Development of Altered Taste Preferences in Tumor-bearing Rats

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Experimental tumors induce a decline in food intake that may derive from changes in taste or the development of taste aversions. The preferences of tumor-bearing (TB) and non-tumor-bearing (NTB) rats for five chemicals (three palatable and two aversive taste stimuli) were studied in an animal model of experimental cancer employing the methylcholanthrene (MCA) sarcoma. In protocol 1, five groups of Fischer 344 rats were given 23-h, two-bottle preference tests (taste solution vs. water) daily from day 3 after tumor implantation until spontaneous death occurred. Both NTB and TB rats avoided quinine hydrochloride and hydrochloric acid solutions throughout the experiment indicating that tumor growth produced no disruption in the animals' perception of these normally aversive tastes. In both groups, preference for sucrose (88% to 97%) and saccharin (75% to 93%) remained high until days 22 and 17 respectively, but tended to decline with advanced tumor growth. In both cases, a reduction in total calorie intake preceded the changes in sucrose or saccharin preference by several days. With or without a tumor, rats exhibited approximately 50% preference for NaCl at all times. In protocol 2, a four-bottle preference test (sucrose vs. saccharin vs. NaCl vs. water) was administered before tumor implantation and again 3 weeks later when a decline in food intake was evident. Both TB and NTB rats displayed a dominant preference for sucrose over saccharin, NaCl, and water at the pre- and posttests. However, a comparison of the difference scores (pre- minus postimplantation) of NTB and TB rats showed a small but significant suppression of TB animals' preference for sucrose. The altered preferences for sweet but not salt taste stimuli suggest that food-related taste cues may be more susceptible to the development of taste aversions during cancer. However the contribution of taste changes to the anorexia of cancer remains unclear and it is possible that the changes in taste preference may be secondary to the reduction in food intake.

INTRODUCTION

Anorexia is a feature of cancer that is seen typically in conjunction with the wasting syndrome of cachexia (Morrison, 1976; Theologides, 1988). Both poor food intake and metabolic abnormalities contribute to the tissue depletion and loss of

weight associated with malignant tumor growth and may develop in as many as 70% of patients with certain types of cancer (Kern & Norton, 1988).

Cancer anorexia could derive from taste changes (DeWys, 1974; DeWys & Walters, 1975; Trant *et al.*, 1982). Changes in taste perception are a frequent symptom in patients with cancer and are often problematic when attempting to maintain adequate nutrient intake (Strohl, 1983). Commonly reported symptoms in both treated and untreated patients include abnormal taste thresholds and preferences, and a general loss of taste for food (Settle *et al.*, 1979). It is apparent that taste alterations often may be the result of cancer therapy (Bécouarn *et al.*, 1991; Huldij *et al.*, 1986; Mulder *et al.*, 1983). However, it has been proposed that tumors alone can alter taste responsiveness in man and laboratory animals (Bernstein, 1986; Bernstein & Bernstein, 1981; DeWys, 1974).

Although changes in taste acuity and preferences in patients with a variety of tumors have been widely documented, they remain ill-defined. Many studies of taste in cancer patients have reported taste threshold abnormalities for one or more of the four classically defined taste qualities: sweet, sour, salty and bitter (Carson & Gormican, 1977; DeWys & Walters, 1975; Williams & Cohen, 1978; Hall *et al.*, 1980; Henkin *et al.*, 1983; Settle *et al.*, 1979; Wall & Gabriel, 1983). Results from these studies have been summarized previously (Theologides, 1988) and generally indicate that persons with cancer have higher recognition thresholds for salt and sweet, and increased or decreased thresholds for sour and bitter tastes. Yet others have reported no differences in taste recognition thresholds (Kamath *et al.*, 1983; Ovesen *et al.*, 1991) or taste hedonics (Trant *et al.*, 1982). The disparate results from studies of taste in cancer patients make it difficult to draw conclusions and have been attributed to differences in methods or to subject characteristics (e.g. age, sex, tumor sites, tumor stage, type of therapy) (Theologides, 1988).

It may be worth noting that there is no clear evidence that age should play a role in taste responsiveness during cancer. Only one study of taste thresholds in children with cancer has been documented (Wall & Gabriel, 1983). Leukemic children were found to have significantly higher detection thresholds for sweet and sour than healthy children, and to have significantly higher recognition thresholds for all four taste qualities. However, all the children were receiving combination chemotherapy with a variety of agents thereby making it impossible to employ statistical control for drug effects.

More consistent results may be obtained from studies where the influence of factors such as tumor type and treatment can be eliminated. For example, Kamath *et al.* (1983) compared the taste acuity of 12 patients with untreated esophageal cancer to that of 14 control subjects matched for age (58–59 ± 8–10 years), smoking and alcohol consumption and found no differences in taste thresholds between the groups. However, a comparison to a young (28 ± 8 years), healthy, non-smoking/alcohol control group revealed that the cancer patients had significantly higher detection (sour and bitter) and recognition (sour, salt, sweet) thresholds indicating the importance of factors other than cancer on taste (Kamath *et al.*, 1983). In another study, no significant differences in recognition thresholds were found when the taste acuity of 27 patients with small-cell lung cancer was compared to that of 22 weight-matched control patients before the start of chemotherapy (Ovesen *et al.*, 1991). Interestingly, the threshold for bitter taste was significantly lower in weight-losing patients compared to weight-stable patients in both the cancer and control groups, suggesting that weight loss *per se* may be a factor in taste sensitivity.

Thus, the phenomena of taste abnormalities secondary to tumors has not yet been established. Taste disturbances could result from some primary effect of the tumor or host-derived product on taste or on feeding centers in the central nervous system. Alternatively, taste disturbances could result from the general metabolic disturbances that alter chemicals in the saliva and/or the plasma and thus affect taste by changing the microenvironment in which taste transduction occurs (Bradley, 1973). In addition, learned taste aversions may develop during cancer. In experimental animals, learned aversions occur in response to the association of a diet with an unconditioned stimulus (US) such as an aversive physiological effect of the tumor (Bernstein & Sigmundi, 1980; Bernstein & Fenner, 1983). Although several possible mechanisms have been proposed, a primary effect of tumors on taste remains to be determined.

Several experimental tumors have been used as models to study tumor-induced anorexia, including the Walker 256 carcinosarcoma (Morrison, 1973), the PW-739 sarcoma (Bernstein & Sigmundi, 1980) and a Leydig cell tumor (Mordes *et al.*, 1984; Mordes & Rossini, 1981). In the present study, we used a methylcholanthrene-induced (MCA) rat sarcoma (Popp *et al.*, 1981; Stovroff *et al.*, 1989) to examine the effects over time of tumor growth on behavioral taste preferences, and in a separate protocol, to compare taste preferences before tumor implant with preferences after a decline in food intake had become evident.

METHODS

Animals

Male, Fischer 344 rats (F344) (specific-pathogen-free, Charles River, Kingston, NY, U.S.A.) weighing 100–120 g were obtained. Animals were housed singly in stainless steel cages ($12 \times 12 \times 6\cdot5$ inches) that accommodated the placement of four water bottles, and were kept in a temperature controlled room ($25 \pm 1\cdot0°C$) where a 12 h light/dark cycle was maintained with lights on at 0600 hrs. Food (Purina 5001) and distilled water were provided *ad libitum* from the day animals arrived in the laboratory. The rodent chow has a gross energy value of $4\cdot0$ kcal/g (Purina Mills, St. Louis, MO, U.S.A.).

Tumor Model

A cryopreserved specimen of the methylcholanthrene sarcoma (MCA) was obtained from Dr Jeffrey Norton at the National Cancer Institute (Bethesda, MD, U.S.A.) and has been maintained by serial subcutaneous passage *in vivo*. The tumor inoculum consisted of a 2–3 mm^3 viable tissue fragment placed subdermally through a small incision on the flank while animals were under light methoxyflurane (Metofane, Pittman-Moore, Mundelein, IL, U.S.A.) anesthesia. Control animals received anesthesia and a sham incision. The MCA sarcoma has been well characterized (Popp *et al.*, 1981; Smith *et al.*, 1993; Stovroff *et al.*, 1989). The tumor grows locally without evidence of metastases, becomes palpable between 5 and 10 days after implantation and induces fatality 35 to 45 days after implantation. We have shown previously that this tumor induces significant anorexia, weight loss and a decline in motor activity when the tumor burden reaches approximately 10–15% of total body weight

(Smith *et al.*, 1993). A significant lowering of body temperature develops 21 days after implant, followed by a 2–3-fold increase in water consumption beginning on days 30 to 35.

Taste Stimuli

Taste solutions were prepared fresh every other day from reagent-grade chemicals dissolved in distilled water. Five chemical stimuli were employed: sucrose (SUCR) (0·20 M), sodium saccharide (SACC) (0·004 M), sodium chloride (NaCl) (0·10 M), quinine hydrochloride (QHCl) (0·0003 M), and hydrochloric acid (HCl) (0·005 M) (Sigma, St. Louis, MO, U.S.A.). All solutions were presented to the animals at room temperature in 250-ml glass bottles equipped with stoppers and stainless steel spouts. The water bottles were weighed on an electronic scale (Sartorius Instruments, Bohemia, NY, U.S.A.) and weights recorded to the nearest 0·1 g. The positions of the bottles on the cage were rotated daily. The concentrations of chemical chosen were those that have been shown to be near the peak of the behavioral preference (SUCR, SACC, NaCl) or aversion (QHCl, HCl) function in other studies (Lasiter *et al.*, 1985; Pfaffmann, 1952; Pfaffmann *et al.*, 1977). Sucrose, a disaccharide, has an estimated caloric value of 4 kcal/g (Sigma).

Protocol 1: Longitudinal Preference Tests in Tumor-bearing Rats
(One Taste Stimulus vs. Water)

In this protocol we examined the effect of progressive tumor growth on preference for a single chemical stimulus over water. Rats were randomly assigned to receive one of five taste stimuli: SUCR, SACC, NaCl, QHCl or HCl. One bottle containing the taste stimulus and one bottle of distilled water were available to each animal in its home cage for 23 h each day, allowing approximately 1 h (0930–1030 hrs) to measure and replace the solutions. Preference for each taste stimuli was expressed as: (grams of taste solution consumed/grams of total fluid intake) × 100 = per cent preference. Taste stimuli were not made available to animals until 3 days postimplant to avoid pairing the taste solution with the effects of the surgical procedure, thus minimizing the likelihood of producing a conditioned aversion. Food and water intake were measured daily.

Protocol 2: Pre- Versus Posttumor Implantation Preference Tests
(Three Taste Stimuli vs. Water)

To avoid the possible development of learned aversions to the taste solutions, a comparison of preference tests pre- versus posttumor implantation was conducted using a four-bottle choice paradigm. Three palatable taste solutions (SUCR, SACC and NaCl) were offered, along with one bottle of distilled water, to sixteen healthy rats for three successive days before tumor or sham implant. At the conclusion of the pretest, four bottles of distilled water were made continuously available to the animals until the tumor-bearing rats displayed an anorexia to food as defined by a 50% reduction in daily food intake (24 or 25 days after tumor or sham implant). Then the preference test was repeated for three successive days. Preference for a given taste solution in one 24-h period was expressed as (grams taste solution consumed/grams total fluid intake) × 100 = per cent preference.

Statistical Analysis

In protocol 1, repeated measures ANOVA was used to examine changes in preference between groups (TB vs. NTB) over time. p values less than 0·05 were considered statistically significant. Pre- and postimplantation preference scores in protocol 2 represent the mean of three days. A multivariate analysis of variance on the vector of the differences (post minus pre) for the three taste solution components: sucrose, saccharin and sodium chloride, was performed. *Post-hoc* comparisons of the difference scores (post minus pre) between TB and NTB animals were made for each taste solution using Student's *t*-test.

Results

Protocol 1: Effect of Tumor Growth on Continuous Preference Tests (One Taste Stimulus)

The effect of tumor growth on preference for SUCR, SACC or NaCl was monitored daily from 3 days before tumor implantation until spontaneous death occurred and is shown in Fig. 1. In a two-bottle preference test, both TB and NTB rats drank more SUCR than water (88% to 97% preference) until day 22 after tumor implantation [Figure 1(A)]. Then, TB rats showed a tendency toward a decreased preference for SUCR compared to NTB rats (days 22 to 28, $p = 0·09$, RM ANOVA). In a separate experiment, both TB and NTB rats also drank more SACC than water (75% to 93% preference) until day 17 when SACC intake of TB animals tended to decline (days 17 to 23, $p = 0·10$, RM ANOVA) [Figure 1(B)]. In response to NaCl, TB and NTB rats did not differ in their preference scores at any time throughout the experimental period, and ingested approximately 50% of their daily total fluid intake as NaCl [Figure 1(C)].

Both NTB and TB rats avoided the aversive taste solutions (QHCl and HCl) throughout the course of the first experiment (data not shown). TB rats' average daily preference for QHCl over the entire experimental period ranged 11% to 23%, and 13% to 35% for HCl, indicating that tumor growth produced no disruption in the animals' perception of these normally aversive tastes.

Figure 2 shows the time course for total kilocalorie intake per day of TB rats in the two-bottle SUCR preference test compared to NTB (SUCR or water) and TB (pellet food only) controls. Data for the pellet-food-only group (see dotted line in Fig. 2) were obtained from weight-matched TB animals in an earlier series of experiments. Both TB and NTB groups in the two-bottle preference test ingested an average of 80 kcal per day for the first 10 days after implantation, approximately 25% to 50% more energy per day than that of healthy rats fed pellet food only. Compared to NTB controls, the energy intake of TB rats decreased markedly beyond 14 days after tumor implantation, falling to an average of 20 kcal daily for the last 10 days before spontaneous death occurred. TB rats with access to a non-caloric taste stimulus only (i.e. SACC vs. water) (data not shown), consumed an average of 65 ± 5 kcal per day before tumor implantation and 30 ± 6 kcal by 25 days postimplantation.

Rats that were allowed access to palatable taste solutions consumed much greater amounts of fluid per day than do rats with only distilled water available. For example, in healthy, growing male rats, the average daily water intake is $11·8 \pm 0·2$ ml/
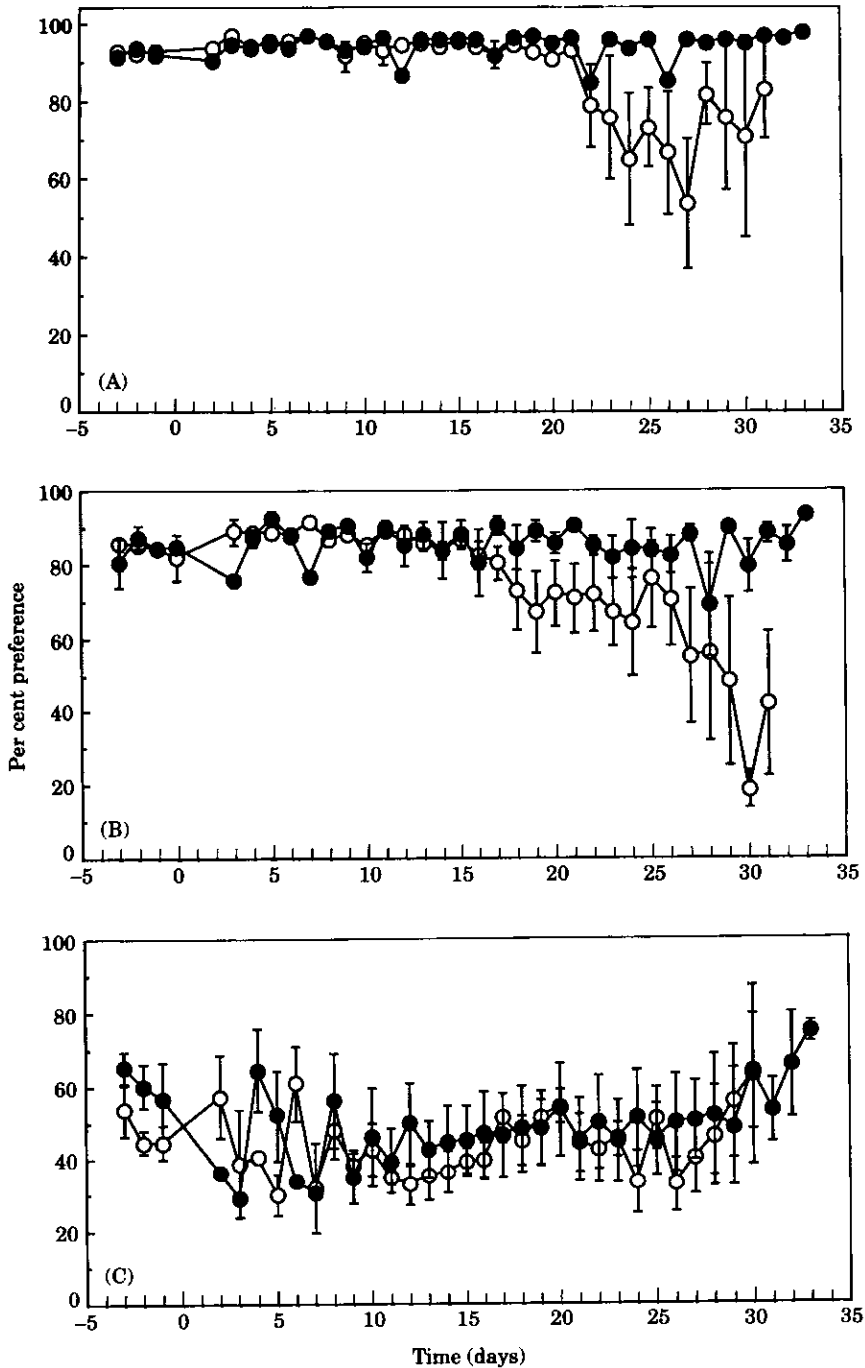
FIGURE 1.   Per cent preference of tumor-bearing (○, $n=6$) and non-tumor-bearing (●, $n=5$) rats for (A) sucrose, (B) saccharin and (C) sodium chloride in two-bottle, longitudinal preference tests. Time 0 = day of tumor or sham implantation. Taste solutions were withheld for 2 days after implant to avoid pairing the taste stimuli with effects of the surgical procedure. Data are represented as mean $\pm$ *SE*. Standard error bars not visible where values are less than 1%.
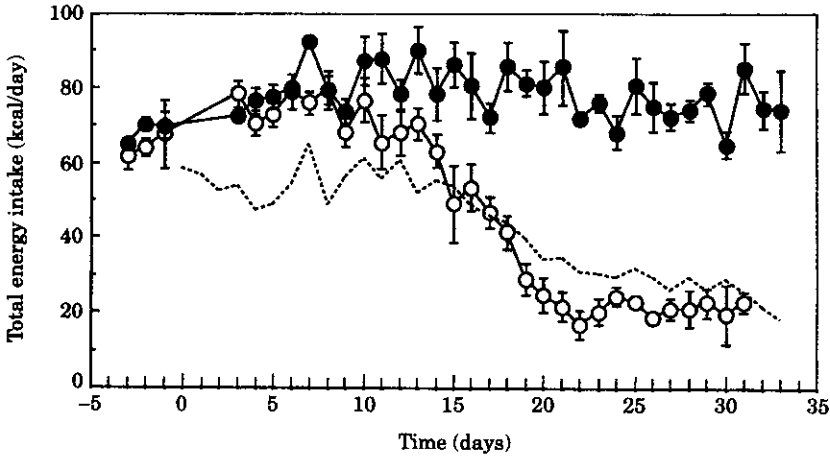
FIGURE 2. Total energy (kcal) intake of tumor-bearing (O, $n = 6$) and non-tumor-bearing (●, $n = 5$) rats in the two-bottle longitudinal preference test (SUCR or water). Control data for the pellet-food-only group (dotted line, $n = 7$) were obtained from weight-matched tumor-bearing animals in an earlier experiment. Time $0 =$ day of tumor or sham implantation. Data represent mean $\pm SE$.
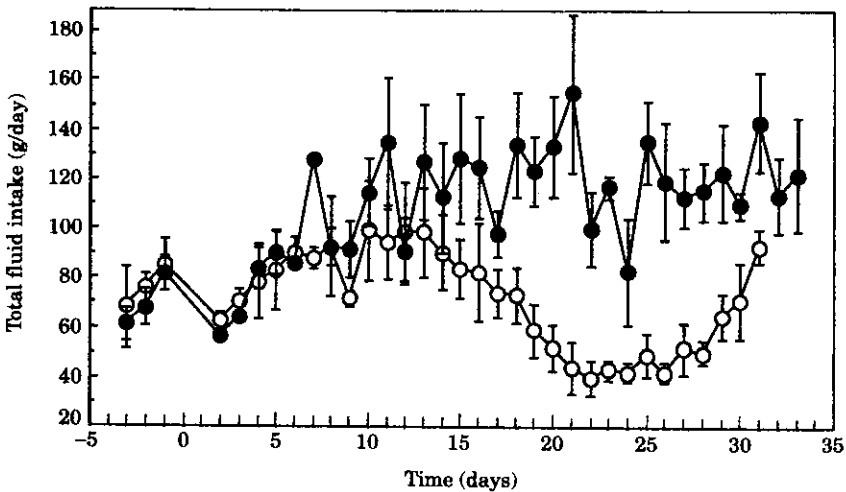

FIGURE 3. Total daily fluid intake (g/day) of tumor-bearing (O, $n = 6$) and non-tumor-bearing (●, $n = 5$) rats in the two-bottle preference test (SUCR or water). Time $0 =$ day of tumor or sham implantation. $p < 0.0005$, RM ANOVA, days 15–28.

100 g body weight (Cizek & Nocenti, 1965). On day 2 after sham implantation, NTB rats consumed a daily average of 40·3 ml/100 g body weight of total fluids, and by day 21, were drinking an average of 64·4 ml/100 g body weight. The total daily fluid intake of rats allowed access to SUCR solution or water was not significantly different between TB and NTB groups until day 15 when the total fluid intake of TB began to decline (days 15 to 28, $p < 0.0005$, RM ANOVA) (Fig. 3). Then, on days 29–31, TB rats began to increase their fluid consumption.
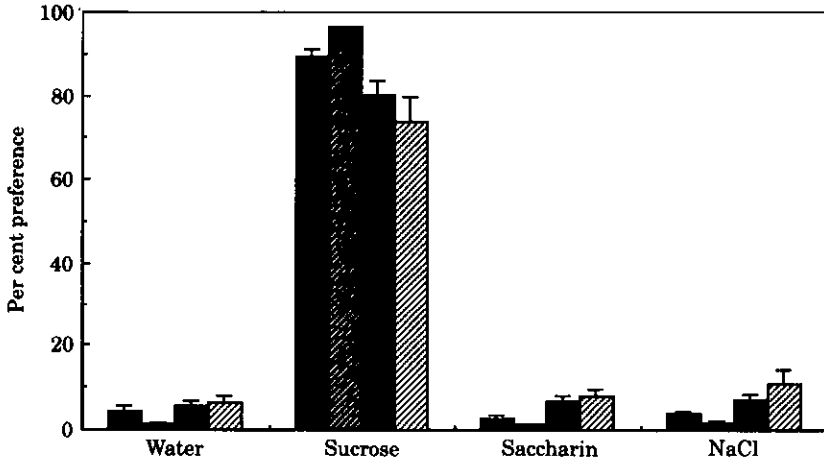
FIGURE 4. Taste preferences of tumor-bearing ($n=8$) and non-tumor-bearing ($n=8$) rats in four-bottle preference tests (three taste stimuli and water) compared pre- vs. postimplantation (■, NTB pre-; ▨, NTB post-; ▤, TB pre-; ▨, TB post-). Data represented as mean $\pm SE$. Standard error bars not visible where values are less than 1%. NTB preference pre- vs. post- for sucrose, $p<0.005$.

Protocol 2: Effect of Tumor Growth on Pre- and Posttumor Implantation Preference Tests (Three Taste Stimuli)

As seen in Fig. 4, both TB and NTB rats exhibited a dominant preference for sucrose over saccharin, NaCl and water when presented simultaneously with three taste stimuli at pre- and posttumor/sham implantation. An overall multivariate analysis of these differences (post minus pre) showed that the mean preferences for the three taste solutions (SUCR, SACC and NaCl) were different between TB and NTB animals ($p<0.005$). *Post-hoc* comparisons of the difference scores (post minus pre) for SUCR revealed a significant difference between groups ($p<0.01$), i.e. NTB rats increased their preference for SUCR by 7% and TB rats decreased their preference by 6% from pre- to postimplantation.

DISCUSSION

It is commonly thought that taste changes are in part responsible for tumor anorexia. However, there have been few studies of altered taste in experimental cancer (Bernstein *et al.*, 1985; DeWys, 1974) partly due to the lack of available animal models. The major finding of the present study is that behavioral taste responses for two sweet stimuli but not the salty stimulus, were altered during MCA sarcoma growth and its accompanying anorexia in F344 rats. Although sucrose and saccharin preferences of tumor-bearing rats in the two-bottle longitudinal design were not significant for these small sample sizes, we observed an attenuation of taste preference that corresponded to advanced tumor growth. Consistent with these observations, anorectic, tumor-bearing rats in the four-bottle posttest preferred sucrose less than non-tumor-bearing controls.

During the first 21 days of tumor growth, rats preferred a sucrose solution (greater than 90% preference) over water, but tended to reduce their preference for sucrose with advanced tumor growth. Similarly, tumor-bearing rats preferred a saccharin solution (greater than 80% preference) until 17 days after tumor implantation, when this preference began to steadily decline. In both cases, a reduction in total calorie intake preceded the changes in sucrose (see Figs 1(A) and 2) and saccharin (kcal data not shown) preference by several days. A decrease in preference for sucrose or saccharin was not evident in non-tumor-bearing, control groups. In addition, tumor-bearing rats displayed no differences over time, or in comparison with control animals, in preferences or aversions for quinine or hydrochloric acid at the chemical concentrations studied, thus ruling out an obvious disruption of the taste system.

With or without a tumor, rats exhibited approximately 50% preference for the NaCl solution daily throughout the entire experiment. This finding is in agreement with other reports of a lack of preference for NaCl in the F344 rat strain (Grill & Bernstein, 1988; Midkiff et al., 1985; Sollars et al., 1991). We studied the percentage preference for 0·10 M NaCl concentration and our results were similar to those of Midkiff et al. (1985) who found that adult F344 rats demonstrated a 40% preference for this concentration of NaCl. Interestingly, F344 rats do not prefer NaCl solutions over water at any concentration and avoid concentrations of NaCl that are strongly preferred by other strains (Midkiff et al., 1985). Recently, studies of the possible mechanism for this NaCl aversion in F344 rats have shown that it can be suppressed by lingual application of amiloride, a sodium-transport blocker (Bernstein et al., 1991), and reversed by bilateral transection of the chorda tympani nerve (Sollars et al., 1991).

Normally, in healthy growing rats, daily water intake is proportional to body weight and food intake (Cizek & Nocenti, 1965). We have shown that when palatable taste stimuli are freely available, this relationship is altered. As seen in Fig. 3, non-tumor-bearing rats consumed as much as 185 g fluid/day (sucrose solution plus water). Previously we have reported a spontaneous 2–3-fold increase in water intake occurring approximately 1 week before death in rats bearing the MCA sarcoma (Smith et al., 1993). This phenomenon was not observed in the present study, although it appears that total fluid intake was beginning to increase on days 29–31 after implantation in tumor-bearing rats presented with the two-bottle sucrose preference test (Fig. 3).

That the declines in sucrose and saccharin preferences are an effect of learned aversions to the taste stimuli cannot be ruled out with the experimental design used in protocol 1. In an attempt to counter this problem, we examined multiple taste preferences in another group of animals before tumor implantation and then again several weeks later when an anorexia to food was evident (protocol 2). When presented with three taste stimuli simultaneously at pre- and postimplantation, tumor-bearing rats showed a strong preference for sucrose over water, saccharin, and NaCl. The results for non-tumor-bearing rats were similar except that they demonstrated a small but significant increase in preference for sucrose at the posttest, accompanied by slight declines in preferences for water, saccharin, and NaCl. A comparison of the difference scores (pre- minus postimplant/sham) for non-tumor-bearing and tumor-bearing rats revealed a significant suppression of the tumor-bearing animals' preference for sucrose.

Similar findings for sucrose preference have been reported with the Walker 256 carcinoma in Sprague–Dawley rats (DeWys, 1974). Tumor-bearing rats with an early tumor preferred a sucrose solution over water (greater than 90% preference) for sucrose concentrations that ranged from 0·3 to 6·0 M. However, animals with advanced tumor growth continued to display a preference for sucrose, but for a narrower range of concentrations (0·6 to 3·0 M) (DeWys, 1974). This difference may be related to the heterogeneity of animal models of tumor anorexia (Bernstein *et al.*, 1985).

The finding of a decreased preference for sweet taste stimuli in this model of experimental cancer is consistent with the clinical literature. Cancer patients who experience changes in food preferences report that sweet foods are generally less palatable (Vickers *et al.*, 1981) although these results may have been confounded by the effects of chemotherapy. Also, cancer patients may have slightly higher recognition thresholds for sweet taste compared to controls (Bernstein & Fenner, 1983; Carson & Gormican, 1977; DeWys & Walters, 1975; Henkin *et al.*, 1983; Mordes *et al.*, 1984; Williams & Cohen, 1978). Our results provide further experimental evidence for the development of altered taste preferences during tumor growth and suggest that sweet taste cues may be more susceptible than salt tastes to the development of taste aversions. However, the contribution of taste changes to the anorexia of cancer is unclear. It remains possible that the changes in taste preference observed in our study are secondary to the reduction in food intake. In this regard, taste changes during cancer may be a function of weight loss (Ovesen *et al.*, 1991) or nutritional deficits (Theologides, 1988). Moreover, correction of nutritional deficits may improve taste function (Russ & DeWys, 1978).

REFERENCES

Bécouarn, Y., Hoerni, B., Dilhuydy, J. M., Stockle, E., Bonneteau, C. & Brunet, R. (1991) Taste alterations in cancer patients. *Bulletin du Cancer, 78,* 901–13.

Bernstein, I. L. (1986) Etiology of anorexia in cancer. *Cancer, 58,* 1881–6.

Bernstein, I. L. & Bernstein, D. (1981) Learned food aversions and cancer anorexia. *Cancer Treatment Reports, 65* (Suppl 5), 43–7.

Bernstein, I. L. & Fenner, D. P. (1983) Learned food aversions: heterogeneity of animal models of tumor-induced anorexia. *Appetite, 4,* 79–86.

Bernstein, I. L., Longley, A. & Taylor, E. M. (1991) Amiloride sensitivity of chorda tympani response to NaCl in Fischer 344 and Wistar rats. *American Journal of Physiology, 261,* R329–33.

Bernstein, I. L. & Sigmundi, R. A. (1980) Tumor anorexia: a learned food aversion? *Science, 209,* 416–18.

Bernstein, I. L., Treneer, C. M., Goehler, L. E. & Murowchick, E. (1985) Tumor growth in rats: conditioned suppression of food intake and preference. *Behavioral Neuroscience, 99,* 818–30.

Bradley, R. M. (1973) Electrophysiological investigations of intravascular taste using perfused rat tongue. *American Journal of Physiology, 224,* 300–4.

Carson, J. A. S. & Gormican, A. (1977) Taste acuity and food attitudes of selected patients with cancer. *Journal of the American Dietary Association, 70,* 361–5.

Cizek, L. J. & Nocenti, M. R. (1965) Relationship between water and food ingestion in the rat. *American Journal of Physiology, 208,* 615–20.

DeWys, W. D. (1974) Abnormalities of taste as a remote effect of a neoplasm. *Annals of the New York Academy of Sciences, 230,* 427–34.

DeWys, W. D. & Walters, K. (1975) Abnormalities of taste sensation in cancer patients. *Cancer, 36,* 1888–96.

Grill, H. J. & Bernstein, I. L. (1988) Strain differences in taste reactivity to NaCl. *American Journal of Physiology, 255,* R424–30.

Hall, J. C., Staniland, J. R. & Giles, G. R. (1980) Altered taste thresholds in gastro-intestinal cancer. *Clinical Oncology, 6*, 137–42.

Henkin, R. I., Mattes-Kulig, D. & Lynch, R. A. (1983) Taste and smell acuity in patients with cancer. *Federation Proceedings, 42*, 550.

Huldij, A., Giesbers, A., Poelhuis, E. H. K., Hart, A. A. M., Hulshof, K. F. A. M. & Bruning, P. F. (1986) Alterations in taste appreciation in cancer patients during treatment. *Cancer Nursing, 9*, 38–42.

Kamath, S., Booth, P., Lad, T. E., Kohrs, M. B. & McGuire, W. P. (1983) Taste thresholds of patients with cancer of the esophagus. *Cancer, 52*, 386–9.

Kern, K. A. & Norton, J. A. (1988) Cancer cachexia. *JPEN, 12*, 286–98.

Lasiter, P. S., Reems, D. A., Oetting, R. L. & Garcia, J. (1985) Taste discriminations in rats lacking anterior insular gustatory neocortex. *Physiology and Behavior, 13*, 91–100.

Midkiff, E. E., Fitts, D. A., Simpson, J. B. & Bernstein, I. L. (1985) Absence of sodium chloride preference in Fischer-344 rats. *American Journal of Physiology, 249*, R438–42.

Mordes, J. P., Longscope, C., Flatt, J. P., MacLean, D. B. & Rossini, A. A. (1984) The rat LTS(m) Leydig cell tumor: cancer anorexia due to estrogen. *Endocrinology, 115*, 167–73.

Mordes, J. P. & Rossini, A. A. (1981) Tumor-induced anorexia in the Wistar rat. *Science, 213*, 565–7.

Morrison, S. D. (1973) Limited capacity for motor activity as a cause for declining food intake in cancer. *JNCI, 51*, 1535–9.

Morrison, S. D. (1976) Control of food intake in cancer cachexia: a challenge and a tool. *Physiology and Behavior, 17*, 705–14.

Mulder, N. H., Smit, J. M., Kreumer, W. M. I., Bouman, J., Sleijfer, D. T., Veeger, W. & Koops, H. S. (1983) Effect of chemotherapy on taste sensation in patients with disseminated malignant melanoma. *Oncology, 40*, 36–8.

Ovesen, L., Hannibal, J. & Sorensen, M. (1991) Taste thresholds in patients with small-cell lung cancer. *Journal of Cancer Research and Clinical Oncology, 117*, 70–2.

Pfaffmann, C. (1952) Taste preference and aversion following lingual denervation. *Journal of Comparative and Physiological Psychology, 45*, 393–400.

Pfaffmann, C., Norgren, R. & Grill, H. J. (1977) Sensory affect and motivation. *Annals of the New York Academy of Sciences, 290*, 18–33.

Popp, M. B., Morrison, S. D. & Brennan, M. F. (1981) Total parenteral nutrition in a methylcholanthrene-induced rat sarcoma. *Cancer Treatment Reports, 65* (Suppl 5), 137–43.

Russ, J. E. & DeWys, W. D. (1978) Correction of taste abnormality of malignancy with intravenous hyperalimentation. *Archives of Internal Medicine, 138*, 799–800.

Settle, R. G., Quinn, M. R., Brand, J. G., Kare, M. R., Muller, J. L. & Brown, R. (1979) Gustatory evaluation of cancer patients: preliminary results. In van Eys, J., Seelig, M. S. and Nichols, B. L. (Eds.), *Nutrition and cancer.* Pp. 171–85. New York: SP Medical and Scientific Books.

Smith, B. K., Conn, C. A. & Kluger, M. J. (1993) Experimental cachexia: effects of MCA sarcoma in the Fischer rat. *American Journal of Physiology, 265*, R376–84.

Sollars, S. I., Sollars, P. J. & Bernstein, I. L. (1991) Reversal of the sodium chloride aversion of Fischer 344 rats by chorda tympani nerve transection. *Behavioral Neuroscience, 105*, 603–5.

Stovroff, M. C., Fraker, D. L. & Norton, J. A. (1989) Cachectin activity in the serum of cachectic, tumor-bearing rats. *Archives of Surgery, 124*, 94–9.

Strohl, R. A. (1983) Nursing management of the patient with cancer experiencing taste changes. *Cancer Nursing, 6*, 353–9.

Theologides, A. T. (1988) Appetite in anorexia of cancer. *Current Concepts in Nutrition, 16*, 101–24.

Trant, A. S., Serin, J. & Douglass, H. O. (1982) Is taste related to anorexia in cancer patients? *American Journal of Clinical Nutrition, 36*, 45–58.

Vickers, Z. M., Nielsen, S. S. & Theologides, A. (1981) Food preferences of patients with cancer. *Journal of the American Dietary Association, 79*, 441–5.

Wall, D. T. & Gabriel, L. A. (1983) Alterations of taste in children with leukemia. *Cancer Nursing, 6*, 447–52.

Walsh, T. D., Bauman, K. & Jackson, G. P. (1982) Taste changes in advanced cancer. *Proceedings of the Nutrition Society, 82*, 108A.

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Williams, L. R. & Cohen, M. H. (1978) Altered taste thresholds in lung cancer. *American Journal of Clinical Nutrition*, *31*, 122–5.