In 1955 Garcia, Kimeldorf and Koelling published a paper in *Science* which has had far reaching implications for many aspects of behavioral science. One of many important conclusions of that paper was that ionizing radiation could act as an unconditioned stimulus, radically altering the drinking behavior of laboratory rats. Animals which ingested a saccharin flavored water while being exposed to gamma rays from a cobalt 60 source avoided the saccharin flavor in subsequent saccharin-water preference tests. With the proper control groups, these investigators demonstrated that laboratory rats could learn to avoid a distinct taste which had been paired with the whole body irradiation. Many studies from Garcia's and others' laboratories manipulated parameters of this radiation-induced conditioning and furthered our understanding about the limitations and the physiological mechanisms underlying this association between tastes and irradiation. Although criticisms were abundant because this phenomenon was found to challenge the current thinking about learning, no scientific investigation refuted the original finding that tastes associated with irradiation were subsequently avoided. Concurrently with the irradiation work, a large literature began to grow which showed that a wide variety of drugs could also be used to condition taste aversions. Observations of drug-induced aversions had been made quite early (Garcia & Hankins, 1977), but it was not until after the Garcia, Kimeldorf and Koelling paper in 1955 that they were subjected to systematic observation with controls such as those used by Garcia et al.

Although there was an early interest in the application of drug-induced taste aversion learning to the treatment of alcoholism, it was not until the middle of the

*My sincere thanks go to Donald J. Kimeldorf, who taught me more than he will ever know.
1970s, some 20 years after the original Garcia et al. paper, that the National Cancer Institute began to request proposals to study the possible role of chemotherapy and irradiation-induced taste aversions in the dietary habits of patients with neoplastic diseases (see Chapter 1). As DeWys and Kisner (1982) have recently pointed out, some attention needs to be given to the antineoplastic therapies themselves as potential contributors to the decreased caloric intake so often seen in the cancer patient.

In our laboratory we have initiated a study of radiation-induced taste aversion as it may affect the human radiotherapy patient. We asked the question "are inadvertent radiation-induced taste aversions being conditioned because various tastants are experienced too close to radiation exposure?" The work has taken two approaches: (1) we have tried to develop a more adequate animal model for studying the role of conditioned taste aversion in the human patient, (2) we have attempted to directly condition a taste aversion in cancer radiotherapy patients and to develop procedures for assessing the impact of potential learned taste aversion on the dietary habits of these patients.

THE ANIMAL MODEL

The Basic Model

The basic demonstration for radiation-induced saccharin aversion which we use differs only slightly from the original Garcia, Kimeldorf and Koelling design. The saccharin flavored water is presented before the irradiation and the duration of the exposure is considerably shorter in our procedure. The procedure and data described in an earlier paper (Spector, Smith & Hollander, 1981) will serve as an example of the basic design which we have used. The rats were housed in individual cages and accustomed to receiving their water ration for ten minutes in the early morning. The conditioning group received saccharin flavored water (1% sodium saccharin) for 10 minutes and were then transported to the Cobalt room where the animals received a whole body exposure to gamma rays for 33.4 minutes. The exposure was measured in air by a Victoreen Thimble Chamber to be 100r. For comparison, the LD 50 for Sprague-Dawley rats (i.e., the dose that is lethal for about 50% of the rats exposed to it) is about 750r (Casarett, 1968). The measure of aversion was like that of Garcia et al. (1955), i.e., a daily water vs. saccharin preference test which was continued over days until a recovery to normal saccharin drinking was observed. Many taste aversion experiments which followed the Garcia et al. (1955) paper measured aversion by some relatively short-term preference test. We thought it was important, in the animal model, to measure the aversion both by its magnitude and its duration. If these aversions were short lived, we would be less interested in their role in the eating behavior of radiotherapy patients. Garcia et al. (1955) found the aversion to last over fifty days which is a significant period in a rat’s life.
We also followed the example of Garcia et al. (1955) and demonstrated that it is the pairing of the saccharin and the gamma rays which results in the long lasting aversion. Control groups which received saccharin and sham exposure, water and gamma exposure, and water and sham exposure on the “conditioning day” were included in the study. An illustration of these groups and typical first day preference scores from our data are presented in Fig. 5.1. The recovery from the aversion of the saccharin-radiation group can be seen in Fig. 5.2. The lack of any learned aversion in the three control groups can also be seen in this figure. Thus, this experiment supports the same conclusion as the original Garcia et al. (1955) study, i.e., the pairing of a normally preferred taste substance with a single sublethal exposure to ionizing radiation results in a profound and rather long lasting aversion to that tastant. Mere exposure to the gamma rays does not result in any aversion. In classical conditioning language, the conditioned stimulus (saccharin flavored water) when paired with the unconditioned stimulus (gamma rays) results in a conditioned aversion to the flavored water.

Human radiotherapy patients seldom receive whole body irradiation, they normally receive more than one exposure, and they do not necessarily (it has been our experience that they are not even likely to) consume novel tastants before they are exposed. For an appropriate animal model for the radiotherapy

<table>
<thead>
<tr>
<th>GROUP</th>
<th>CONDITIONING PERIOD</th>
<th>MEASUREMENT OF AVERSION</th>
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<tbody>
<tr>
<td></td>
<td>2 BOTTLE PRECONIFIC TET</td>
<td>SACCHARIN SCORE</td>
</tr>
<tr>
<td></td>
<td>100 R GIG-EXPOSURE</td>
<td>1/6</td>
</tr>
<tr>
<td>I</td>
<td>0.1% SACCHARIN INGESTION</td>
<td>1/6</td>
</tr>
<tr>
<td></td>
<td>100 R GIG-EXPOSURE</td>
<td>8/1</td>
</tr>
<tr>
<td>II</td>
<td>0.1% SACCHARIN INGESTION</td>
<td>8/1</td>
</tr>
<tr>
<td></td>
<td>GIG-EXPOSURE</td>
<td>7/0</td>
</tr>
<tr>
<td>III</td>
<td>WATER INGESTION</td>
<td>7/0</td>
</tr>
<tr>
<td></td>
<td>100 R GIG-EXPOSURE</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>WATER INGESTION</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 R GIG-EXPOSURE</td>
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FIG. 5.1. A schematic diagram of our experimental design. The resulting saccharin scores (taken from Spector, Smith, & Hollander, 1981) are typical of almost all radiation-induced taste aversion experiments.
FIG. 5.2. Recovery from saccharin aversion is shown where median saccharin preference scores are plotted as a function of postconditioning test days. The group which received saccharin paired with radiation (solid squares) shows the average gradual recovery from the conditioned aversion. The control groups described in Fig. 5.1 show no aversion at any time to the saccharin.

Patient we needed to demonstrate a conditioned taste aversion in a rat which was thoroughly familiar with the tastant and which was given several partial body exposures. If these manipulations were to result in a profound and long lasting aversion it would give more impetus to test for learned aversions in the radiotherapy patient.

Partial Body Exposures

From the literature it is apparent that many of these manipulations have been made, but not all in the same animal. Garcia and Kimeldorf (1960) have demonstrated that aversions can be conditioned with partial body exposures. In fact, they showed that abdominal exposure was more sensitive in conditioning the aversion than was head, thoracic or pelvic exposure. Smith, Hollander and Spector (1981) tested the effects of head, abdomen, or whole body exposure with the procedure described above, i.e., 20 minutes of saccharin followed by gamma ray exposure, and used a 10-minute saccharin drinking aversion test on the next day. Their results, which replicated Garcia and Kimeldorf's (1960) findings, are shown in Fig. 5.3. The extinction curves for the 200r exposure of head and abdomen can be seen in Fig. 5.4. These data show that the recovery from head exposure is much more rapid than that from abdominal exposure. In fact, tests on other rats receiving 200r abdominal exposure revealed that they had not recovered normal saccharin drinking after more than 50 days of post-exposure testing.
Effects of Prior Saccharin Experiences

Numerous investigators have shown that familiarity with the taste solution prior to conditioning day markedly attenuates the magnitude and duration of the learned aversion (e.g., Smith, 1971). This was certainly true with our procedure. Rats given ten preconditioning sessions (10 minutes each) with the saccharin flavored water showed little, if any, conditioning unless they were given 200 r whole body exposure. This is illustrated in Fig. 5.5. Recovery from the aversion was also much more rapid in the rats which were familiar with the saccharin. It can be seen in Fig. 5.6 that the recovery in the 300r exposed group is quite
profound as compared to the rats with no prior saccharin experience. In this 300r group the initial conditioning of the saccharin experienced animals was as strong as that for the taste naive rats. The attenuating effects of preconditioning saccharin habituation are so strong that the animal model would predict that learned taste aversions in radiotherapy patients would be trivial unless they ate novel foods. One must remember, however, that the results were from experiments where only one conditioning trial was administered.

**Multiple Radiation Exposures**

Garcia and Koelling (1967) reported over fifteen years ago that three conditioning trials with saccharin and x-rays could overcome a lifetime of experience with saccharin. In order to test the effects of multiple saccharin-whole body radiation pairings in rats familiar with the tastant on the long-term recovery from a saccharin aversion, we compared groups of rats that had: (1) ten habituations to saccharin and one saccharin-radiation pairing; (2) no habituation to saccharin and one saccharin-radiation pairing; and (3) ten habituations to saccharin followed by
FIG. 5.6. Mean saccharin preference score plotted as a function of postconditioning testing days for groups receiving 50r, 100r, 200r, or 300r exposures.

three saccharin-radiation pairings. The long term recovery from the aversions conditioned in these groups is illustrated in Fig. 5.7. Here it can be seen that 10 habituations to saccharin followed by one saccharin-radiation pairing resulted in no conditioning. Rats treated identically, but given three saccharin-radiation
pairings on three consecutive days, showed a profound aversion which was not overcome in more than fifty days.

The next step was to test rats with multiple partial body exposures during the conditioning trials. All of these rats had received 10 daily habituation trials to the saccharin flavored water. Rats were exposed to 100r to the head or the abdomen. Each conditioning day they were given 10 minutes of saccharin followed by the 100r gamma exposure until their 10 minute saccharin intake mean was not significantly different from a criterion group mean. The "criterion" group had no experience with saccharin prior to the conditioning day, when they received a single 100r whole body exposure following 10 minutes of saccharin ingestion. The "criterion" was the amount of saccharin they consumed in a single bottle test on the day following conditioning. As can be seen in Fig. 5.8, this criterion value was about 4 ml. The abdomen group took only three trials before they were "conditioned" by the criterion described above. The head group took five pair-
FIG. 5.8. Mean saccharin consumption in a ten-minute drinking period as a function of number of conditioning days. Animals exposed to the abdomen were not statistically different from the criterion intake level (see text) after three conditioning trials (open circles) and those exposed to the head took five trials (closed circles) to reach the criterion.

ings of the saccharin and irradiation to reach the same criterion. The last data point for each group was not followed by irradiation. Control animals received either water and irradiation or saccharin and sham irradiation on conditioning day. The partial recovery from these conditioning trials is seen in Fig. 5.9. The combined control animals showed no sign of aversion. The recovery to normal saccharin drinking for both groups was incomplete even after 50 days. The course of recovery for these groups was not statistically different. One could conclude that multiple partial body exposures during conditioning trials with rats that were not naive to saccharin resulted in profound and long lasting aversions to the tastants. It also appears that head irradiation can be as effective as abdominal irradiation if enough saccharin–radiation pairings have been made. This latter conclusion is limited, however, to this particular 100r exposure. The final step in developing our current animal model was to compare head, abdominal and whole body exposures with several radiation levels in rats that were thoroughly familiar with saccharin.

Eighty-one male rats were given ten days of habituation trials (10 minutes per day) to saccharin flavored water. After drinking saccharin for 10 minutes on the conditioning day they were confined to plexiglas tubes and given either a whole body, head, or abdominal exposure to gamma rays. Each of the three groups was further subdivided into three groups which received either a 25r, 50r or 200r exposure (N = 9 in each group). Conditioning trials were continued for each group until the mean fluid consumption during the CS period was less than 20% of that consumed on the first conditioning day. In order to avoid severe depriva-
Fig. 5.9. Mean saccharin preference score as a function of postconditioning testing days. Recovery for rats conditioned with radiation to the head (open triangles) and to the abdomen (open circles) followed the same course and was not complete after 52 days. Data for control rats that received either saccharin-sham trials or water-radiation trials were combined (closed circles).

During these multiple conditioning trials, all rats were given a 10 minute water supplement about five hours after conditioning each day. Four of the groups failed to reach the conditioning criterion and conditioning trials were discontinued on these groups after two weeks of exposures. Table 5.1 shows the number of days for conditioning in each of the groups.

From Table 5.1, one would conclude that 25r to whole body, abdomen, or head and 50r to the head was not a strong enough dose to condition the rats. As expected whole body exposure took fewer trials than did abdominal exposure, and abdominal exposure was more sensitive than head exposure.

Once the conditioning criterion was met (or after 14 days of CS-US pairings if conditioning did not occur by this time), 24-hour two-bottle preference testing was initiated. The mean saccharin preference scores for the first 24-hour postexposure preference test are presented in Fig. 5.10. From these data it can be seen that conditioning did occur at the 25r level for the whole body and abdominal groups in spite of the failure to meet the conditioning criterion. At the 50r level all three groups were conditioned, but in the abdominal and whole body groups.
TABLE 5.1
The Number of Pairings of Saccharin With Cobalt 60 Exposure for Each Treatment Condition

<table>
<thead>
<tr>
<th>Number of Conditioning Days</th>
<th>Whole Body</th>
<th>Abdomen</th>
<th>Head</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 r</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>50 r</td>
<td>3</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>200 r</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

the conditioning was stronger. At the 200r level all groups became well conditioned. The recovery from these aversions is plotted in Fig. 5.11. Here it can be seen that whole body exposure generally resulted in stronger conditioning than abdominal exposure and head exposure except at the 200r level. The recovery to normal drinking for the whole body exposure groups does not seem to depend on the daily exposure. This is also probably true for the abdominal groups. For the head groups, there was considerable difference in the time for recovery. Initially, the 25r group showed almost no aversion. The 50r group showed some aversion.
and a slower recovery rate. The 200r group showed about the same recovery rate as the 50r group, but the initial aversion was much more profound. Even after 52 days the 50r group is not completely recovered and the 200r group has barely reached a point of indifference. In the head groups, the difference between the 50 and 200r groups cannot be accounted for by the total radiation exposure. The 200r group received a total of 800r in four days when the 50r group received 700r in 14 days. There seems to be something qualitatively different about the 200r group and head irradiation, a point we will return to later in the chapter.

It can be concluded from the animal model studies that rats irradiated under conditions similar to those experienced by radiotherapy patients indeed do develop profound and long lasting aversions to a familiar tastant. The next step in our program was to demonstrate taste aversion in a radiotherapy patient.

TASTE AVERSION CONDITIONING IN HUMANS

Thirty-four adults ranging in age from 18 to 78 years volunteered as subjects for an experiment to test for radiation-induced taste aversion in humans. Twenty of the subjects were radiotherapy patients at the Tallahassee Memorial Regional Medical Center. These outpatients were receiving abdominal or pelvic radiation for a variety of different neoplastic diseases. None of them had had prior radiation or chemotherapy treatments. The other 14 subjects were normal adults with no known neoplastic diseases (Smith, Blumsack, Bilek, Spector, Hollander & Sakur, submitted). They were selected from a group of nonfaculty employees at the Florida State University and had no knowledge about the project at the hospital. Ten of the radiotherapy patients were informed that they were part of a study to investigate taste preferences and eating patterns during the period when they were receiving radiation treatments. They were informed that they would be asked to answer questions about their diet, to respond to a rating scale about certain foods and to select a fruit juice for refreshment during their interview. These patients were offered a choice of apple, orange or grape juice 15 to 60 minutes prior to their first irradiation. The patient selected one juice and indicated the amount he or she wished to consume. This averaged 201 ml and ranged from 89 to 400 ml. On each subsequent treatment day during the interview the patient was offered only the same juice that was selected on the first treatment day. This group served as a tastant-radiation group. The rating scale was a modification of a scale developed by Peryam and Pilgrim (1957). A nine point rating from “dislike extremely” to “like extremely” was used for each of the eleven following substances: apple juice, fried chicken, coffee, mashed potatoes, orange juice, cooked carrots, sweet rolls, grape juice, lima beans, white rice, and

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FIG. 5.11. Mean saccharin preference scores as a function of postconditioning testing days for the radiation exposures and treatment sites indicated.
ham. The rating scale was presented to the patient for completion during approximately 40% of the interviews. From this procedure we could measure on each treatment day the quantity of juice consumed prior to irradiation and we could periodically measure the patient's attitude toward that particular juice and toward 10 other tastants.

The fourteen normal adults were treated in a similar fashion as the patients except that they received no irradiation. They were told that they were part of a study in which we were studying eating behavior in cancer patients and that they were to serve as a nondisease control group. They were also told that we would ask them to complete a rating scale about food and that they would receive a refreshment of their choice during the interview period. These subjects were seen daily for 15 consecutive working days. This group served as a taster-no irradiation control.

The second group of ten radiotherapy patients was offered no juice or rating scale. The patients were selected from a larger group which we had been interviewing daily throughout radiotherapy. They were selected because they were being treated in the abdominal or pelvic region and because they indicated in their interviews that they were regular drinkers of some particular, distinctive tasting liquid, such as orange juice or others. This taster, however, was not systematically consumed by the patient at any particular time and definitely not during the interview period prior to irradiation. On each treatment day these patients were interviewed either before or after their radiation treatment, so that their dietary intake since the last interview could be recorded. They served as an irradiated group which received no taster close in time to therapy.

All patients in the taster-irradiation group developed an aversion to their particular juice. Whether it was apple, grape or orange juice the amount requested and the amount consumed dropped radically after the first treatment day. In fact, all but one of the patients refused to taste the juice at all after from one to 13 pairings. The average number of pairings until this complete cessation was six. It appeared that the demand characteristics of the procedure and not a desire for grape juice kept the 10th patient drinking a small quantity throughout radiotherapy. He was convinced that the doctor wanted him to drink the grape juice for therapeutic reasons. The data for one patient who showed an aversion to grape juice and a change in attitude toward grape juice are seen in Fig. 5.12. The amount of grape juice consumed dropped rapidly to zero and he continued to refuse any of this taster throughout the therapy period. It can be seen that his rating scale indicated a similar growing dislike for grape juice. His ratings of the other foods and juices were constant. Consistency in rating the nonconditioned tasters was also seen in the other nine patients. Although they all showed the marked change in behavior toward their selected juice, they did not all show a change on their rating scale, as did the patient illustrated in Fig. 5.12. In fact only four of the 10 patients indicated a decreased preference for their particular juice on this rating scale. Several of the patients rated their juice as "like extremely"
FIG. 5.12. Upper panel: Rating scores from like extremely (1) to dislike extremely (9) as a function of six rating days distributed throughout the course of radiotherapy. For all of the tastants except grape juice, only the first and last rating days are recorded. Lower panel: Grape juice consumption as a function of the same rating days indicated in the upper panel.
and at the same time would not drink it. These data, although preliminary, are interesting in themselves in showing the lack of correlation between the verbal report and the eating behavior of the patient.

The normal tastant-no irradiation subjects showed no signs of decreasing their juice intake. Eleven of the subjects were extremely consistent in the amount they drank each day and the other three subjects showed a slight increase over the fifteen day period. There were no significant changes in their rating scales for any of the tastants during the fifteen day period. Only one subject changed as much as two units on the nine point scale of any tastant. These data show that continued daily drinking of these fruit juices does not result in a decrease in amount consumed.

The analysis of the data from the irradiation control group was somewhat different. From the interviews with these ten patients we found that three of these patients were regular orange juice drinkers, one drank Gatorade, one drank grapefruit juice, one drank orange soda, one drank Koolade and three drank milk. These beverages were imbibed regularly throughout the course of radiation therapy at various times of the day. They were not consumed close in time to treatment. The data from this group suggest that pelvic or abdominal radiation itself does not necessarily result in a decrease in the intake of flavored liquids.

The two "control groups" are not comparable to the experimental group in all aspects, and our data cannot be considered definitive. However, when taken together there is considerable evidence that supports a learned aversion interpretation of the data obtained from the patients where the distinctive tastant was paired with irradiation. These results concern only a short term aversion and no tests were run to examine how long this aversion would last or to study what effect this aversion could have on the overall eating patterns of the patients.

Including the 10 patients we saw in the no tastant-irradiation group above, we interviewed approximately 60 radiotherapy patients about their daily dietary intakes. They ranged in age from 18 to 78 and represented a broad spectrum of disease types and stages. They also differed widely in their prior medical histories. We interviewed them on each treatment day and with many patients we were able to gain additional information in follow-up interviews. We paid special attention to indications of learned food aversions, i.e., did any of the patients show specific aversions to foods which they ate close in time to exposure.

Indications of learned taste aversion were observed in a few of these patients from their comments about food preference and appetite changes. Four of the patients, all of whom were treated in the abdominal area, reported a strong and specific aversion to a particular food consumed close in time to a radiation treatment. These aversions lasted from several weeks to several months. Although we observed many other changes in food preference behavior, perceived taste sensitivity, and appetite, these changes did not appear to be radiation-induced learned food aversions.
In the animal work, we systematically have paired tastants with radiation exposure to determine the conditions under which learned taste aversions occur. It appears from the present work that aversions can be conditioned in humans undergoing irradiation if a tastant is systematically paired with the exposures to radiation. It is quite likely that the varied eating and drinking patterns of human radiotherapy patients provide considerable protection against the formation of learned taste aversion in the routine course of radiotherapy. One would assume that there would be little taste aversion conditioned in a rat if the animal received numerous trials of tastant with no irradiation and/or trials with no tastant and irradiation interspersed with tastant-irradiation trials.

In conclusion, our data suggest that aversive conditioning is a possible contributing factor to eating problems in cancer radiation patients, but that this contribution does not seem to be overwhelming in magnitude. However, since we know that aversive conditioning can lead to dietary problems, it might be useful for oncologists and radiotherapists to be aware of these data in treating their patients. In some cases it may be advisable to discourage patients from eating (particularly new foods or beverages) close in time to radiotherapy treatments. The obvious question is: "What is 'close in time'?". One can only speculate about this question in the work with radiotherapy patients, but there are considerable data on this question from the rat studies which will be considered in the next section.

HOW TO PREVENT RADIATION-INDUCED TASTE AVERSIONS

There are several ways that radiation-induced taste aversion could be avoided. The first, and most obvious, is to insure that no tastant is "paired" with irradiation. It was stated in the earlier discussion of the animal research that radiation without the tastant produced no saccharin aversion. This statement must be qualified because one of the early findings in this research was that radiation (the US) could be given either before or after the tastant (the CS) and yet this "loose pairing" would still result in the conditioned aversion to saccharin. Although research on this topic has been quite difficult for the traditional learning theorist to accept, it has been shown that in the rat the CS could precede the US by as long as six hours and still produce significant aversion (Smith & Roll, 1967). In addition, it has been shown that the US could precede the CS by 6 hours and conditioning would result (Smith, 1971). In fact, this postexposure condition (i.e., where the US precedes the CS) proved in many cases to result in even stronger initial conditioning than the more traditional CS–US pairing (Barker & Smith, 1974). Many studies showed that if the rat drank saccharin either several hours before or after irradiation, it would develop an aversion to saccharin.
These studies all were done with a 100r whole-body exposure. No systematic studies which combined partial body exposures, multiple exposures, or the novelty of the tastant with the manipulation of the temporal relations of the saccharin and radiation have been done. Furthermore, in the studies which manipulated the CS–US relationship no measures were taken to see how long the aversion lasted. Preliminary studies from this laboratory indicate that if the whole-body irradiation exposure was increased from 100r to 300r, that the irradiation could precede the saccharin by 24 hours or more and still produce saccharin aversion. Considerably more data must be collected before any speculation could be made regarding a time safety factor for radiotherapy patients.

A second approach to prevent radiation-induced taste aversions in cancer radiotherapy patients would be to block the aversive aspect of the radiation exposure. There is some evidence from the animal literature about what the aversive aspects of the radiation exposure are and how to prevent the aversions. Hunt, Carroll, and Kimeldorf (1968) generated strong evidence that the aversive aspect of irradiation which resulted in taste aversion learning was humoral mediated. Their studies with parabiotic pairs of rats (i.e., rats whose blood circulatory systems were surgically connected) showed that if one member of the pair drank saccharin while the partner was being irradiated, the saccharin-drinking rat would subsequently avoid the saccharin. Further, Garcia, Ervin and Koelling (1967) showed that rats that drank saccharin and were injected with serum from irradiated donors developed an aversion to the saccharin. Levy, Ervin, and Garcia (1970) were able to block the contractile response to irradiation in an *in vitro* gut preparation with an injection of chlorpromazine. In our laboratory we conducted behavioral tests to see if the humoral-mediated aversive substance which caused radiation-induced taste aversions was histamine (Levy, Carroll, Smith & Hofer, 1974). We were able to produce an aversion in rats which had tasted saccharin followed by an injection of histamine diphosphate. Rats which had been pretreated with chlorpheniramine, an active H₁ histamine antagonist, failed to develop a radiation-induced taste aversion. Tigan, an effective antihistamine drug, did not block the formation of the radiation-induced taste aversion. Capitalizing on the fact that radiation-induced taste aversion can best be conditioned if the radiation precedes the saccharin drinking by 30–90 minutes, we injected the chlorpheniramine, exposed the rats to cobalt 60 and then gave the animals access to the saccharin until they consumed 10 ml of saccharin-flavored water. This avoided conditioning an aversion to chlorpheniramine; it is not possible to do "backward" conditioning with drug injections. Sessions (1975) and Cairnie and Leach (1982) have criticized this procedure and have failed to block radiation-induced taste aversion with chlorpheniramine when they followed the sequence of saccharin ingestion, chlorpheniramine injection, and irradiation. In both of their studies they produced saccharin aversions to the chlorpheniramine alone, so their failure to block the aversion may merely reflect an aversion to the chlorpheniramine. As Sessions has pointed out (1975), before
the hypothesis that histamine release is responsible for radiation-induced taste aversion conditioning is tenable, the procedures for administration of the antihistamine must be clarified. Levy (1975) has shown stronger saccharin aversion in adrenalectomized rats than in control animals following a weak radiation exposure of 50r whole body. She speculated that adrenalectomized rats were more sensitive to histamine than normal rats. Furthermore, she showed that chlorpheniramine maleate could inhibit formalin-induced taste aversions and again postulated a histamine release as the basis of formalin-induced taste aversions. Needless to say, considerable research is needed with animals before the use of antihistamine is considered for human radiotherapy patients.

We have spent some time in studying the recovery of rats from radiation-induced taste aversion in order to develop ways to hasten the recovery process. In Fig. 5.2 of this chapter an extinction curve for aversion is illustrated based on the median scores for 32 rats. What is not seen here is the tremendous variability among the rats in rates of recovery. As Fig. 5.13 illustrates, a few of the animals recover from the aversion in two or three days (panel A), a few more in five to six days, and a few more in 11 days (panel B). For some the recovery is slower (panel C) and for some there is no recovery (panel D). In fact, the orderly median curve of Fig. 5.2 really reflects "how many rats have recovered by a certain time." Furthermore, when recovery starts, its course is rapid. This led us to speculate that some rats for some reason taste the saccharin and, receiving no bad effects, begin to taste it more and more. We tested this idea of recovery by allowing different groups of rats "saccharin alone" experience for varying times after conditioning to see if this hastened extinction of the aversion (Spector, Smith & Hollander, 1983). Figure 5.14 shows saccharin preference scores for a 24-hour test after conditioning and following a "saccharin alone" experience for 0, 3, 6, 12, 24, and 46 hours. It can be seen from the clear bars in the graph that the longer the saccharin-alone period following conditioning, the less the subsequent aversion. If the rat receives the saccharin alone for 24 hours after conditioning, there is no evidence for subsequent learned taste aversion. The finding is consistent with the idea of Revusky and Garcia (1980) that the one-bottle test creates a conflict situation for the fluid-deprived animal pitting the aversiveness of the saccharin against thirst. It is clear from these data that the profound and long-lasting taste aversion described earlier in this paper is at least in part the result of restricting the rat to a two-bottle preference test. When the rat has the option of drinking saccharin or not drinking at all, it chooses the former alternative and subsequently overcomes the aversion. It may be that human cancer radiotherapy patients, although not forced to ingest a substance they have developed an aversion to, may do so out of force of habit, e.g., the person may without thought sip coffee or eat toast at breakfast the day after radiotherapy even though on the previous day these substances were associated with the adverse consequences of radiotherapy. Discovering that the substance in question (e.g., the coffee or toast) was not followed by any adverse consequences, the person,
FIG. 5.13. In order to show the wide variability in recovering from a radiation-induced taste aversion conditioning, individual saccharin preference scores are plotted as a function of postconditioning test days for 32 rats, which all received identical conditioning treatment, i.e., 10 minutes of saccharin ingestion followed by a 100r whole-body exposure. The nine animals shown in panel A were recovered to normal saccharin drinking by Day 5. The six in panel B were recovered by Day 11 and the 18 rats in panel C showed a much more gradual recovery over the 16 testing days. The five rats in panel D showed no signs of recovery in 16 days.
like our rats, may quickly overcome any aversion that had been developed to the substance. Such a process would help to explain the fact that there appear to be relatively few taste aversions in cancer radiotherapy patients. However, it might be helpful to the radiotherapist to be aware of the possibility of the formation of learned taste aversions in his/her patients, especially in patients treated in the abdominal area, and to consider ways to minimize the aversive conditioning process.

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FURTHER CONSIDERATIONS ABOUT RADIATION-INDUCED TASTE AVersions

Whether one considers the role of radiation-induced taste aversions in cancer radiotherapy or merely addresses the problem as a basic research issue, there are many unresolved questions about the physiological basis of this unconditioned stimulus. Although the histamine hypothesis may be tenable for some levels of irradiation, it is most likely that many other factors are involved at the higher radiation doses. When a rat is given saccharin before a 300r exposure, the resulting aversion to the sweetened solution is much more profound and long lasting than the aversion from the conditioning with 100r exposure. Data for a single rat are presented in Fig. 5.15, where it can be seen that even after 23 days.
FIG. 5.15. Saccharin and water intake on 23 daily preference tests for one rat following a saccharin-300r radiation pairing. Water drinking averaged about 25 ml/day and saccharin drinking never exceeded 3 ml/day, indicating no signs of recovery from aversion.

There are no signs of a return to normal saccharin drinking. In fact, none of the many rats we tested ever drank more than three ml of saccharin during a 24-hour preference test after the 300r exposure. Similar results were obtained with abdominal exposure but not with head exposure as can be seen in Fig. 5.16. It is quite likely that the physiological basis for the aversion from a 300r exposure is qualitatively as well as quantitatively different from the 100r exposure. No attempts have been made yet to block these profound aversions with antihistamines.

Another issue involves several peculiarities about taste aversions with head-only exposures. Although exposure of the head is not a necessary condition for forming a saccharin aversion with radiation exposure, there is evidence that head exposure can be an important and perhaps a facilitating factor in conditioning the aversion, as shown by the following studies.

Dinc and Smith (1966) reported that bilateral ablation of the olfactory bulbs resulted in a reduction of the magnitude of radiation-induced saccharin aversion.

FIG. 5.16. Recovery from aversion (or lack thereof as seen in the abdominal exposed group) when median saccharin preference score is plotted as a function of 19 postconditioning preference test days.
One implication could be that olfaction plays some role in radiation-induced aversions. It is obvious, however, that removal of the olfactory bulbs could have effects other than anosmia. However, Reigel (1968) reported that occlusion of the nasal passages inhibited the formation of the aversion. It is known that rats can detect the presence of ionizing radiation through the olfactory system if the exposure rate is high enough (Dinc & Smith, 1966; Cooper, Kimeldorf & McCarky, 1966), so it is possible that in the whole-body radiation-induced taste aversion experiments, stimulation of the olfactory system abets other physiological reactions resulting in a facilitated aversive response.

Smith, Hollander and Spector (1981) observed a marked difference in the recovery from radiation-induced taste aversions when the head was the target for exposure rather than the abdomen. As with whole-body exposure, the aversion resulting from abdominal exposure became more severe as the radiation exposure was increased. On the other hand, increasing the exposure to the head beyond the threshold level made no difference in the severity of the aversion or in the rat’s recovery to normal drinking. This is illustrated in Fig. 5.17. Here it can be seen

![Graph](FIG. 5.17. Recovery from head-radiation-induced taste aversion; median saccharin preference scores are plotted as a function of post-conditioning test days for the exposure levels indicated.)
that the 100, 200 and 300 r exposures to the head resulted in comparable levels of aversion and comparable courses of recovery. Here again the implication is that some mechanism other than histamine production may be involved in the aversiveness of head-only exposure.

Further evidence for some facilitating role with head exposure was reported by Hunt et al. (1968). They found no saccharin aversion in the shielded partner at either 180 r or 360 r exposures when the irradiated partner of a parabiotic pair had the head shielded. This would make it appear that the radiation-induced taste aversion in the parabiotic rats resulted from causes which are different from those in the single rat treated with a pairing of saccharin and irradiation.

SUMMARY

In this chapter the suggestion has been made that taste aversion conditioning which has been induced in rats following irradiation may serve as a useful model for ascertaining the extent to which such conditioning could occur in human radiotherapy patients. We tested the assumption that some of the human dietary problems associated with cancer may be due to conditioned taste aversions inadvertently formed during the course of radiotherapy. The data presented here strongly suggest that such conditioning is possible in human patients. The data also suggest, however, that although learned taste aversions may contribute to the dietary problems, they do not seem to constitute a major part of the problem. The data also indicate that among the radiotherapy patients, those who are irradiated in the abdominal and pelvic region are more apt to show specific learned taste aversions than patients exposed in other body areas. It might be helpful to the radiotherapist and the oncologist to be aware that such aversions can be learned and that, potentially, steps can be taken to develop procedures to inhibit the radiation-induced conditioning process.

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