Learned Taste Aversions in Children Receiving Chemotherapy

Abstract. *Children with neoplastic diseases were offered an unusual ice cream before their drug treatments. Patients experiencing gastrointestinal toxicity due to the drugs were subsequently less likely to choose that ice cream again than controls. This suggests that taste aversions induced by drug-associated symptoms may contribute to the appetite loss experienced by cancer patients.*

Garcia and others (*1*) have demonstrated the development of specific taste aversions in a wide variety of animal species. In general, these investigators presented a solution to rats prior to administration of a drug or radiation treatment that presumably induced gastrointestinal (GI) discomfort. The animals subsequently developed significant aversions to the flavor of the solution, as indicated by their reluctance to ingest it. Substantial aversions have been achieved in a single trial; these aversions occur even when there are long intervals (6 to 12 hours) (*2*) between exposure to the flavor and onset of illness. Therefore, the acquisition of taste aversions is a persistent form of learning. To our knowledge there have been no controlled studies of such aversions in humans. Several therapies used in the treatment of cancer (certain chemotherapeutic drugs; abdominal radiotherapy) are the same as those used to produce conditioned taste aversions in laboratory animals (*3*). We therefore evaluated patients undergoing such treatments to determine whether similar learned food aversions also occur in humans. Since cancer patients frequently suffer loss of appetite (*4*), the demonstration of such aversions would suggest that food aversions may be one factor contributing to their anorexia. In the present study we investigated whether children receiving GI toxic chemotherapy for the treatment of neoplastic disease would acquire aversions to an unusual ice cream consumed prior to drug treatment.

A total of 41 patients ranging in age from 2 to 16 years participated in the study (*5*). All were being treated as outpatients at the Children's Orthopedic Hospital and Medical Center Hematology Clinic. Patients with advanced or refractory disease were excluded. Patients received intravenous doses of chemotherapeutic drugs, except as noted. Drugs considered significantly toxic to the gastrointestinal tract (GI toxic)—for example, adriamycin, cyclophosphamide, and cytosine arabinoside—are generally associated with a moderate to high degree of nausea or emesis at the doses given patients in this study (*6*). The onset of these symptoms may occur a few minutes to a few hours after drug administration. Vincristine, a chemotherapeutic agent not associated with these symptoms, served as a control drug.

Patients receiving GI toxic chemotherapy were stratified on the basis of age and number of prior GI toxic drug treatments and then randomly assigned to one of two groups: the experimental group (group 1) which received a paired association between an unusual ice cream and GI toxicity; the control group (group 2) which experienced GI toxicity without receiving any ice cream. Patients receiving chemotherapy not associated with GI symptoms (vincristine) or no drug at all, were placed in a second control group (group 3) and received the ice cream without experiencing GI toxicity (*7*). During session 1 children in groups 1 and 3 were given 80 g of the novel ice cream, Mapletoff (prepared with maple and black walnut flavor extracts), 15 to 60 minutes prior to their receiving a drug treatment (or for some patients in group 3 prior to a routine checkup). Children in group 2 were not offered ice cream during session 1 but were occupied for a comparable amount of time with a toy prior to their drug treatment. At this time patients, and their parents, in all groups also filled out diet questionnaires.

Two to four weeks later (session 2) the acceptance (or rejection) of Mapletoff ice cream was measured by offering children in all groups a choice between eating the ice cream or playing with a game.

Results (Table 1) indicate that only 21 percent of patients in group 1 chose Mapletoff ice cream during session 2 compared to 67 percent in group 2 and 73 percent in group 3. The difference between the two proportions obtained when the control groups were combined and compared to group 1 was significant ($z = 3.06$; $P \leq .001$). Therefore, the consumption of the ice cream before GI toxic chemotherapy resulted in a lower likelihood of a subsequent choice of that ice cream again than did the GI toxic therapy alone or the previous sampling of that ice cream without toxic therapy.

It could be argued that a choice between eating the ice cream and engaging in some other activity is not specific enough to offer evidence of an actual taste aversion. We therefore retested all patients that were still coming to the Hematology Clinic, using a blind procedure, by offering them both Mapletoff ice cream and another relatively novel ice cream (Hawaiian Delight: Foremost Ice Cream, Seattle, Washington). During these retests patients were asked to taste both ice cream flavors, indicate which they preferred, and eat as much of each as they wished. Flavor preference and amount consumed were recorded. Although these retests occurred an average of 4½ months after session 1, only 25 percent (3 of 12) of the patients in the experimental group (group 1) said they preferred Mapletoff while 66 percent (4 of 6) in group 2 and 50 percent (4 of 8) in group 3 preferred Mapletoff. For each patient a preference measure based on consumption was calculated by determining the percentage of total ice cream consumed during retest which was Mapletoff. Preference for Mapletoff ice cream in the experimental group was significantly lower than in the control groups (*8*). Total ice cream consumption of the groups did not differ.

Thus aversion to the Mapletoff ice cream appears to be a specific, learned response and not an effect of the GI toxic drugs alone, since group 2 patients were not averse to eating the ice cream. That the Mapletoff ice cream was not distasteful was indicated by the acceptance of it by patients in group 3, who had tasted it before. Therefore, these results demonstrate that humans, like a number of other species, acquire aversions to a novel flavor when it is consumed before a treatment which induces GI discomfort.

Table 1. Choice made by patients during session 2.

Treatment in session 1	Total number of patients	Patients selecting ice cream	
		Number	Percentage
Group 1			
Mapletoff ice cream paired with GI toxicity	14	3	21
Group 2			
GI toxicity alone	12	8	67
Group 3			
Mapletoff ice cream alone	15	11	73

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Prior experience with drug treatment markedly attenuates the formation of conditioned taste aversions in rats (*9*). Our results are interesting in that most of the patients in this study had received many prior treatments that caused GI discomfort (the average number per child was 23). Furthermore, most of the patients were aware that the cause of their nausea and vomiting was their therapy. These factors, however, did not preclude the formation of long-lasting taste aversions, suggesting that humans have a strong propensity to form these aversions.

Further data were obtained through the use of questionnaires, the results of which support and extend these findings. Patients completed diet inventory forms during sessions 1 and 2 to provide information about their food preferences and usual diet, as well as specific foods eaten before drug treatments. These data (*10*) revealed that patients receiving GI toxic chemotherapy were significantly more likely to report avoiding or disliking a specific food eaten before a clinic visit than control (group 3) patients. Thus, learned taste aversions may occur not only to a novel food presented by the experimenter just prior to drug administration, but also to foods in the patients' diets which happen to be eaten up to several hours before treatment. This is consistent with the findings of Garb and Stunkard (*11*) that human subjects report the development of aversions to a wide variety of foods consumed coincidentally before a bout of illness.

The demonstration of taste aversions in children receiving chemotherapy treatments may prove to be of importance to physicians who administer treatments which induce nausea and vomiting. Such aversions may be one of the factors contributing to the anorexia and weight loss seen in patients with cancer. Additional work is needed to delineate the factors controlling the occurrence of these aversions in order to develop methods for minimizing or eliminating them.

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References and Notes

1. J. Garcia, W. G. Hankins, K. W. Rusiniak, *Science* **185**, 824 (1974); D. Kimeldorf, J. Garcia, D. O. Rubadeau, *Radiat. Res.* **12**, 710 (1966); C. R. Gustavson, J. Garcia, W. G. Hankins, K. W. Rusiniak, *Science* **184**, 581 (1974); C. Johnson, R. Beaton, K. Hall, *Physiol. Behav.* **14**, 403 (1975).
2. J. Garcia, F. R. Ervin, R. A. Koelling, *Psychonom. Sci.* **5**, 121 (1966); J. G. Smith and D. L. Roll, *ibid.* **9**, 11 (1967); S. H. Revusky, *J. Comp. Physiol. Psychol.* **65**, 17 (1968).
3. S. H. Revusky and J. Garcia, in *Psychology of Learning and Motivation*, G. Bower and T. T. Spence, Eds. (Academic Press, New York, 1970), vol. 4, pp. 1–77.
4. G. Costa, *Prog. Exp. Tumor Res.* **3**, 321 (1963); W. DeWys, *Cancer Res.* **30**, 2816 (19 → S. D. Morrison, *Physiol. Behav.* **17**, 705 (1976).
5. The diagnoses of the patients in this study were: group 1: lymphoma (4), lymphosarcoma (1), acute lymphocytic leukemia (2), acute myelogenous leukemia (2), Wilms tumor (3), Ewings sarcoma (1), Hodgkins disease (1); group 2: lymphoma (3), acute lymphocytic leukemia (2), Wilms tumor (1), Ewings sarcoma (1), Hodgkins disease (1), osteogenic sarcoma (1), rhabdosarcoma (1), otiosarcoma (1), astrosarcoma (1); group 3: acute lymphocytic leukemia (10), ideopathic thrombocytopenia (3), astrocytoma (1), undifferentiated leukemia (1).
6. L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics* (Macmillan, New York, ed. 5, 1975), pp. 1254–1307.
7. Patients in groups 1 and 2 received one of the following doses of chemotherapeutic agents known to cause significant GI discomfort: (numbers in parentheses indicate the number of patients in groups 1 and 2, respectively, receiving this dose), adriamycin, 20 to 60 mg/m² (2, 4); daunomycin, 45 to 60 mg/m² (0, 2); cyclophosphamide, 500 to 1200 mg/m² (5, 0); cytosine arabinoside, 100 to 150 mg/m² (1, 2); actinomycin D, 316 μg/m² (1, 0); nitrogen mustard, 6 mg/m² (0, 1); procarbazine, 100 mg/m² orally (1, 0); or a combination of GI toxic drugs: adriamycin, 20 to 40 mg/m², plus cytosine arabinoside, 100 mg/m² (3, 1); 5 aza cytidine, 100 mg/m², plus cytosine arabinoside, 75 mg/m² (1, 0); cyclophosphamide, 300 mg/m², plus adriamycin, 60 mg/m² (0, 1); cyclophosphamide, 300 mg/m², plus 5-fluorouracil, 225 mg/m² (0, 1). In addition to the GI toxic drugs, 9 of 14 patients in group 1 and 6 of 12 patients in group 2 received antiemetics; 6 of 14 patients in group 1 and 6 of 12 patients in group 2 received vincristine (1.5 mg/m²). Reports of nausea or emesis, or both, ranging from mild to severe occurred in 11 of 14 patients in group 1 and 8 of 12 patients in group 2. In group 3, 11 patients received vincristine (1.2 to 2.0 mg/m²), 4 patients received no drug treatment. There were no reports of nausea or emesis in this group.
8. A significantly lower percentage of the ice cream consumed by group 1 (experimental) patients was Mapletoff as compared to the combined control groups (Mann-Whitney U test: $P \leq .05$).
9. R. L. Elkins, *Physiol. Psychol.* **2**, 341 (1974); A. J. Goudie, M. Taylor, H. Atherton, *Pharmacol. Biochem. Behav.* **3**, 947 (1975).
10. I. L. Bernstein, in preparation.
11. J. L. Garb and A. J. Stunkard, *Am. J. Psychiatry* **131**, 1204 (1974).
12. I thank M. J. Wallace, J. Hartmann, I. D. Bernstein, R. Chard, and W. A. Bleyer for invaluable assistance in the implementation of this study. Supported by the Diet, Nutrition, and Cancer Program of the National Cancer Institute (CP 65790-68). I also thank R. Bolles and S. Woods for their critical reading of the manuscript.

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Genetic Method for the Preferential Elimination of Females of *Anopheles albimanus*

Abstract. *Recent field experiments demonstrated the possibility of using the sterile male method for the control of* Anopheles albimanus *Wiedemann, the most important vector of human malaria in Central America. Until now there was no practical method for excluding females from the releases of sterile males. A genetic method was developed for the preferential elimination of females during any of the four life stages. This genetic sexing system utilizes propoxur (o-isopropoxyphenyl methylcarbamate) susceptibility as a recessive conditional lethal, a T(Y:2R) translocation, and an In(2R) inversion. The propoxur resistance allele (dominant) was linked to the Y chromosome via a radiation-induced translocation, and genetic recombination was suppressed by inversions. In one of the strains produced, 99.7 percent of the females are eliminated when treated with propoxur, without male loss.*

During an experiment conducted in El Salvador, Lofgren *et al.* (*1*) demonstrated the possibility of using the sterile male method for the control of *Anopheles albimanus*, an important vector of human malaria in Central America. In view of the widespread occurrence of insecticide resistance in this species, the development of this alternate control method is most desirable and appropriate at this time. The success of the sterile male method relies on the efficient distribution of inundative releases of competitive, sterile males into the natural habitat of the target species. Therefore, a sound system must be available for the mass production of sterile males, but since the females of anopheline species are potential malaria vectors, they should be excluded from the releases. Also, if the females could be eliminated during the egg or early larval stages, the mass production of males could be conducted less expensively.

Since currently available methods for elimination of *A. albimanus* females in a mass production process are only 85 to 95 percent effective (unpublished data), we undertook the development of a genetic method for the preferential killing of females. We now describe the synthesis of a female-killing system for use in a mass production facility.

The genetic sexing scheme utilizes propoxur (*o*-isopropoxyphenyl methylcarbamate) susceptibility (pr^s) as a recessive conditional lethal, a T(Y;2R) translocation, and an In(2R) inversion. The locus for propoxur resistance (pr^r), a dominant trait, is on the right arm of chromosome 2, and this allele was linked to the Y chromosome via a radiation-induced translocation. Adult homozygous resistant males (pr^r/pr^r), less than 24 hours old, were irradiated with 1700 R (dose rate 212 R/min) from an x-ray machine operated at 90 kV (peak). These irradiated males were crossed to suscep-

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