Radiation-Induced Taste Aversion as a Factor in Cancer Therapy


Cancer patients can experience significant loss of appetite during the course of illness (1). It is possible that patients who are undergoing radiation therapy might have this problem intensified by the development of radiation-induced conditioned taste aversions (2). Indeed, there is strong evidence that learned chemical-induced taste aversions do occur when patients are undergoing chemotherapy (3). Evidence is presented in this paper demonstrating that laboratory rats develop strong and long-lasting learned taste aversions when that taste had been paired with gamma-ray exposure. This occurs in rats that receive low levels of radiation to relatively small areas of the body, provided that multiple pairings of the taste and the irradiation are administered. Although considerable data are available regarding radiation-induced conditioned taste aversions in rats (4–9), an effort was made in the present research to test these learned aversions in animals subjected to conditions which more closely simulate those under which humans receive radiation treatment. In addition to the animal studies, the results of preliminary observations in human radiotherapy patients will be presented which suggest that fruit juice taken in close conjunction with radiation therapy results in the development of a conditioned taste aversion. In addition, from patient interviews we have made observations in which several patients reported a strong aversion to a particular food consumed in close temporal relationship to radiation therapy.

METHODS

Animals

Experimental animals.—The experimental animals were Sprague-Dawley adult male albino rats (Southern Animal Farm, Prattville, AL). The rats were housed individually in Hoeltge Cages and were provided Wayne Rat Chow and water except when noted below. Rats were acclimated to the laboratory for a minimum of 2 weeks, where the room illumination was on a 12-hour light/12-hour dark schedule, with light onset at 0700 hours.

Irradiation procedures.—Cobalt-60 was used for the radiation exposures. For the whole-body irradiations the rats were exposed while riding in Plexiglas boxes (20 × 9 × 9 cm) which were mounted on a motor-driven wheel. Rotation in front of the radiation source provided an equal exposure of 2.67 R/minute. For sham irradiation, the rats were placed in the boxes and rotated without radiation exposure. For partial-body exposures the rats were restrained in smaller Plexiglas cylinders and appropriately positioned in front of a 2.5-cm slit in the lead shielded housing of the Cobalt-60 source (25.4 R/minute).

Experimental procedure.—The experimental procedure consisted of three phases: preconditioning, conditioning, and postconditioning. During preconditioning an effort was made to acclimate the rats to drink their daily fluid at 0800 hours and to allow the rats to become familiarized to the flavor of saccharin. The preconditioning phase began on Day 1 with removal of water bottles from the cages and on successive days the animals were allowed access to water at 0800 hours as follows: Day 2, 60 minutes; Day 3, 30 minutes; and Day 4, 10 minutes. On Days 5–14 the rats had access to saccharin-flavored water (0.1%) for 10 minutes. Control animals did not receive preconditioning experience with saccharin during Days 5–14. The conditioning phase began on Day 15 where immediately after the 10-minute saccharin presentation the rats were irradiated and returned to their cages. The number of conditioning days for each group is shown in table 1. The postconditioning phase began on the day after the last conditioning day with a 10-minute single-bottle saccharin consumption test followed immediately by a 23-hour 2-bottle preference test between saccharin and water. The saccharin preference score was the percent of total fluid intake which was saccharin. These daily preference tests were continued for the number of days indicated.

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TABLE 1.—Radiation procedures

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<tr>
<th>Experiment No*</th>
<th>No. of conditioning days</th>
<th>Radiation exposures for each group (R)</th>
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*No. of rats used in each experiment is shown in parentheses.


cated in the various figures pertaining to each experiment.

Experimental designs.—The conditions for the radiation exposures and the number of conditioning days for the four animal experiments are described in table 1.

Human studies.—The effect of drinking a fruit juice immediately prior to abdominal or pelvic irradiation on subsequent preference for this particular juice was evaluated in a three-group study with the following design: group 1 received the fruit juice followed by irradiation; group 2 received radiation only; and group 3 (a nonpatient control group) received the fruit juice and no irradiation. On each test day the subjects in groups 1 and 3 were offered the same juice and the amount the patient desired and the amount actually consumed were recorded. These subjects also completed a rating scale (9) (fig 1). Patients in group 2 were interviewed prior to or immediately after radiation treatment but no tastant was offered. Dietary intake, including intake of fruit juice for the previous 24 hours, was recorded. In an additional study, patients receiving radiation therapy were interviewed to discover whether any foods which they had taken in close conjunction with radiation therapy had resulted in subsequent aversion for these foods.

RESULTS AND DISCUSSION

Animal Studies

Experiment 1.—Mean saccharin consumption during the 10-minute test on the first postconditioning day is shown in figure 2 for each of the whole-body radiation-exposure groups which had pre-exposure saccharin familiarity trials. An analysis of variance across these five groups was significant (F = 88.84, df = 5, 42, P < 0.01). Subsequent comparison showed that the 25-, 50-, and 100-R groups were not different from each other, but each of these groups was different from the 200- and 300-R groups. The mean saccharin intakes from animals that had no preconditioning experience with saccharin are also shown. With these animals it can be seen that the higher the radiation exposure the stronger the aversion to saccharin. It is obvious that experience with the tastant prior to conditioning greatly attenuated the conditioned taste aversion. The results from the two-bottle preference tests also showed that the rats recovered from the aversion much faster if they had prior experience with the saccharin. Based on these results it seems as though the radiotherapy patient would not be likely to develop radiation-induced taste aversions unless the tastant ingested prior to exposure was novel. However, these results are based on only one taste-radiation pairing.

Experiment 2.—In this experiment the rats were given 3 conditioning days, i.e., three saccharin-radiation (whole-body 100-R) pairings. Mean saccharin preference is plotted for 50 days following conditioning for animals in both Experiments 1 and 2. As can be seen in figure 3, the results here were quite different from those in which the rats had only one conditioning trial. The rats that had only one conditioning trial recovered to normal saccharin drinking in 4 days, but the rats with three conditioning trials had not recovered in nearly 2 months. The inference one could make for the human patient is that if the tastant-radiation pairing occurs several times, familiarity of the taste solution would not necessarily protect the patient from the radiation-induced conditioned taste aversion.

Experiment 3.—The first two experiments involved whole-body exposures. Experiment 3 demonstrates that a saccharin aversion can be conditioned in rats with either head or abdominal irradiation. From previous experiments it has been shown that the abdominal exposure is more effective than the head exposure in conditioning the aversion to saccharin (6). Therefore, in this experiment rats in the head group were given 6 conditioning days and those in the abdominal group were given only 4 con-
Please use the scale below to show your attitude by putting a check mark at the point which best describes your feeling about the food. Keep in mind that you are the judge. You are the only one who can tell what you like. Nobody knows whether these foods should be considered good, bad, or indifferent. An honest expression of your personal feeling will help us decide.

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<th>Dislike Moderately</th>
<th>Dislike Slightly</th>
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<td>5</td>
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Apple Juice
Fried Chicken
Coffee
Mashed Potatoes
Orange Juice
Cooked Carrots
Sweet Rolls
Grape Juice
Lima Beans
White Rice
Ham

FIGURE 1.—Rating scale completed by each patient and each control subject on the first and last day of contact and about 40% of the days in between. The scale is a modification of that used by Peryam and Pilgrim (ref 9).
conditioning days. Mean saccharin preference is plotted as a function of days after conditioning in figure 4. When compared to sham-exposed control rats it can be seen that both head and abdominal groups show a profound and long-lasting conditioned taste aversion.

Experiment 4.—In this experiment a criterion was set for the number of conditioning days as follows: each group continued to receive daily saccharin-radiation pairings...
ings until its saccharin intake in the 10-minute drinking period diminished to 20% of its saccharin intake on the first conditioning day. If criterion had not been met after 14 conditioning days, conditioning was discontinued. The number of conditioning days required to meet this criterion for each group is noted in table 1. The mean preference scores for each of the nine groups on the first post-conditioning day are seen in figure 5. A two-way analysis of variance showed that the differences between body areas, the difference between radiation doses, and the interaction between body area and doses were all significant (all \( P < 0.01 \)). From both the number of conditioning days required to meet the criterion and the preference scores in figure 5, it can be concluded that whole-body exposure is more effective than abdominal exposure and that abdominal exposure is more effective than head exposure in conditioning the aversion at the lower radiation exposures. However, when the level of radiation exposure is high, the area of the body exposed does not seem to matter. As can be seen in figure 6, the recovery from the aversions for these nine groups leads one to the same conclusion as that drawn from the first-day scores. The results of this experiment show that rats treated with irradiation conditions which are more like those experienced by the human radiotherapy patient (i.e., multiple partial-body exposures near in time to ingestion of familiar tastes) develop significant and long-lasting taste aversions. Moreover, in the rat model, even low-level partial-body exposures can lead to profound and enduring taste aversions with familiar flavors, provided that multiple pairings of the tastant and irradiation are employed.

**Human Studies**

The purpose of the first human study was to determine if a learned taste aversion could be demonstrated in human radiotherapy patients with abdominal or pelvic irradiation.

Within the tastant-radiation group (group 1), all ten patients showed a marked decrease in the amount of their chosen juice requested and in the amount of juice consumed over the course of the treatment period. In fact, nine of the ten patients refused to taste the juice after several pairings of that particular juice with the radiotherapy treatment. The mean number of days before complete cessation of juice intake was 6, with a range of 1-13 days.

In contrast to the above behavioral indications of a reduced preference for the juice, only four of the ten patients indicated a decreased preference for their particular chosen juice on the rating scale. Several patients gave their juice a "like extremely" rating while refusing to drink any of it.

The data from one patient for whom drinking behavior and test juice rating are consistent can be found in figure 7. It is evident that the amount of grape juice consumed dropped rapidly and that the rating of grape juice changed from "like very much" to "dislike extremely" during the course of radiotherapy. For clarity, only the
first and last rating days for the other ten foods are shown. For this patient the ratings of these other foods remained constant throughout the radiotherapy period. A similar consistency over time in rating of the nonconditioned stimulus foods and juices was seen in nearly all of the patients. In figure 7, the data from a second patient illustrate the interesting finding where a marked decrease in grape juice intake was noted, but with no decrease in the rating of the juice. This patient, who is representative of one-half of the sample, verbally reported no loss in “liking” grape juice, yet refused to continue drinking it.

The second group of ten patients had received no distinctive taint prior to irradiation. In this group, there were no signs of a decrease in consumption of fruit juices by any of the patients throughout the course of radiotherapy. These data suggest that irradiation per se does not result in a diminution of flavored liquid intake.

The group of 14 normal adults (group 3) was given a daily opportunity to sample a single fruit juice, but received no radiotherapy. Eleven of the subjects showed a very consistent level of consumption across the 15 days of testing. Three of the subjects showed a slight increase in amount consumed over the 15 days and none showed any decrease. There were no significant changes in the subjects’ ratings of their chosen juices over the 15-day period. These data show that prolonged “forced” drinking of the taint did not change the amount consumed or the attitude of the subject toward the juice.

It is important to note that the juice-radiation pairing data were obtained from patients treated with abdominal and/or pelvic exposure. One additional patient who was treated with clavicular radiation exposure and who consumed juice prior to treatment asked for and drank a relatively constant quantity of juice each day throughout the course of radiotherapy. There was no evidence of a learned taste aversion in this patient. This preliminary result is consistent with the findings in the animal studies, indicating that the abdominal area is more sensitive than other areas in producing the learned aversion.

It is recognized that neither group 2 nor group 3 is an ideal control group. It is significant that patients with neoplastic disease undergoing abdominal and/or pelvic radiotherapy could drink fruit juice throughout the course of treatment when the juice was not “paired” close in time with irradiation (group 2). It is also significant that normal subjects showed consistent behavior regarding quantity of juice imbibed over a 15-day period (group 3). Both of the above findings support a learned aversion interpretation of the data obtained from the patients in group 1.

A second study was conducted to determine from extensive interviews of 56 radiation therapy patients treated in a variety of body regions if there is evidence for learned food aversions in radiation therapy patients in the clinical setting. The dietary interviews included recalled dietary intake, food preference changes, appetite changes, etc. No attempt was made in this study to control or in any way influence dietary intake and food preference during the course of treatment.

Indications of taste aversions occurred primarily in spontaneous reports of aversions, comments regarding food preference changes, and reported changes in appetite which were concomitant with reports of nausea. Four of the patients interviewed reported a strong and explicit aversion to a particular food consumed in temporal association with radiation treatment. These aversions were reported to continue for periods ranging from several weeks to several months. Ten patients reported a decreased food preference (ie, the food was described as “less appealing” or “not liked as much as usual”) for specific foods consumed over the course of treatment. In response to daily questions and/or follow-up questions regarding appetite, 15 patients reported a decrease in appetite over the course of treatment although their reported appetite prior to treatment initiation had been normal. In all cases for which 2-4-week follow-up information was available, an improvement in appetite was reported after treatments were concluded.

The above indications of learned food aversions were most common among patients treated in the pelvis and upper abdomen and were frequently accompanied by reports of nausea associated with treatment. Specifically, of the patients interviewed, 14% had treatment which included the upper abdomen. Of these patients, 88% reported nausea associated with treatment and 50% gave
FIGURE 6.—Recovery from radiation-induced conditioned taste aversion is compared in groups of rats that received either head, abdominal, or whole-body exposure at the 3 radiation exposures indicated.
Figure 7 — Left: Like-dislike ratings for 11 tasters are plotted as a function of 6 rating days during the course of radiotherapy for a patient who reported a growing dislike for the grape juice which was daily paired with the radiation treatment. The actual daily consumption of grape juice over the same time period is plotted in the lower portion of the figure. Right: Similar data for a 2nd patient are shown where the consumption of grape juice decreases to 0 by the 4th rating day, but the rating of grape juice was reported as “liked very much” throughout the course of radiotherapy.
indications of a food aversion as defined above. Similarly, of the 36% of the patients with treatment restricted to the pelvic area, 56% reported nausea and 30% gave evidence of a food aversion. In contrast, of the 16% of the patients treated only in the thorax specifically for lung disease, 10% reported nausea associated with treatment and none gave an indication of a food aversion; of the 12% of the patients treated in the head and neck region (excluding the brain), 29% reported nausea associated with treatment and none gave an indication of a food aversion (although taste change reports were common in these patients). When all patients with indications of an aversion are considered, 86% reported nausea associated with treatment. In contrast, of the patients without indications of aversions, 36% reported nausea associated with treatment.

While the above findings are compatible with a learned food aversion interpretation, it is important to note that other factors (e.g., taste sensitivity changes, altered metabolism, etc.) (10,11) can affect food preference and appetite. In our analysis of the data an attempt was made (as far as possible) to differentiate possible learned taste aversions from other factors affecting diet and food preference. For example, preference changes and/or taste sensitivity changes unrelated to treatment have been reported by others for sweets, coffee, and meat (10,11). Similar changes were reported in the present study. However, none of these reports was included in our analysis as an instance of a learned food aversion.

The present observations of human patients lack scientific rigor, but it appears that several patients in this study, particularly those treated in the upper abdomen and/or pelvis who experienced gastrointestinal distress, developed learned taste aversions during the course of their radiation treatments. The extent to which eating problems in radiotherapy patients are the result of a learned radiation-induced taste aversion remains unknown. It seems clear at this point that aversive conditioning is a possible contributing factor to eating problems in the cancer patient and that this phenomenon should be taken into consideration by radiotherapists and oncologists. It might be advisable in some cases, for example, to consider discouraging eating (especially novel tastants) close in time to radiotherapy treatments.

Other methods for preventing possible radiation-induced taste aversion in radiotherapy patients cannot be recommended at this time, because the nature of the physiological reaction to irradiation which forms the basis for this motivating aversive stimulus is not fully understood. There is some evidence that a rise in histamine might cause the aversion experience since antihistamine injections have been shown in one study to block the formation of radiation-induced taste aversions in rats (12). However, recent disagreement regarding this finding (13,14) indicates a need for further research.

REFERENCES

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