animals. Although AP lesions themselves lead to hypophagia and weight loss, the pattern of results does not suggest that lesion effects obscured the appearance of tumor-induced symptoms. Rather we found that AP-Tumor animals consumed significantly more food and lost significantly less weight than Sham-Tumor animals.

We observed complementary effects of AP lesions on tumor-induced food aversions. As can be seen in TABLE 4 significant severe aversions were evident in Sham-Tumor animals but not in AP-Tumor animals. Thus, the area postrema appears to be involved in the development and/or expression of LTW(m) tumor-induced anorexia, weight loss, and food aversions since its destruction prevents or postpones the appearance of the symptoms that generally follow implant. These findings are important because they suggest that detection by the area postrema of some blood-borne chemical may be involved in the aversions and anorexia produced by the LTW(m) tumor. They also provide another line of evidence for a direct relationship between aversions and anorexia in this tumor model. It remains to be determined whether the role of the area postrema in tumor anorexia is largely due its detection of chemical unconditioned stimuli in aversion conditioning or whether direct effects on the regulation of food intake and body weight are involved. This is an interesting question because of the apparently multiple functions of area postrema in regulation of food intake and body weight as well as food aversion learning.

SUMMARY AND CONCLUSIONS

The studies included in this chapter examine the learned food aversions that develop as a result of cancer and cancer treatment. Clinical studies have shown that cancer patients can develop learned aversions to a novel ice cream flavor when it is consumed before drug treatments that produce nausea and vomiting. They also provided evidence that patients can acquire aversions to food in their usual diets when these foods are eaten before similar drug treatments. Observations in the clinic, supported by complementary studies with animal models, suggest that learned aversions are more likely to arise to protein foods than to other nutrient sources and that the presentation of a novel food in association with drug treatments may act as a "scapegoat" in blocking the development of aversions to foods in the normal diet.

Laboratory studies using transplantable tumors in rats have shown that tumor growth can be associated with the development of strong aversions to the available diet. These

aversions are specific to the diet eaten during tumor growth and they appear to play a causal role in the development of tumor-induced anorexia. The food aversions apparent in animals with certain experimental tumors point to physiological consequences of tumor growth that act as unconditioned stimuli in taste aversion conditioning. The identification of these changes and development of methods for correcting them are the current goals of our research in this area.

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REFERENCES

1. LAZSLO, J. 1983. Nausea and vomiting as major complications of cancer chemotherapy. Drugs **25** (Suppl. 1): 1-6.
2. GARCIA, J., W. G. HANKINS & K. W. RUSINIAK. 1974. Behavioral regulation of the milieu interne in man and rat. Science **185**: 824-831.
3. RILEY, A. L. & C. M. CLARKE. 1977. Conditioned taste aversions: A bibliography. *In* Learning Mechanisms in Food Selection, L. M. Barker, M. R. Best & M. Domjan, Eds. Baylor University Press. Waco, TX.
4. NESSE, R. M., T. CARLI, G. C. CURTIS & P. D. KLEINMAN. 1980. Pretreatment nausea in cancer chemotherapy: A conditioned response? Psychosom. Med. **42**(1): 33-36.
5. MORROW, G. R. & C. MORRELL 1982. Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. N. Engl. J. Med. **307**(24): 1476-1480.
6. REDD, W. H. & G. V. ANDRESEN. Conditioned aversion in cancer patients. Behav. Therapist **4**(2): 3-4.
7. BERNSTEIN, I. L. & R. A. SIGMUNDI. 1980. Tumor anorexia: A learned food aversion? Science **209**: 416-418.
8. BERNSTEIN I. L. & D. P. FENNER. 1983. Learned food aversions: Heterogeneity of animal models of tumor-induced anorexia. Appetite **4**: 79-86.
9. GARB, J. L. & A. J. STUNKARD. 1974. Taste aversions in man. Am. J. Psychiatry **131**: 1204-1207.
10. BERNSTEIN, I. L. 1978. Learned taste aversions in children receiving chemotherapy. Science **200**: 1302-1303.
11. REVUSKY, S. H. & E. W. BEDARF. 1967. Association of illness with prior ingestion of novel foods. Science **155**: 219-220.
12. BERNSTEIN, I. L. & M. M. WEBSTER. 1980. Learned taste aversions in humans. Physiol. Behav. **25**: 363-366.
13. BERNSTEIN, I. L., M. V. VITIELLO & R. A. SIGMUNDI. 1980. Effects of interference stimuli on the acquisition of learned aversions to food in the rat. J. Comp. Physiol. Psychol. **94**: 921-931.
14. BERNSTEIN, I. L., L. E. GOEHLER & M. E. BOUTON. 1983. Relative potency of foods and drinks as targets in aversion conditioning. Behav. Neural Biol. **37**: 134-148.
15. BERNSTEIN, I. L., L. E. GOEHLER & D. P. FENNER. 1984. Learned aversions to proteins in rats on a dietary self-selection regimen. Behav. Neurosci. **6**: 1065-1072.
16. BERNSTEIN, I. L., M. M. WEBSTER & I. D. BERNSTEIN. 1982. Food aversions in children receiving chemotherapy for cancer. Cancer **50**: 2961-2963.
17. ELKINS, R. L. 1974. Conditioned flavor aversions to familiar tap water in rats: An adjustment with implications for aversion therapy treatment of alcoholism and obesity. J. Abn. Psychol. **83**(4): 411-417.
18. CONGER, A. D. 1973. Loss and recovery of taste acuity in patients irradiated to the oral cavity. Rad. Res **53**: 338-347.

19. DEWYS, W. D. 1974. Abnormalities of taste as a remote effect of a neoplasm. Ann. N.Y. Acad. Sci. **230**: 426–434.
20. BERNSTEIN, I. L. & L. E. GOEHLER. 1983. Chronic lithium chloride infusions: Conditioned suppression of food intake and preference. Behav. Neurosci. **97**: 290–298.
21. BERNSTEIN, I. L., C. M. TRENEER, L. E. GOEHLER & E. MUROWCHICK. 1985. Tumor growth in rats: conditioned suppression of food intake and preference. Behav. Neurosci. (In press.)
22. NOVIN, D. 1976. Visceral mechanisms in the control of food intake. *In* Hunger: Basic Mechanisms and Clinical Implications. D. Novin, W. Wyrwicka & G. Bray, Eds. Raven Press. New York.
23. OPSAHL, C. A. & T. L. POWLEY. 1977. Body weight and gastric acid secretion in rats with subdiaphragmatic vagotomy and lateral hypothalamic lesions. J. Comp. Physiol. Psychol. **226**: 25–33.
24. POWLEY, T. L. & C. A. OPSAHL. 1974. Ventromedial hypothalamic obesity abolished by subdiaphragmatic vagotomy. Am. J. Physiol. **226**: 25–33.
25. KENNEDY T. 1974. The vagus and the consequences of vagotomy. Med. Clinics N. Am. **58**: 1231–1246.
26. BERNSTEIN, I. L. & L. E. GOEHLER. 1983. Vagotomy produces learned food aversions in the rat. Behav. Neurosci. **97**: 585–594.
27. SCLAFANI, A. & H. S. KOOPMANS. 1981. Intestinal bypass surgery produces conditioned taste aversion in rats. Int. J. Obesity **5**: 497–500.
28. MORRISON, S. D. 1973. Control of food intake during growth of a Walker 256 carcinosarcoma. Cancer Res. **33**: 526–528.
29. KRAUSE, R., J. H. JAMES, V. ZIPARO & J. E. FISCHER. 1979. Brain tryptophan and the neoplastic anorexia-cachexia syndrome. Cancer **44**: 1003–1008.
30. MORDES, J. P. & A. A. ROSSINI. 1981. Tumor-induced anorexia in the Wistar rat. Science **213**: 565–567.
31. MORRISON, S. D. 1976. Control of food intake in cancer cachexia: A challenge and a tool. Physiol. Behav. **17**: 705–714.
32. ROZIN, P. & J. W. KALAT. 1971. Specific hungers and poison avoidance as adaptive specializations of learning. Psychol. Rev. **78**: 459–486.
33. LAWSON, D. H., A. RICHMOND & D. RUDMAN. 1982. Metabolic approaches to cancer cachexia. Annu Rev. Nutr. **2**: 277–301.
34. BAILLIE, P., F. K. MILLAR & A. W. PRATT. 1965. Food and water intakes and Walker tumor growth in rats with hypothalamic lesions. Am. J. Physiol. **209**: 293–300.
35. LIEBELT, R. A., A. G. LIEBELT & H. M. JOHNSTON. 1971. Lipid mobilization and food intake in experimentally obese mice bearing transplanted tumors. Proc. Soc. Exp. Biol. **138**: 482–490.
36. BERGER, B. D., C. D. WISE & J. STEIN. 1973. Area postrema damage and bait shyness. J. Comp. Physiol. Psychol. **82**: 475–479.
37. COIL, J. D. & R. NORGREN. 1981. Taste aversions conditioned with intravenous copper sulfate: Attenuation by ablation of the area postrema. Brain Res. **212**: 425–433.
38. HYDE, T. M. & R. R. MISELIS. 1983. Effects of area postrema/caudal medial nucleus of solitary tract lesions on food intake and body weight. Am. J. Physiol. **244**: R577–R587.
39. BORISON, H. L. & S. C. WANG. 1953. Physiology and pharmacology of vomiting. Pharmacol. Rev. **5**: 193–230.
40. BERNSTEIN, I. L., C. M. TRENEER & J. N. KOTT. 1985. Area postrema mediates tumor effects on body weight, food intake and learned aversions. (Submitted for publication.)
41. MCGLONE, J. J., S. RITTER & K. W. KELLEY. 1980. The antiaggressive effect of lithium is abolished by area postrema lesion. Physiol. Behav. **24**: 1095–1100.