AVERSION CONDITIONING IN RESPONSE TO CANCER AND CANCER TREATMENT

Ilene L. Bernstein

University of Washington

ABSTRACT. Cancer patients appear to be at high risk for the development of conditioned responses that can contribute to the discomfort they experience as a consequence of their treatments as well as their disease. Chemotherapy treatments which induce nausea and vomiting can be associated with the acquisition of aversions to novel and familiar foods. Such treatments can also lead to the conditioning of anticipatory symptoms of nausea and vomiting. The disease itself can lead to the development of food aversions and appetite problems. An understanding of the learning processes underlying the generation of these symptoms can contribute importantly to the development of successful behavioral interventions.

More than 20 years have passed since John Garcia and his colleagues published their original papers characterizing taste aversion conditioning in the rat (Garcia, Ervin, & Koelling, 1966; Garcia & Koelling, 1966). The impact of those findings on conditioning theory continues to be felt by theorists as well as by those interested in the application of conditioning theory to clinical problems. This is due, in part, to a number of features of taste aversion learning which are strikingly dissimilar from more traditional forms of learning (Riley & Tuck, 1985; Barker, Best, & Domjan, 1977). These unusual features include its rapid acquisition, its tolerance of a long delay between conditioned stimulus and unconditioned stimulus and the tendency for particular classes of stimuli, such as taste and gastrointestinal signals, to be more readily associated with each other. It has proven challenging for learning theorists to incorporate these features into their analysis of basic learning processes. One valuable product of the revolution begun by Garcia's brief experimental reports has been the promotion of serious consid--

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Correspondence should be addressed to Ilene L. Bernstein, Department of Psychology, NI-25, University of Washington, Seattle, WA 98195.
eration of evolutionary constraints on what is learned and how it is learned (e.g., Seligman & Hager, 1972; Bülles, 1970; Rozin & Kalat, 1971).

The work on taste aversion learning has had other important consequences. The evident potency of this learning led investigators to consider the clinical utility of this phenomenon. Aversion therapy for alcoholism and smoking cessation are examples of clinical applications of CTA work (Wiens, Montague, Manaugh, & English, 1976; Wiens & Menustik, 1983). Knowledge about the strength and ease of acquisition of conditioned taste aversions alerted us to situations where such learning may be an inadvertent consequence of particular stimulus exposures. For example, many of the therapies used in the treatment of cancer, including drugs and radiation therapy, are known, from animal studies, to be effective unconditioned stimuli in the acquisition of learned taste aversions. Thus, patients with cancer appear to be at high risk for the development of learned food aversions. Studies will be reviewed here which were aimed at assessing the incidence of learned food aversions in cancer patients receiving chemotherapy and developing effective clinical interventions. In addition to the effects of chemotherapy on food aversions, animal studies will be described which indicate that tumor growth alone, in the absence of any therapy, can lead to the development of significant aversions to the available food and that these aversions can contribute to the anorexia displayed by tumor-bearing animals (Bernstein & Sigmundi, 1980). Finally, another type of conditioning known as pretreatment nausea and vomiting will be discussed. These are symptoms experienced by cancer patients in anticipation of chemotherapy treatments, triggered by the situational cues associated with prior treatments (Carey & Burish, 1988).

**LEARNED FOOD AVERSIONS AND CHEMOTHERAPY**

Our initial work in this area examined learned taste aversions in pediatric cancer patients receiving chemotherapy (Bernstein, 1978). We asked whether children receiving drugs which were associated with nausea and vomiting would acquire aversions to a novel ice cream consumed before their drug treatments. We found that children who consumed the ice cream before receiving gastrointestinally (GI)-toxic chemotherapy were much less willing to eat that ice cream again some weeks later than were children in control groups who had either been exposed to the ice cream or the drug treatments but not both. Thus, children avoided eating a food which previously had been associated with GI-toxic chemotherapy. Similar results were obtained with adult patients (Bernstein & Webster, 1980). These findings clearly indicated that human subjects could acquire learned taste aversions in a single trial when consumption of food was followed by nausea and vomiting. Aversion learning occurred in spite of the fact that most subjects had a thorough understanding that the cause of their symptoms was the drugs and not something they ate. This observation implies that food aversion learning in humans is a rather basic conditioning process which occurs independent of cognition or reasoning.

The demonstration that cancer patients readily acquired aversions to a novel food consumed before their treatments suggested that they were at risk for developing aversions to foods in their normal diet. The development of such aversions would likely worsen any appetite problems experienced by these patients. Questionnaires and interviews have been utilized to evaluate the incidence
of learned food aversions to normal diet items associated with cancer chemotherapy. A significant incidence of aversions to familiar foods in patients' routine diets has been reported in pediatric (Bernstein, Webster, & Bernstein, 1982) and adult (Mattes, Arnold, & Boraas, 1987a) patients. Aversions were evident even when foods were eaten up to several hours before treatment. Because cancer patients receive many such treatments, opportunities for the development of aversions are frequent and these aversions may be a significant etiologic factor in the common reports of capricious and frustrating changes in food preferences experienced by these patients (Nielsen, Theologides, & Vickers, 1980).

TARGETS OF AVERSIONS

To assess the potential impact of learned food aversions on the nutritional status of cancer patients, it is useful to consider whether some types of foods are more likely to be the targets of food aversions than others. Early questionnaire results suggested that chemotherapy-induced aversions frequently appeared to be directed at foods which were protein sources (eggs, cheese, meat) while aversions to carbohydrates were infrequent. This observation was based on a small number of subjects and its reliability and generality were difficult to assess. To examine the generality of this finding, a large group of normal human subjects (i.e., college undergraduates) were surveyed for spontaneously occurring food aversions. The targets of these aversions were identified and classified into general food categories. A prominent category for human aversions proved to be foods which were protein sources, with aversions arising significantly more often than would be expected by chance (Midkiff & Bernstein, 1985).

Additional support for the prevalence of proteins as targets for learned aversions comes from a series of studies with rats. Rats were allowed to self-select from separate protein and carbohydrate macronutrient sources during a sequence of GI-toxic chemotherapy treatments (Bernstein, Goehler, & Fenner, 1984). Significant aversions to the protein but not the carbohydrate source were displayed in a number of studies that varied the composition of protein and carbohydrate diets. Thus, the tendency to associate proteins with drug-induced illness more readily than carbohydrates is not limited to humans. Subsequent studies examined the question of whether the salience of proteins was based on flavor or postingestional properties (Brot, Braget, & Bernstein, 1987). We were able to exclude postingestional events as necessary for the salience of proteins in this conditioning. In contrast, we found that the presence of a strong odor, as well as a taste, may be important in making a food a potent target for aversion conditioning. Thus, proteins as well as other foods, such as chocolate and coffee, may frequently become the targets for aversions because of these flavor properties.

INTERVENTION STRATEGIES

Our approaches to the prevention of chemotherapy-induced food aversions come from animal research and from clinical intervention trials. A suggestion derived from the learning literature is that a novel taste, interposed between a pretreatment meal and drug administration, could interfere with the development of aversions to nutritious items in the meal by acting as a scapegoat (Bernstein,
Vitiello, & Sigmundi, 1980). We investigated this possibility in a study with pediatric cancer patients receiving chemotherapy treatments (Broberg & Bernstein, 1987). Candy (coconut or root beer Lifesavers) was used as a scapegoat and given between the consumption of a meal and the administration of chemotherapy to determine whether this would lead to a greater willingness to consume items in that meal at a future test. Scapegoat exposure was found to have a significant protective effect; children were twice as likely to eat some portion of their test meal at the time of assessment if they had received the scapegoat during conditioning than if there had been no intervention. Thus, the consumption of strongly flavored candies before chemotherapy appears to be a simple and effective way to reduce the impact of chemotherapy on preference for normal menu items. In a similar study with adults, patients forming aversions to a scapegoat drink showed a much lower incidence of diet aversions than patients not exposed to the scapegoat (Mattes, Arnold & Boraas, 1987b). The success of these intervention studies supports the application of learning principles to the solution of problems in health-related fields.

**LEARNED FOOD AVersions AND TUMORS**

We have evidence that the impact of learned food aversions on cancer patients may not be limited to aversions which arise in conjunction with chemotherapy. In rat studies, we investigated whether learned food aversions arise in response to the association of a diet with aversive physiological effects of the tumor itself. In such conditioning, the unconditioned stimulus would be some chronic symptom of tumor growth rather than the acute effects of a drug injection. Anorexic, tumor-bearing rats were found to have developed a profound aversion for the specific diet they had been eating during the period of tumor growth. Furthermore, when an alternate diet was available during the preference test, immediate elevations of food intake were seen in tumor-bearing animals, such that their anorectic symptoms were markedly alleviated. These findings indicate that tumor-induced appetite loss is due, at least in part, to the development of learned aversions to the available food. We next investigated whether elevations in food intake, as observed during the preference test, would be sustained if we continued to provide new foods to these rats (Bernstein, Treneer, Goehler, & Murowchick, 1985). We found that frequent changes in the diet available to tumor-bearing rats led to a significantly greater intake of those foods than when a single, initially highly palatable food was available for the entire observation period. These results indicate that when learned food aversions were prevented, or aversive foods were replaced by new, nonaversive ones, the impact of aversion conditioning on food intake of tumor-bearing animals was minimized.

The learning implicated in these studies with tumor-bearing animals is rather unusual because it appears to lack any explicit temporal association between CS and UCS. That is, the food is available continuously and the growing tumor apparently provides a chronic source of aversive symptoms. We have considered whether there might be mechanisms that could introduce temporal pairing. For example, because exposure to the CS (taste) is temporally associated with meals, it is possible that discomfort arises or intensifies in tumor-bearing animals after meals. Such a relationship could generate an associative relationship between CS and US which would be more likely to promote strong conditioning.
The experimental observation that significant food aversions arise as a consequence of tumor growth and that these aversions contribute to appetite and weight loss has yet to be extended to clinical studies with cancer patients (Bernstein & Borson, 1986). Our demonstration of food aversion acquisition in pediatric and adult cancer patients receiving chemotherapy clearly establishes that humans are susceptible to the development of such aversions. The direct demonstration of disease-associated food aversions in cancer patients would be useful. However, the chronic nature of the illness and the fact that the clinical problem is characterized by considerable heterogeneity makes this a difficult approach. In clinical situations where food aversion learning is likely to be involved, findings from the animal laboratory may point the way toward effective treatments. For example, the observation that a varied diet may alleviate symptoms of anorexia suggests straightforward clinical interventions. If future laboratory studies are successful in identifying specific physiological mechanisms involved in tumor-induced aversions and anorexia, it may be possible to develop interventions which are directed specifically at normalizing these changes.

**PRETREATMENT NAUSEA AND CANCER CHEMOTHERAPY**

In addition to the usual side effects of cancer chemotherapy, some patients experience symptoms of nausea and vomiting in anticipation of pharmacological treatments (Carey & Burish, 1988). These symptoms, which can be quite severe, have been referred to as *pretreatment nausea and vomiting*. Reported prevalence rates vary, but generally range from about 20 to 40% of patients undergoing cancer chemotherapy (Morrow & Dobkin, 1988). A number of studies indicate that heightened anxiety is associated with increased risk of developing anticipatory symptoms (Carey & Burish, 1988; Morrow & Dobkin, 1988).

Careful analyses of the variables associated with the development of *pretreatment nausea and vomiting* have led most researchers to conclude that these symptoms are acquired through a classical conditioning process in which environmental cues become associated with drug delivery and later act to trigger responses similar to those which are elicited by the drugs (Carey & Burish, 1988; Morrow & Morrell, 1982; Nesse, Carli, Curtis, & Kleinman, 1980). For example, the probability of developing anticipatory symptoms increases with number of chemotherapy treatments as well as with the severity of posttreatment symptoms of nausea and vomiting (Andrykowski et al., 1988; Andrykowski, Redd, & Hatfield, 1985; Morrow & Dobkin, 1988). The occurrence of posttreatment nausea appears necessary for the development of anticipatory symptoms (Andrykowski et al., 1988).

*Pretreatment nausea and vomiting* represent a striking clinical example of the conditioning of drug-induced physiological reactions, similar to those reviewed by Eikelboom and Stewart (1982). As they discussed, conditioned drug responses may be either similar, in form, to those induced by the drug itself or be compensatory. When conditioned responses are compensatory or opposite from the effects of the drug, they may contribute to the appearance of drug tolerance (Siegel, 1979). Unfortunately, the conditioned drug responses which have been observed in cancer patients are similar to the direct effects of these drugs and clearly act to exacerbate drug side effects. It is intriguing to speculate about whether it might be possible to identify factors responsible for the *direction* of conditioned responses
and eventually develop interventions which could reverse the direction of these responses, and contribute to the development of tolerance.

On a more practical note, a variety of existing treatment methods have been used to significantly reduce the incidence of anticipatory nausea and vomiting symptoms. Controlled studies have evaluated the effectiveness of hypnosis, progressive muscle relaxation training with guided imagery, systematic desensitization, distraction and biofeedback, with generally positive results (Carey & Burish, 1988). Different mechanisms have been proposed to explain the efficacy of these treatment modalities. It has been suggested that a critical feature of most successful interventions is anxiety reduction (or a relaxation response) which is thought to reduce aversive conditioning. Alternatively, counterconditioning and distraction have been suggested as important to the success of psychological interventions. Although there is general agreement that a variety of treatment approaches can successfully alleviate many of the aversive symptoms associated with chemotherapy, there is less agreement regarding their mechanism of action (Carey & Burish, 1988; Morrow & Dobkin, 1988).

CONCLUSION

The work reviewed here addresses the way in which conditioned responses contribute to the problems experienced by cancer patients as a consequence of their treatments as well as their disease. By understanding that a learning process plays a role in generating symptoms of appetite loss, as well as nausea and vomiting, it has been possible to begin to develop successful behavioral intervention approaches. Considerable work remains, particularly in the area of tumor-induced appetite loss, where an extension of animal observations to the clinical situation has yet to be accomplished. However, the application of conditioning principles to the problems of cancer patients would appear to provide an excellent model for approaching other clinical problems.

REFERENCES


