The highlight for May is by Dr. Bernard Rabin, Department of Psychology, University of Maryland, Baltimore County in Baltimore, Maryland. In this highlight, Dr. Rabin describes his introduction to taste aversion learning (working on ionizing radiation with Walter Hunt at the Armed Forces Radiobiology Research Institute, AFRRI) and his eventual application of the phenomenon of taste aversion learning to his current interest in the types of radiation encountered during space travel. At the outset of his work at AFRRI, Dr. Rabin's interests were directly related to examining the effects of radiation, and in so doing he and his group used the taste aversion procedure to determine the physiological mediation of some of the effects of radiation as well as possible pharmacological antagonism of these effects. In this early work, Dr. Rabin described the interesting differences between the effects of radiation and other aversion-inducing agents and the differential effects of antiemetics on a number of responses induced by radiation exposure (e.g., vomiting, nausea and taste aversions) that highlighted a dissociation between these various indices of radiation sickness. Subsequent to this work, Dr. Rabin and his collaborators began using the taste aversion baseline to explore and characterize types of radiation other than gamma rays, e.g., high linear energy transfer (LET) types of radiation such as iron-56 and niobium-93. From these investigations, he extended the use of the taste aversion model to not only characterize the aversive effects of exposure to these energy sources but to assess the specific effects (e.g., disruption of dopamine function) that might be induced by such exposure. His most recent work showing that free radical scavengers can ameliorate these specific effects of radiation illustrates even further the utility of the aversion design in an applied behavioral setting. Dr. Rabin's work has been embedded in application throughout his career. His highlight provides an interesting review of his use of a basic behavioral tool to ask important questions with both theoretical implications for aversion learning and clinical implications for radiation exposure.

Taste Aversion Learning as a Tool

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I got into this business rather late in my career. My dissertation research was concerned with the hypothalamic regulation of food intake and my early research at UMBC involved a further exploration of the relationship between lesions of the ventromedial nucleus of the hypothalamus and the development of hyperphagia and obesity. In 1980, I received a National Research Council Associateship to study the effects of radiation on behavior at the Armed Forces Radiobiology Research Institute with Walter Hunt. The primary concern of the Institute was to study the effects of exposure to ionizing radiation on a variety of physiological and behavioral endpoints with the aim of finding treatments that could prevent the debilitating effects of irradiation, particularly nausea and vomiting. The research program that we developed derived from the seminal research of John Garcia (*e.g.*,1978) using taste aversion learning in the rat as a model system for the study of radiation and toxin-induced nausea and vomiting.

Basic Studies of Radiation- and Toxin-Induced Taste Aversion Learning
The initial research program focused on attempts to understand the factors that influenced the acquisition of a CTA and, by extension nausea and vomiting, following exposure to ionizing radiation or other toxic stimuli. There were three interacting components to this research: (1) physiological and neural mechanisms related to radiation-induced CTA learning; (2) evaluation of pharmacological treatments to prevent radiation-induced CTA learning and vomiting; and (3) the interactions between various toxic and non-toxic unconditioned stimuli in producing CTA learning and the relationship with nausea and vomiting.

Our first study was an attempt to replicate an experiment that reported that treating rats with antihistamines could prevent the acquisition of a radiation-induced CTA. We failed to replicate this study (Rabin *et al.*, 1982a). It turned out that the original results showing a radioprotective effect of antihistamines was due to the failure to control for the confounding effects of state-dependent learning (Rabin *et al.*, 1982b). The next study in this series evaluated the effects of treatment with standard antiemetics, prochorperazine, trimethobenzamide or cyclizine, on radiation- and lithium chloride-induced CTA learning. As with the initial experiments, pretreatment with these antiemetics had no effect on CTA learning (Rabin *et al.*, 1983b, c). These studies raised, at least for us, some questions about the role of nausea and emesis in the acquisition of a CTA. The final experiment in this series looked at the effects of the $5HT_3$ receptor antagonist Ondansetron on emesis and taste aversion learning in the ferret. The results showed that Ondansetron prevented vomiting produced by exposure to ionizing but had no effect of the acquisition of a taste aversion. These results further question the use of the conditioned taste aversion as a model system for the study of

vomiting and nausea (Rabin & Hunt, 1990; Rabin & Hunt, 1992).

In contrast to the failure of conventional antiemetics to disrupt radiation-induced CTA learning, we found that making rats tolerant to ethanol was effective in attenuating taste aversion learning (Hunt & Rabin, 1988). Based upon some reports in the clinical literature that alcoholic patients were more resistant to the emetic effects of radio- and chemotherapy, we decided to evaluate whether or not alcohol tolerance would provide similar protection against the acquisition of a radiation-induced CTA. We found that making rats tolerant to alcohol produced a significant shift of the dose-response curve to the right.

The second line of our research involved determining some of possible physiological mechanisms underlying radiation- and toxin-induced CTA learning. Many of these experiments were concerned with evaluating the role of the area postrema in radiation- and toxin-induced CTA learning (Rabin *et al.* 1983a; 1984a,b). As reported by other investigators (*e.g., Ossenkopp, 1983*), our results with rats and cats indicated that an intact area prostrema was necessary for the acquisition, but not the recall, of a CTA produced by exposure to ionizing radiation or other toxic stimuli. An intact area postrema was not necessary for the acquisition of taste aversions produced by amphetamine, which can cross the blood-brain barrier and may therefore involve direct effects on central nervous system mechanisms (Rabin & Hunt, 1989a; 1992b; Hunt *et al.*, 1987). Additional experiments in this series involved working with hypophysectomized or vagotomized rats (Rabin *et al.*, 1983b; 1985; 1987d). Overall, the results of these studies indicated that radiation- or toxin-induced CTA learning did not require that these organs/systems be intact.

The third line of our research involved studying the relationships between various unconditioned stimuli that could be used to produce a CTA and the relationships between the acquisition of a CTA and vomiting. The first series of experiments used a preexposure design to study the relationships between different unconditioned stimuli (Rabin *et al.*, 1987a, b; 1988a). If the underlying mechanisms were the same, preexposing a rat to one unconditioned stimulus should prevent the acquisition of a CTA to a second unconditioned stimulus. The results of these experiments indicated that taste aversions produced by radiation and lithium chloride involved similar mechanisms because preexposing a rat to one unconditioned stimulus did affect the acquisition of a CTA when the other stimulus was administered. In contrast to radiation and lithium chloride, there were no preexposure effects when one of the unconditioned stimuli was amphetamine.

The second series of studies utilized species that were capable of vomiting, such as cats and ferrets. In general the results of these experiments showed that emetic stimuli did produce taste aversion learning, but that is was possible to produce a dissociation between the two (Rabin *et al.*, 1986; Rabin & Hunt, 1992; Rabin & King 1994). Treatments such as 5-HT_3 receptor antagonists that blocked vomiting in ferrets did not prevent the acquisition of a CTA. This finding was consistent with the observation that self-administered drugs can lead to the development of a CTA. Interestingly, despite

blocking unconditioned vomiting these antiemetics did not prevent the occurrence of conditioned vomiting.

Behavioral Toxicity of Different Types of Radiation

A new phase of our research started in 1988 when John Ainsworth invited Walter Hunt, James Joseph and I to test our behavioral and neurochemical endpoints with heavy particles using the particle accelerator at Lawrence Berkeley National Laboratory. Up until that point, our research with radiation involved low linear energy transfer (LET) types of radiation, primarily gamma rays. One way of categorizing radiation is in terms of the amount of energy imparted to tissue: LET. Previous work with physiological endpoints, including carcinogenesis, had shown a greater efficacy with higher LET types of radiation. However, no data was available about whether or nor there would be a similar relationship with behavioral endpoints. We felt that the CTA could be used to provide an initial assessment of the relationship between LET and the effects of irradiation on behavior.

The results of these experiments are shown below. Fig. 1 shows the effectiveness of different types of heavy particles. These figures show that the dose of radiation needed to produce a CTA was a function of the LET of the radiation. In this regard, the behavioral effects of exposure to different types of radiation were similar to the effects of irradiation on physiological endpoints such as carcinogenesis (Rabin *et al.*, 1989b; 1991). Fig. 2 shows a comparison of the behavioral toxicity of heavy particles (iron-56) compared to that of low LET cobalt-60 and fission spectrum neutrons.

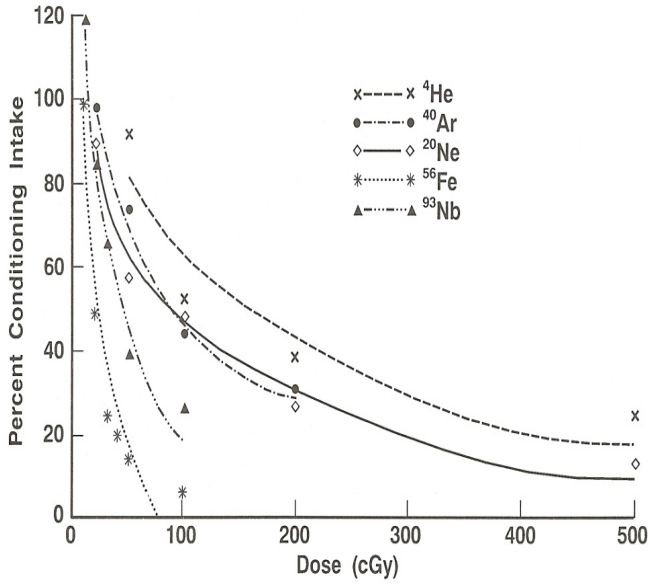


Fig. 1. Taste aversion learning produced by exposure to various heavy particles using a ground-based model for exposure to cosmic rays. Test day intake as a percent conditioning day intake. Of these types of radiation, iron-56 and niobium-93, which have the highest LET are the most effective in producing a CTA. (Rabin *et al., 1989b).*

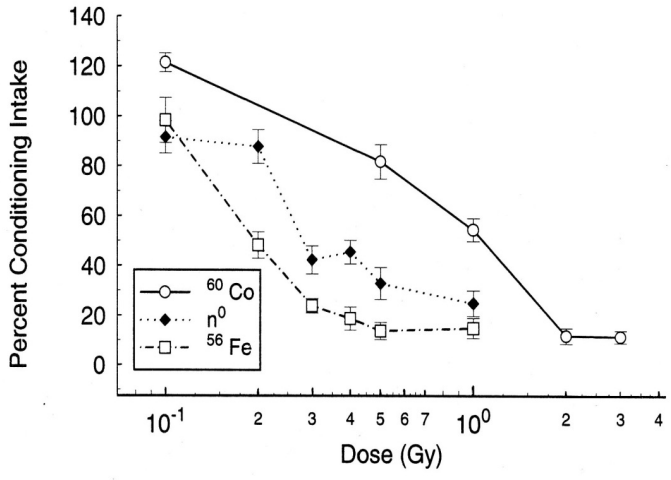


Fig 2. Comparison of the relative biological effectiveness of iron-56, cobalt-60 and fission spectrum neutrons in producing a CTA. Rabin *et al*., 1989b, 1991).

Effects of Exposure to Cosmic Rays on Centrally-Mediated CTA Learning

On exploratory class missions, such as a return to the moon or a voyage to Mars, astronauts will be exposed to types and doses of radiation that are not experienced in low earth orbit where the International Space Station and Space Shuttle operate. In low earth orbit, astronauts are protected against the effect of exposure to cosmic rays by the magnetic field of the earth. Exposing organisms in a particle accelerator provides a ground-based model for exposure to cosmic rays. One of our early findings was that exposure to iron particles (^{56}Fe) disrupted dopaminergic function. This observation suggested that it might be possible to use an amphetamine-induced CTA as a screen for the effects of exposure to heavy particles on a behavior mediated by the dopaminergic system. Previous research had shown that disruption of dopaminergic function by administering the dopamine antagonist haloperidol prevented the acquisition of an amphetamine-induced CTA, but not lithium chloride-induced CTA.

As shown below, a similar effect was observed following exposure to ^{56}Fe particles: irradiation prevented the acquisition of an amphetamine-induced CTA, but not one produced by injection of lithium chloride.

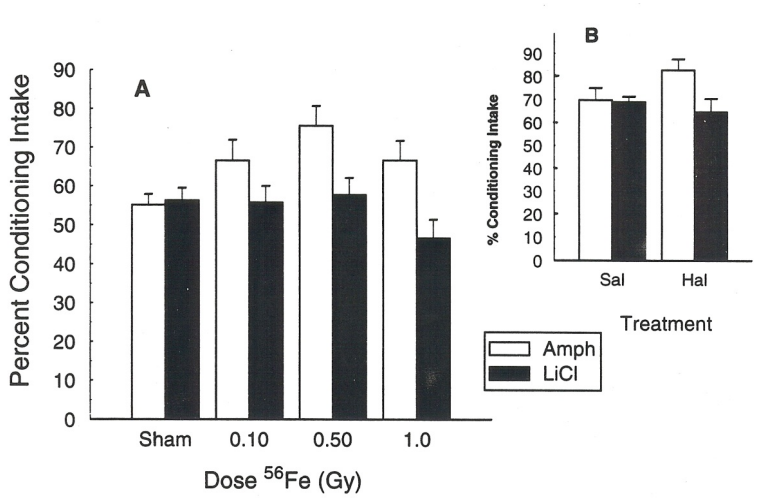
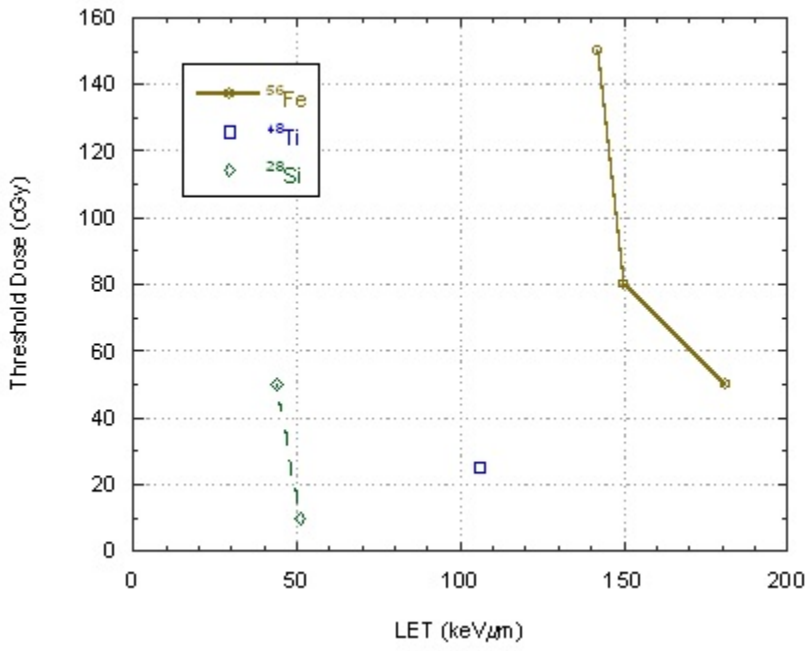


Fig. 3. Effects of exposure to ^{56}Fe particles or injection of haloperidol on the acquisition of an amphetamine-induced CTA. (Rabin *et al.*, 1998).

Following the initial research, additional studies with different energies of ^{56}Fe as well as other heavy ions, including ^{48}Ti and ^{28}Si, were conducted using the amphetamine-induced CTA. These experiments using CTA learning were designed to provide preliminary information on the effectiveness of different particles on a behavior mediated by the central nervous system. This information would then be used to determine a range of probable effective doses for the disruption of cognitive behavior, including operant responding and spatial learning and memory using the Morris water maze.

Fig. 4. Relationship between particle LET and the threshold dose of radiation needed to disrupt the acquisition of an amphetamine-induced CTA. The graph shows that the relationship between LET differs depending on whether the comparison is between different energies of the same particle or between different particles. (Rabin *et al.,* 2007, in press).



As illustrated above, the results with the CTA were not completely expected. What was expected was the observation that for different energies of ^{56}Fe of ^{28}Si particles, the effectiveness of the particle in disrupting the dopamine-mediated CTA paralleled particle LET: the higher the LET the lower the threshold for the disruption of CTA learning. The surprising results were that, compared to the higher LET ^{56}Fe particles, a lower dose was needed to disrupt the acquisition of an amphetamine-induced CTA following exposure to the lower LET ^{48}Ti particles and ^{28}Si particles. Among other things, these results illustrate the utility of the CTA as a screen for the effects of exposure to heavy particles on a behavior mediated by the central nervous system

A final study using amphetamine-induced CTA learning was designed to evaluate the role of free radicals in mediating the effects of exposure to heavy particles. To do this we placed rats on diets containing strawberries and blueberries which can function as free-radical scavengers (Rabin *et al*., 2002). As shown below, both diets were successful in preventing the disruption of the amphetamine- but not the lithium chloride-induced CTA. These results suggest that heavy particle-induced free radical damage plays an important role in mediating the behavioral effects of exposure to ^{56}Fe particles. Based upon this experiment, rats were tested on other neurocognitive tasks. Performance on these tasks were also responsive to the protective effects of diets containing anti-oxidant phytochemicals (Shukitt-Hale *et al.*, in press).

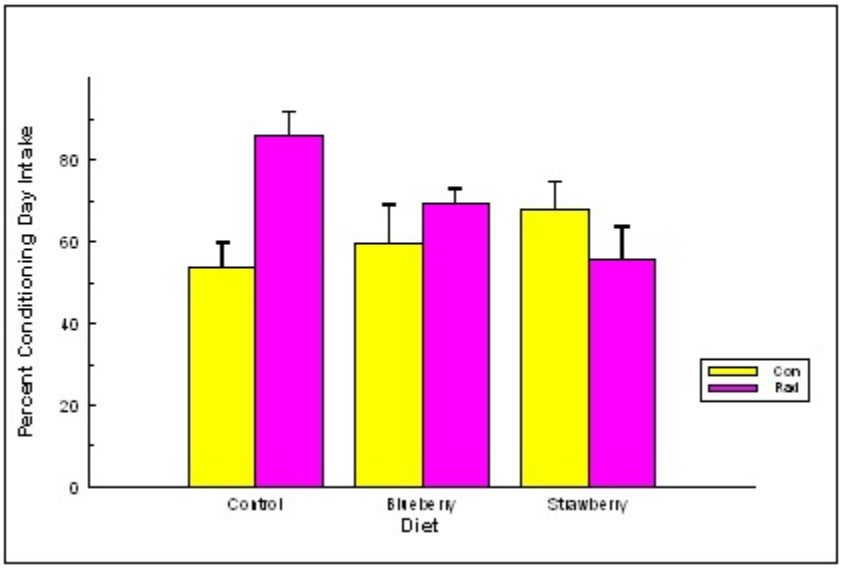


Fig 5. Effects of antioxidant diets (strawberry or blueberry extract) on the radiation-induced disruption of amphetamine-or LiCl-induced CTA learning (Rabin *et al*., 2002).

Coda

The research described in this Highlight shows the versatility and utility of the conditioned taste aversion (avoidance) paradigm. While our initial research was concerned with the CTA for its own sake, over the last ten years we have used the

amphetamine-induced CTA to evaluate the characteristics of cosmic rays and the relationship between heavy particle irradiation and behavior. The amphetamine-induced CTA has proven to be a reliable and useful tool for the analysis of the effects of a variety of manipulations related to the effects of exposure to cosmic rays on dopamine-mediated behaviors.

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