INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI®
Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600
VALIDATING CONDITIONED ANTISICKNESS THEORY:
THE EXPLANATION FOR THE AVERTION FAILURE PHENOMENON
AND THE BASIS OF A CLINICAL NONDRUG CONDITIONING STRATEGY
FOR THE ALLEVIATION OF NAUSEA AND EMESIS

by

Valerie Anne Davey, M. Sc.

A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy
Graduate Department of Psychology
University of Toronto

© Valerie A. Davey, 1999
The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author’s permission.

L’auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

L’auteur conserve la propriété du droit d’auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.
TO GERRY

SINE QUO NON
VALIDATING CONDITIONED ANTISICKNESS THEORY:
THE EXPLANATION FOR THE AVERSION FAILURE PHENOMENON
AND THE BASIS OF A CLINICAL NONDRUG CONDITIONING STRATEGY
FOR THE ALLEVIATION OF NAUSEA AND EMESIS

Doctor of Philosophy, 1999

Valerie Anne Davey

Department of Psychology

University of Toronto

Abstract

Many species learn an aversion to a novel taste if made sick within hours of consumption. Most drugs induce such conditioned taste aversions (CTAs) and are therefore supposed to produce nausea or sickness, but such drugs are variably effective at optimal doses. By traditional Pavlovian conditioning principles, it should be possible in theory to increase the effectiveness of a drug that induces a mild CTA by first pairing it with a more effective drug that induces a strong CTA. In Pavlovian terminology, if a conditioned stimulus (CS) drug such as pentobarbital—known to induce weak CTAs—is paired with an unconditioned stimulus (US) drug such as lithium—known to induce strong CTAs—on several occasions, the CS drug should come to induce stronger CTAs in a subsequent procedure than would otherwise be expected. The CS drug should produce conditioned sickness in addition to its unconditioned effect. Contrary to
expectation, however, the surprising finding is that the prior drug–drug pairings eliminate or reduce the ability of the CS drug to induce a CTA.

One possible account of this aversion failure (avfail) phenomenon hinges on selective association of an internal drug state CS with a hypothetical homeostatic or antisickness aftereffect of sickness. According to conditioned antisickness (CAS) theory, drug states model naturally occurring sequences of internal states. The CS drug corresponds to naturally occurring internal signals, the US drug to naturally occurring aftereffects, and conditioning enables the animal to better regulate its internal environment by anticipating the US. Drug–drug conditioning provides a general model for the involvement of Pavlovian conditioning in homeostatic regulation.

The drug–drug pairings methodology has made CAS theory difficult to validate because nonindependence of the two drug states invites a pharmacological drug interaction alternative to a conditioning interpretation. The joint presence of particular CS and US drugs in the experimental group but not in Pavlovian controls could produce unique pharmacological effects that somehow mimic avfail. This sort of alternative was ruled out by successfully substituting the nondrug events of rotational stimulation (Experiment 1) or an increase in ambient temperature (Experiment 2) for a drug CS in the avfail procedure in rats. Demonstrating avfail in the absence of any drug–drug pairings makes a Pavlovian conditioning interpretation more convincing and further warrants examination of the key theoretical question: Is avfail due to CAS?

In an indirect test of CAS theory, Lett (1992) paired drug or place cues with
lithium and found that rats with an experimental or forward pairings history ate less food on test, consistent with a traditional conditioned sickness account rather than with CAS. But rats eat dirt or clay in response to sickness and adaptively eat small amounts of food when clay is not available: Paradoxically, perhaps rats with a forward pairings history ate less food than controls because they were less rather than more sick. Experiment 3 substituted clay (kaolin) for food and found that rats with a forward pairings history ate less kaolin, consistent with CAS. The empirical evidence is thus largely consistent with CAS but all previous studies are indirect tests of CAS—in the sense that nausea or sickness must be inferred from changes in consummatory behavior in the rat, a nonvomiting species—and as such are subject to misinterpretation. In the first direct test with a vomiting species, Experiment 4 found that ferrets with a forward pairings history had fewer and shorter bouts of retching and vomiting whether induced by lithium or by the highly emetogenic anticancer drug cisplatin. These findings provide strong support for CAS theory and suggest the basis for a nondrug conditioning countermeasure to severe nausea in clinical settings.
I am grateful for the insightful and acute analysis that Professor Constantine X. Poulos generously provided. Professor Poulos shared his research talents and gave excellent advice and encouragement at each stage in the design and execution of this research. I have also learned much from his truly distinguished research efforts, and he has my thanks for his participation and for the opportunity to work with him.

My sincere thanks go also to Professor Colin M. MacLeod for bringing the breadth of his knowledge and distinguished research experience to this area and for providing me with a refreshingly different and valuable perspective on my work. His unstinting and insightful commentary were very much appreciated and clearly made a significant contribution both to the thesis and to my own thinking.

I am indebted to Professor Jonathan L. Freedman, Director of Graduate Studies for the Department of Psychology, who provided much-needed support and advice. His efforts on my behalf are very much appreciated as are his understanding and kindnesses. He has provided a clear model for me in my future dealings with students.

Words cannot express my gratitude for the patience, knowledge, wisdom, and support of my supervisor, Professor Gerald B. Biederman, to whom this work is dedicated.

The following published papers are included as part of the dissertation with written authorizations appended:


Thanks to David Feld and Dina Franchi for their able assistance in data collection and to Faulding (Canada), Vaudreuil, Québec J7V 5V5 for generously donating the cisplatin.
Learning Laboratory
Division of Life Sciences
University of Toronto at Scarborough
1365 Military Trail
Scarborough, Ontario
M1C 1A4 Canada

Tel (416) 287-7434
Fax (416) 287-7842
e-mail davey@scar.toronto.ca

June 23, 1998

Ms. Karen Thomas
Permissions Office
American Psychological Association
750 First Street NE
Washington, DC USA
20002-4242

FAX 202 336 6549

Dear Ms. Thomas:

I request permission to include the following published works as part of my doctoral dissertation:


I would appreciate your facsimile permission to me at the number above.
My co-author and sponsor is also signing this request to indicate his agreement for this material to appear in my thesis.

Sincerely yours,

V. A. Davey, M.Sc.
Doctoral Candidate

G. B. Biederman, Ph.D.
Professor

APA permission granted without fee for author’s reuse of own material as outlined in this request. Please provide full bibliographic citation and the following notice:
Copyright 19_—by the American Psychological Association.
Reprinted (or Adapted) by permission of the publisher.

Karen a. Thames, 7-8-98
Permissions Office
American Psychological Association
September 14, 1998

Valerie A. Davey
Fax No.: 416-287-7642

Dear Ms. Davey:

Thank you for your request to use material from your work published in an Academic Press publication.

It is now the policy of Academic Press that authors need not obtain permission in the following cases: (1) to use their original figures or tables in their future works; (2) to make copies of their papers for their classroom teaching; and (3) to include their papers as part of their dissertations. Of course, citation to the original source should be included.

Sincerely,

Cindy MacDonald
Editorial Manager
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>ii</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>v</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>ix</td>
</tr>
<tr>
<td>List of Tables</td>
<td>xii</td>
</tr>
<tr>
<td>List of Figures</td>
<td>xiii</td>
</tr>
<tr>
<td>List of Appendices</td>
<td>xvi</td>
</tr>
<tr>
<td><strong>CHAPTER 1: HISTORICAL BACKGROUND</strong></td>
<td>1</td>
</tr>
<tr>
<td>1.1 Conditioned Taste Aversion (CTA) and Selective Association</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Discovery of the Aversion Failure (Avfail) Phenomenon</td>
<td>5</td>
</tr>
<tr>
<td>1.3 Conditioned Antisickness (CAS) Explanation of Avfail</td>
<td>11</td>
</tr>
<tr>
<td>1.4 Associative Blocking Explanation of Avfail</td>
<td>16</td>
</tr>
<tr>
<td>1.5 Conditioned Inhibition Explanation of Avfail</td>
<td>22</td>
</tr>
<tr>
<td>1.6 Occasion Setting Explanation of Avfail</td>
<td>24</td>
</tr>
<tr>
<td>1.7 Validating CAS Theory: Pharmacological Controls</td>
<td>27</td>
</tr>
<tr>
<td>1.8 Validating CAS Theory: Simple Conditioning Procedures</td>
<td>29</td>
</tr>
<tr>
<td>1.9 Validating CAS Theory: Selective Association, Response Competition, and Positive Transfer</td>
<td>34</td>
</tr>
<tr>
<td>1.10 Statement of Purpose</td>
<td>36</td>
</tr>
<tr>
<td><strong>CHAPTER 2: ANTISICKNESS CONDITIONING USING ROTATION AND HEAT AS NONDRUG STIMULUS EVENTS</strong></td>
<td>41</td>
</tr>
<tr>
<td>2.1 Experiment 1: Rotational Stimulation as an Avfail CS</td>
<td>50</td>
</tr>
<tr>
<td>Page</td>
<td>Section</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>A1-4</td>
<td>Experiment D: Heat Dose Effects</td>
</tr>
<tr>
<td>A1-5</td>
<td>General Discussion</td>
</tr>
</tbody>
</table>

**APPENDIX 2: HEAT-INDUCED TASTE AVERSIONS: THE ROLE OF TASTE INTENSITY AND PREEXPOSURE**

| A2-1 | Experiment E-1 and E-2: The Role of Taste Intensity at 35°C and 38°C | 145 |
| A2-2 | Experiment F: The Role of Taste Preexposure                       | 154 |
| A2-3 | General Discussion                                                 | 159 |

**APPENDIX 3: HEAT-INDUCED TASTE AVERSIONS: UNCONDITIONED EFFECTS, MEMORIAL PROCESSES, AND THE ATTENUATION OF NEOPHOBIA**

| A3-1 | Experiment G: State Dependency Design with Heat                   | 165 |
| A3-2 | Experiment H: State Dependency Design with Pentobarbital         | 169 |
| A3-3 | Experiment I: State Dependency Design with Footshock             | 174 |
| A3-4 | General Discussion                                                | 176 |

References                                                                 | 178 |
List of Tables

Table 1  Outline of the typical aversion failure (avfail) procedure ............ 10
Table 2  Group mean cumulative kaolin consumption for each 
measurement interval on the baseline and forward test 
trials of Experiment 3 ............................................ 79
Table 3  Characteristics of lithium-induced emesis for individual 
ferrets on test, Experiment 4 ..................................... 92
Table 4  Characteristics of cisplatin-induced emesis for individual 
ferrets on test, Experiment 4 ..................................... 95
Table 5  Apple juice consumption in a retroactive state dependency 
(2 x 2) design using 38 °C heat exposure, Experiment G ......... 168
Table 6  Apple juice consumption in a retroactive state dependency 
(2 x 2) design using pentobarbital, Experiment H .............. 173
Table 7  Apple juice consumption in a taste aversion conditioning 
design using pentobarbital, Experiment H ........................ 175
List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Unadjusted saccharin acceptance scores across saccharin conditioning days in an avfail procedure using a rotational avfail CS, Experiment 1</td>
<td>55</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Unadjusted saccharin acceptance scores across saccharin conditioning days in an avfail procedure using a heat avfail CS, Experiment 2</td>
<td>69</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Mean number of sickness events in ferrets as a function of number of pairings of observation box cues with lithium sickness during the place pairings phase of Experiment 4</td>
<td>90</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Mean number of episodes of emesis on lithium test as a function of time from the lithium injection for ferrets with histories of forward and control arrangements of pentobarbital and lithium, Experiment 4</td>
<td>94</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Mean number of episodes of emesis on cisplatin test as a function of time from the cisplatin injection for ferrets with histories of forward and control arrangements of pentobarbital and lithium, Experiment 4</td>
<td>97</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion procedure using heat as the nausea-inducing US, Experiment A</td>
<td>124</td>
</tr>
</tbody>
</table>
Figure 7 Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion procedure using heat as the US and with or without a context change correlated with heat exposure, Experiment B ........................................ 129

Figure 8 Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion procedure using heat as the US and with gradual or abrupt heat exposure, Experiment C ........................................ 134

Figure 9 Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion procedure using heat as the US in an unheated baseline group and in low (32 °C), medium (35 °C), and high (38 °C) temperature forward pairings groups, Experiment D ..................... 138

Figure 10 Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion procedure with 0.10% saccharin solution as the CS and 35 °C heat exposure as the US, Experiment E-1 ........................................ 150

Figure 11 Saccharin acceptance scores across saccharin conditioning days with 0.10% saccharin solution as the CS and 38 °C heat exposure as the US, Experiment E-2 ..................... 153
Figure 12  Saccharin acceptance scores across saccharin preexposure and conditioning days with 0.75% saccharin solution as the CS and 38°C heat exposure as the US, Experiment F  . . . . . . . . . 157
List of Appendices

Appendix 1  Taste aversion conditioning with heat as the US .............. 119
Appendix 2  Heat-induced taste aversions: The role of taste intensity and preexposure ........................................ 143
Appendix 3  Heat-induced taste aversions: Unconditioned effects, memorial processes, and the attenuation of neophobia ......................... 162
CHAPTER 1
HISTORICAL BACKGROUND
Conditioned Taste Aversion (CTA) and Selective Association

Learning has been characterized as a generalized biological process that bestows adaptive advantage by allowing animals to adjust to causal relations between events through individual experience (e.g., Revusky, 1977b, 1984; cf. G. Davey, 1989, pp. 172-190). Various parameters of learning permit valid inferences and focus the learning process on what is biologically important for the animal to know. Among the parameters are predispositions toward selective association between particular classes of events. If events A and B both precede X and Y, A may become more strongly associated with X than with Y, whereas the opposite may occur for B. In the classic demonstration of selective association (Garcia & Koelling, 1966), thirsty rats were given access to a sweet-tasting solution, with licks of solution producing a flashing light and clicking sound ("bright, noisy, and tasty water"). Nausea or sickness (from lithium chloride injection or X-irradiation) and pain (from footshock) were made contingent on fluid consumption for different groups. When subsequently given separate access to "bright, noisy water" and "tasty water," rats that had been poisoned refused to drink tasty but not bright, noisy water, whereas rats that had been shocked refused to drink bright, noisy but not tasty water: The taste cue was preferentially associated with the sickness consequence, whereas the visual and auditory cues were preferentially associated with the pain consequence, of drinking.

Characteristic of the selective association of tastes with sickness is its
occurrence over delays of many hours, often after only a single pairing of the events (Revusky & Garcia, 1970). Such selectivity is presumably required if the animal is to form an association between these two particular events from a potentially much larger number of events that occur during the delay (Revusky, 1971, 1977b). Some investigators consider selective association to be the equivalent of innate knowledge about the sorts of event classes likely to be causally related (e.g., Garcia, Hankins, & Rusiniak, 1974; Revusky, 1984; cf. Bolles, 1970; Domjan, 1997; Hogan, 1988). For example, an innate predisposition to associate particular foods with the delayed consequences of ingestion presumably evolved because digestion and absorption are slow, thus making selective association relevant for the avoidance of poisons. Of course, events often occur in sequence without being causally related. Selective association also acts to prevent the maladaptive learning of spurious causal relations. The failure to associate environmental cues with gastrointestinal consequences is adaptive because the animal would otherwise avoid the environment in which it became sick, driving itself out of its ecological niche for no good reason (Revusky, 1984).

As a parameter of a generalized learning process, selective association is presumed not to be a specific adaptation peculiar to a particular species or to that species' ecological niche. Rather, the selective association of tastes with sickness, for example, is a phylogenetically primitive adaptation reflecting a pattern of brain organization common to all vertebrates (Garcia, Lasiter, Bermudez-Rattoni, & Deems, 1985). Moreover, the selective association of tastes with sickness is
arguably presumed to be an example of a more ubiquitous process. The conditioned taste aversion (CTA) paradigm considers how learning affects what the animal eats or drinks, but a more general question is how learning affects not only what but when the animal eats or drinks and when it stops a meal or drinking bout. Revusky and Garcia (1970) postulated that the internal stimulus characteristics of hunger, thirst, and satiety become associated with the delayed consequences of ingestion in much the same manner as tastes. They reasoned as follows. The animal eats when hungry and stops eating when satiated partly because the internal consequences of eating while hungry are rewarding whereas the internal consequences of eating while satiated are punishing\(^1\) (i.e., sickening). The selective association of tastes and internal stimulus states such as hunger or thirst with the delayed consequences of ingestion serve to refine an innate regulatory feeding system and can override the system if necessary, as when sweet substances somehow make individual animals sick. This implies a predisposition not only for tastes but also for internal states or cues to become selectively associated with the internal consequences of ingestion.

Revusky, Pohl, and Coombes (1980) described what they considered at the

\(^1\) The seminal 1970 paper by Revusky and Garcia is couched in operant conditioning terms. S. Revusky credits B. F. Skinner for the suggestion during a chance meeting that the CTA phenomenon might better be understood in Pavlovian conditioning terms (S. Revusky, personal communication, March, 1986).
time to be a serious practical difficulty in demonstrating selective association of the internal states of hunger and thirst with the internal consequences of ingestion. Suppose the animal is simply punished for eating while hungry by making it sick. Revusky et al. reasoned that because the animal must eat some particular substance, an aversion will necessarily develop to the taste of the substance, and this will interfere with an association between the internal state and sickness. They proceeded to attempt to demonstrate the associative roles of hunger and thirst with a conditional discrimination procedure of the form AX+, BY+, AY-, BX-, where A and B refer to milk and grape juice flavors, X and Y refer to hunger and thirst deprivation states, and + and - refer to reinforcement (i.e., ingestion contingent lithium sickness) and nonreinforcement. One group of rats was made sick after milk consumption while hungry but was not made sick after milk consumption while thirsty; the same group was made sick after grape juice consumption while thirsty but not after grape juice consumption while hungry. The expectation for this group was a lower relative preference for milk while hungry than while thirsty, and a lower preference for grape juice while thirsty than while hungry. The design as a whole was considerably more sophisticated, but the obtained discrimination was weak at best. Revusky, Coombes, and Pohl (1982a) reasoned that perhaps the incidental conditioning of hunger and thirst states with the aftereffects of ingestion outside of the experimental context interfered with their earlier, deliberate conditioning attempts. To improve upon the procedure, they substituted novel internal drug state cues (provided by pentobarbital and
d-amphetamine injections) for the deprivation states, but again the discrimination was weak at best. Contrary to the hypothesis (cf. Revusky & Garcia, 1970), any association of the drug states with sickness was much weaker than the association of the flavors with sickness.

Perhaps the procedure was too complicated or too artificial. The original motivation for favoring a conditional discrimination procedure over a simple conditioning procedure was to control for the expected interference with an association between deprivation state and sickness produced by an association between taste and sickness. The substitution of drug states for deprivation states by Revusky, Coombes, and Pohl (1982a) invites the alternative strategy of simply eliminating the taste cue altogether. This strategy was first used within an applied research program designed to improve chemical aversion therapy for alcoholism (Voegtlin, 1940; Voegtlin & Lemere, 1942) as detailed below. It was to lead to the discovery of what could prove to be an entirely new kind of selective association with strong theoretical and practical implications.

Discovery of the Aversion Failure (Avfail) Phenomenon

Lithium chloride injection is the most common means of inducing sickness and CTAs, but virtually any drug (and several nondrug treatments) can also be used. Indeed, even low doses of commonly abused psychoactive drugs such as pentobarbital can be used but they are not very effective (for references, see Riley & Baril, 1976; Riley & Clarke, 1977; Riley & Tuck, 1985). According to traditional Pavlovian conditioning principles, however, it should be possible to increase
pentobarbital's effectiveness by first pairing it with a high dose of a more effective
drug such as lithium. Rats should learn an aversion to pentobarbital, much as they
might learn an aversion to a taste paired with lithium, and this should make the
pentobarbital more effective in a subsequent CTA procedure than would otherwise
be expected.²

Different rationales have been offered for investigating this sort of
procedure. Consider first the rationale offered by Revusky, Taukulis, Parker, and
Coombes (1979). These researchers set out to improve chemical aversion therapy
for alcoholism. Chemical aversion therapy pairs alcoholic beverages with
drug-induced sickness in a Pavlovian procedure for the purpose of producing an
aversion to the beverage, but the therapy is not very effective unless the client is
highly motivated to stop drinking. Revusky (1973) had earlier used the close
parallel between the CTA and chemical aversion therapy procedures to suggest
several changes by which the latter might be made more effective (for empirical
findings, see Boland, Mellor, & Revusky, 1978; Pohl, Revusky, & Mellor, 1980;
Revusky & Gorry, 1973; Revusky, Parker, Coombes, & Coombes, 1976; Revusky
² Little is known of the mechanisms by which particular drugs and other
treatments induce CTAs (cf. Gamzu, 1977; Gamzu, Vincent, & Boff, 1985; Garcia
et al., 1985; Grant, 1987; Grigson, 1997; T. Hunt & Amit, 1987; Parker, 1995), and
different models have been proposed. Only the conditioned sickness model
postulates a common mechanism and places the phenomenon within an adaptive
evolutionary framework.

__________________
By the sort of reasoning outlined in the immediately preceding section, for example, perhaps the alcohol state fails to become aversive because the taste competes with and overshadows the alcohol state for association with induced sickness. Because the aversion is to the taste of the beverage rather than to the state of intoxication, a confirmed drinker will "force booze down for the pleasure of intoxication" (Revusky, 1985, p. 251) and this will extinguish the CTA. By this reasoning, eliminating the taste cue in a modification of the standard therapeutic procedure might be an effective strategy for improving chemical aversion therapy by producing an aversion to the alcohol state. Moreover, the modified procedure might be used to treat drug dependencies not involving tastes. With this rationale and using an animal model, Revusky, Taukulis, Parker, and Coombes induced an equivalent to the alcohol state by injecting rats with a low dose of pentobarbital. Alcohol and pentobarbital have similar behavioral effects, and pentobarbital is known to be unusually effective as a discriminative stimulus (Overton, 1964). A high dose of lithium was used to induce sickness. Whether pairings of pentobarbital and lithium produce an aversion to the pentobarbital state was assessed by testing for a change in the pentobarbital's ability to produce an aversion to a novel saccharin taste in a subsequent CTA procedure.

The rationale offered by Cunningham and Linakis (1980) was very different. These investigators independently set out to show that intraperitoneal injection of ethanol produces a taste. Humans report a sweet taste following intravenous
injection of saccharin (Fishberg, Hitzig, & King, 1933), and saccharin injected intravenously or intraperitoneally is effective as a cue in a CTA procedure (Bradley & Mistretta, 1971; Burešova & Bureš, 1977). Substances other than saccharin may have similar properties (cf. Nor, Fox, Metcalfe, & Russell, 1996; Tarr, 1933). Cunningham (1978) had earlier found that whether intraperitoneal ethanol injection retarded, enhanced, or had no effect on extinction of a lithium-induced aversion to an orally ingested taste solution depended on the particular taste of the solution. Different tastes produced different outcomes. Could this interaction between injected ethanol and ingested taste be mediated by an ethanol taste? Cunningham and Linakis later confirmed the existence of such a taste by demonstrating an aversion to the taste of oral ethanol following paired injections of ethanol and lithium. To assess whether properties of ethanol injection other than its taste were entering into association with the lithium, these researchers further tested for a change in the ethanol's ability to condition an aversion to the taste of saccharin.

Revusky, Taukulis, Parker, and Coombes (1979) and Cunningham and Linakis (1980) viewed this sort of procedure, in which a low dose of a psychoactive drug is first paired with more severe toxicosis and is then tested for a change in its ability to condition a taste aversion, as a higher-order conditioning procedure. In Pavlovian terminology, pentobarbital or ethanol serves as a first-order conditioned stimulus (CS1) and is expected by traditional Pavlovian precedents to acquire some of the unconditioned stimulus (US) properties of the lithium through association. A property of lithium is its effectiveness as a reinforcer
in a CTA procedure in which the US is commonly supposed to be the nausea or sickness produced by lithium injection or by some other means (Garcia et al., 1985; Grant, 1987; but cf. Grigson, 1997; T. Hunt & Amit, 1987; Parker, 1995).

Pairings of drug CS and lithium US are expected to increase the ability of the CS drug to reinforce an aversion to a novel taste serving as CS2 in a second-order test (Pavlov, 1927; B. F. Skinner, 1938).

The expected higher-order conditioning does not occur. On the contrary, the surprising finding is that pairings of drug CS and lithium US appear to eliminate or reduce the ability of the CS drug to condition a taste aversion. The procedure typical of the Memorial University laboratory is outlined in Table 1 (see Revusky, 1985). In the first conditioning phase, an experimental or forward pairings group receives pentobarbital followed by lithium with an interinjection interval of 30 minutes. The length of the interval is intended to ensure that pentobarbital is having a substantial internal effect prior to the onset of lithium sickness. A backward pairings control receives the two drugs in reverse temporal order. In the second conditioning phase, brief access to novel saccharin solution is immediately followed by pentobarbital or physiological saline in a CTA test of whether conditioning has occurred in the first phase of the procedure. Rats with a history of forward drug–drug pairings given saccharin followed by pentobarbital typically do not differ from rats with forward or backward histories given saccharin followed by saline. Both groups increase their consumption over exposures as they recover from the intense neophobia produced by the strong-tasting saccharin
### Table 1. Outline of the typical aversion failure (avfail) procedure.

<table>
<thead>
<tr>
<th>Group</th>
<th>Group Name</th>
<th>Drug—Drug Conditioning Phase</th>
<th>Taste Aversion Conditioning Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>experimental</td>
<td>forward</td>
<td>pentobarb—&gt;lithium CS1—&gt;US</td>
<td>saccharin—&gt;pentobarb CS2—&gt;CS1</td>
</tr>
<tr>
<td>control (avfail)</td>
<td>backward</td>
<td>lithium—&gt;pentobarb US—&gt;CS1</td>
<td>saccharin—&gt;pentobarb CS2—&gt;CS1</td>
</tr>
<tr>
<td></td>
<td>unpaired</td>
<td>pentobarb—(24 hr)—&gt;lithium CS1—/—US</td>
<td>saccharin—&gt;pentobarb CS2—&gt;CS1</td>
</tr>
<tr>
<td></td>
<td>CS-only</td>
<td>pentobarb only CS1 alone</td>
<td>saccharin—&gt;pentobarb CS2—&gt;CS1</td>
</tr>
<tr>
<td></td>
<td>US-only</td>
<td>lithium only US alone</td>
<td>saccharin—&gt;pentobarb CS2—&gt;CS1</td>
</tr>
<tr>
<td>control</td>
<td>baseline</td>
<td>pentobarb—&gt;lithium ^a CS1—&gt;US</td>
<td>saccharin only CS2 alone</td>
</tr>
</tbody>
</table>

**Note.** An experimental group receives drug—drug pairings in the first or drug—drug conditioning phase and taste—drug pairings in the second or taste aversion conditioning phase. Avfail controls receive Pavlovian control arrangements of CS and US during the first phase, and a baseline control receives a Pavlovian control arrangement during the second phase. The symbol —> refers to a forward pairing arrangement; —/—> and —(24 hr)—> refer to an unpaired or 24-hr delayed arrangement. Pentobarb is pentobarbital, CS1 is the first-order or drug—drug conditioning CS, and CS2 is the second-order or taste aversion conditioning CS. ^a Backward, CS-only, and US-only treatments have also been used. The different treatments do not affect the results.
solution typically used. The groups given saccharin followed by saline cannot have
developed a CTA because saccharin consumption is not followed by an
appropriate consequence. It therefore appears that the pentobarbital has lost its
ability to condition a saccharin aversion. By comparison, rats with a history of
backward pairings given saccharin followed by pentobarbital show at least a
relative failure to increase consumption over exposures. This diminished recovery
from neophobia is taken as evidence of a mild saccharin aversion. The effect has
been called avfail (aversion failure; Revusky, Taukulis, Parker, & Coombes, 1979,
p. 186). CS- and US-only controls have also been used in the first conditioning
phase. Backward, CS-, and US-only controls have repeatedly been found not to
differ (Martin, 1983; Revusky & Coombes, 1982; Revusky, Coombes, & Pohl,
1982b; Revusky, Taukulis, Parker, & Coombes, 1979; Revusky, Taukulis, & Peddle,
1979). Because backward pairings control for total drug exposure, a backward
control has been the single most commonly used control. In a somewhat different
procedure using ethanol as the CS drug, a long-delayed (i.e., unpaired) control
that receives the two drugs 24 hours apart has also been used successfully
(Cunningham & Linakis, 1980).

Conditioned Antisickness (CAS) Explanation of Avfail

The strong Pavlovian precedents for higher-order conditioning notwithstanding, the
avfail effect is the opposite of that expected. How is it to be explained? In 1983,
Lett proposed a conditioned antisickness (CAS) explanation. The dose of lithium
required to produce avfail is high and might be supposed to trigger substantial
physiological homeostatic adjustments that could then become conditioned to an appropriate cue preceding their occurrence. These putative homeostatic responses are supposed to serve as a Pavlovian unconditioned response (UR): They are collectively labelled "antisickness." When pentobarbital is paired with lithium, it may come to elicit a conditioned response (CR) that is similar to the postulated lithium antisickness UR. The antisickness CR triggered by pentobarbital attenuates the mild sickness that the pentobarbital would otherwise produce and thereby precludes the conditioning of a taste aversion on test.

Lithium-paired taste CSs thus come to elicit conditioned sickness (for references, see Riley & Baril, 1976; Riley & Clarke, 1977; Riley & Tuck, 1985), but lithium-paired drug state CSs are supposed to come to elicit conditioned antisickness. How is it that tastes and certain drug states can be supposed to promote such different outcomes when one or the other precedes sickness? CAS theory has sometimes been considered an extension of Siegel's (e.g., 1983) Pavlovian model of drug tolerance in which drug compensatory responses are conditioned to external cues such as those provided by the injection procedure (e.g., Lett, 1983; Taukulis, 1982; cf. Revusky, 1985; Taukulis & Brake, 1989). But the two theories are actually quite different. The direction of the CR elicited by external cues that accompany drug administration is determined by the US drug. In an early and highly influential model of the conditioning of physiological responses, for example, Eikelboom and Stewart (1983) argued that traditional stimulus substitution theory (Pavlov, 1927) can account for conditioned drug
tolerance and sensitization if the observed drug effect is properly identified as a stimulus or response, based on the drug's site of action within a centrally mediated homeostatic system. More recent dynamic conditioning models dispense with this identification requirement by postulating that the effective US may include components of the effect of the nominal CS, but have in common with the Eikelboom and Stewart model the notion that the effective US determines the direction of the CR (Dworkin, 1993; Poulos & Cappell, 1991; Ramsay & Woods, 1997).

Within CAS theory, the direction of the CR is also determined by the nature of the CS and involves a new kind of selective association. The theory assumes that drug states model naturally occurring sequences of internal states. Just as tastes are readily associated with sickness and poorly associated with pain (e.g., Garcia & Koelling, 1966), internal cues are readily associated with homeostatic responses to sickness and poorly associated with the sickness itself (Revusky, 1984). Any propensity for selective association is presumed to have evolved because it is biologically adaptive. Consider the case of ingestion of poisoned bait. The conditioning of a sickness response to the taste—and possibly to other external stimulus features—of the bait has obvious survival value because such conditioning permits the animal to taste and reject the bait on subsequent occasions. Tastes can themselves be avoided and are selectively associated with sickness because avoidance of the taste enables avoidance of the sickness. CAS theory arose in the context of unavoidable sickness in which no ingestion occurs,
that is, in which the animal cannot escape or avoid impending sickness. In this case, naturally occurring internal cues are selectively associated with homeostatic antisickness because such cues cannot themselves be avoided. CAS enables the animal to cope with unavoidable sickness (Lett, 1983). Antisickness is presumed to act against sickness responses such as nausea and vomiting, and to be conditionable to appropriate cues, that is, to antecedent internal stimulus events.

By extension, drug–drug conditioning may provide a general model for the involvement of Pavlovian mechanisms in homeostatic regulation (Revusky, 1985).

Evidence consistent with a CAS interpretation of avfail has been found by interpolating lithium-conditioned pentobarbital between saccharin consumption and lithium injection in a two-phase conditioning procedure that is nominally an associative blocking procedure (Lett, 1983). The first phase of a blocking procedure pairs a CS1 with the US, and the second phase pairs a CS2–CS1 compound with the same US (Kamin, 1968). The avfail procedure is similar to a blocking procedure except that, in the avfail procedure, the lithium US is omitted from the second conditioning phase. Lett reasoned that an antisickness response conditioned with a high dose of lithium should be able to attenuate not only mild sickness produced by pentobarbital (as in the avfail procedure) but also more intense lithium sickness (as in the nominal blocking procedure). This nominal blocking procedure yields an effect, similar to avfail, that is arguably due to CAS rather than to associative blocking as commonly conceived (e.g., Balaz, Gutsin, Cachiero, & Miller, 1982; Kamin, 1968; Pearce & Hall, 1980; Rescorla & Wagner,
Because the nominal blocking effect is obtained whether the US used during the initial drug—drug pairings phase is the same as or different from the US subsequently used to condition a taste aversion, it may not depend on amelioration of the particular physiological effects of a toxin, but rather on amelioration of the distress that might be produced in common by a variety of toxins (Revusky & Harding, 1986). That is, the nominal blocking effect is apparently not based on conditioning of the particular physiological effects of lithium, such as bradycardia (Wilkin, Cunningham, & Fitzgerald, 1982) or hypothermia (Taukulis, 1982), because these physiological effects are not common to the class of US drugs successfully used in both the avfail and nominal blocking procedures. Rather, the nominal blocking effect appears to be based on the conditioning of a homeostatic response to a more general effect common to the class of successfully used US drugs. The antisickness response—originally defined as a collection of physiological homeostatic adjustments (Lett, 1983)—is understood by the present reasoning to be a single adjustment or mediational process that may be directed against the distress produced by subjective sickness.

---

3 This distinction will be examined more fully in the section titled Associative Blocking Explanation of Avfail (pp. 16–22).

4 See the section titled Validating CAS Theory: Pharmacological Controls (pp. 27–29) for information on the various drugs used successfully in the avfail procedure.
regardless of the particular mechanism of action of the sickness-inducing drug or other agent. If this is true, and by analogy to conditioned analgesia mediated by endorphins in anticipation of pain (e.g., Fanselow & Bolles, 1979), perhaps CAS is mediated by an endogenously occurring antiemetic substance in anticipation of sickness (Revusky & Harding, 1986).

**Associative Blocking Explanation of Avfail**

CAS theory is elegant and compelling. But empirical support for the theory is based on a nominal associative blocking procedure and is consistent with an alternative blocking interpretation (Lett, 1983; Revusky & Harding, 1986). The nominal blocking procedure is hereafter called the CAS/blocking procedure—different from the avfail procedure—and the outcome of a CAS/blocking procedure will be called a CAS/blocking effect—different from the avfail effect—in an attempt not to prejudge whether it is due to CAS or blocking.

Blocking is typically said to occur when prior conditioning to a stimulus prevents conditioning to a second stimulus that is presented in compound with the first and paired with the original US (Kamin, 1968). Whereas CAS theory maintains that pentobarbital injection furnishes an internal drug state cue that selectively enters into association with the lithium antisickness UR, a straightforward blocking account would maintain that such a cue competes with other conditionable features of pentobarbital injection for association with the lithium sickness US. Taste aversion conditioning subsequently fails to occur because saccharin fails to enter into association with the sickness US when that US is predicted by
preconditioned pentobarbital (e.g., Rescorla & Wagner, 1972). A practical consequence is that, by this and indeed by most other blocking theories (e.g., Balaz et al., 1982; Kamin, 1968; Pearce & Hall, 1980; Wagner, 1981), the sickness is not reduced.

Indirect support for a blocking interpretation of the CAS/blocking effect is provided by evidence that the drug–drug pairings of the first conditioning phase endow features of the CS drug with conditioned aversive properties. The presence of these features during the subsequent taste aversion conditioning phase could then block an association between saccharin consumption and lithium sickness. How is such conditioned sickness—not apparent in the avfail or CAS/blocking procedures—to be measured? Consider a straightforward drinking suppression procedure in which the usual drug–drug pairings phase of the avfail and CAS/blocking procedures is followed not by a second conditioning phase but by a CS-only test trial. On test, the CS drug is injected prior to flavored or unflavored water access in thirsty animals. In addition to the findings of Cunningham and Linakis (1980) mentioned earlier (pp. 7–8), Revusky, Taukulis, and Peddle (1979) demonstrated suppression of saccharin drinking following injection of lithium-conditioned pentobarbital. This nominal conditioned sickness effect was not found with substitution of amphetamine or chlordiazepoxide for the pentobarbital and was therefore attributed to a pharmacological drug interaction. Martin, Bechara, and van der Kooy (1987) and Martin, Gans, and van der Kooy (1990) similarly failed to show suppression of fluid consumption following injection of
lithium-conditioned morphine. The drinking suppression measure thus offers little or no evidence that drug—drug pairings endow avfail CS drugs with conditioned aversive properties.

Lett attempted to validate CAS theory using stomach emptying time (1986) and feeding suppression (1992) as dependent measures but instead found more convincing, albeit indirect, support for a blocking interpretation of the CAS/blocking effect. Inhibition of gastric motility—measured as a delay in the stomach emptying time of a test meal—is correlated with vomiting (Abrahamsson, 1973) and has been supposed to be an analog of vomiting in the rat, a nonvomiting species (Hulse & Patrick, 1977; Swift, Taketa, & Bond, 1955). In the 1986 paper, Lett paired pentobarbital, morphine, or place CSs with lithium as the US in separate experiments and found that CS exposure enhanced the slowing of stomach emptying induced by the lithium on a forward pairing test trial. She argued from archival precedents that delayed stomach emptying indexes activation of emetic mechanisms, and therefore that the various CSs had acquired conditioned aversive properties. In the 1992 paper, Lett replicated her 1986 design with feeding suppression as the dependent measure and found that CS exposure produced greater suppression on a forward pairing test, consistent with a conditioned sickness interpretation. These findings cannot be attributed to a pharmacological drug interaction and appear to offer a well-controlled challenge to Lett’s (1983) CAS hypothesis.

Lett’s (1986, 1992) findings provide indirect support for a blocking
interpretation of the CAS/blocking effect in that they are consistent with but one component of blocking, namely, that drug–drug pairings endow the CS drug with conditioned aversive properties. The response systems involved in stomach emptying time and feeding suppression may not be the same as the response system involved in the CTA measure of the avfail and CAS/blocking procedures. Direct support for a blocking interpretation might be found by substituting place cues for the pentobarbital drug cue in the CAS/blocking procedure. Successful substitution would weaken the empirical basis of CAS theory—because CAS is based on selective association of internal cues (such as drug state cues) but not external cues (such as place cues) with the hypothetical antisickness response—but would not disprove the theory. An association between the external features of a lithium-predictive cue (such as a taste, a place, or the handling typically involved in drug injection) with lithium sickness might be expected to occur and moreover to produce a genuine blocking phenomenon in the CAS/blocking procedure. Such an association would not be expected to interfere with an independent association between the internal features of a lithium-predictive cue (such as a drug state) and the postulated lithium antisickness UR. CAS and blocking accounts of the CAS phenomenon are therefore not readily dissociable.5

5 The logic of independent associations—external cues with sickness, and internal cues with homeostatic antisickness—will be revisited in the section titled Validating CAS Theory: Selective Association, Response Competition, and Positive Transfer (pp. 34–36).
The CAS/blocking effect is consistent with an associative blocking alternative to a CAS explanation, although the evidence is indirect. Unlike the CAS procedure, avfail is not a blocking procedure because the original lithium US is omitted on test (cf. Klein, Mikulka, & Lucci, 1986; Randich & Ross, 1985). But is the avfail phenomenon nevertheless also consistent with an associative blocking explanation? Cunningham and Linakis (1980) offered a blocking interpretation of the avfail effect described earlier (pp. 7–8). They hypothesized that the conditioning of an aversion to the intraperitoneally mediated taste of injected ethanol during the drug–drug pairings phase of their procedure could subsequently block the conditioning of an ethanol-induced aversion to an orally ingested saccharin taste. They failed to substantiate this hypothesis but did find evidence suggesting that handling cues might serve a similar role. However, Martin (1982) was unable to demonstrate extinction of the postulated association between handling cues and the forward pairings drug state, and he attributed the discrepancy between laboratories to procedural differences militating for or against the participation of external cues, such as handling cues, in the avfail procedure. Martin also modified the typical avfail procedure by presenting a novel vinegar taste together with the usual pentobarbital injection, delivered as a compound and paired with the usual lithium injection, during the drug–drug conditioning phase. Pairings endowed the vinegar taste with conditioned aversive properties but did not weaken the ability of conditioned pentobarbital to attenuate a subsequent saccharin CTA. A weakened avfail effect is expected if avfail is based on an
association between pentobarbital and lithium sickness because the vinegar taste should compete with and overshadow such an association (see also Martin & Doyle, 1989).

Lett (1992) also offered a straightforward blocking interpretation of the avfail effect, based on the indirect evidence reviewed earlier (pp. 18–19), that ignores the formal distinction between the higher-order (i.e., avfail) and associative blocking paradigms. By her reasoning, pentobarbital–lithium pairings produce an association between the pentobarbital CS and intense lithium sickness; the pentobarbital CS subsequently blocks an association between saccharin and the mild sickness produced by the pentobarbital. Perhaps the most serious problem with this sort of blocking explanation is its assumption that the rat cannot distinguish the mild sickness of preexposed pentobarbital from the intense sickness of a dose of lithium an order of magnitude higher than that required to condition a taste aversion. Pentobarbital has presumably come to signal lithium or its aftereffects during the pentobarbital–lithium pairings phase of the avfail procedure. Omission of an expected, high dose of lithium during the saccharin–pentobarbital pairings phase must be unsurprising in some sense if blocking is to occur (Kamin, 1968, 1969; Mackintosh, 1983, pp. 236–239; Mackintosh, Dickinson, & Cotton, 1980; Rescorla & Wagner, 1972).

Evidence for or against the associative blocking explanation is thus inconclusive or inconsistent. That is, the CAS and blocking explanations of the CAS/blocking effect—based on a nominal blocking procedure—are not readily
dissociable, and the blocking explanation of avfail either fails in replication (Martin, 1982, 1989) or makes the unlikely assumption that the rat cannot distinguish mild pentobarbital sickness and intense lithium sickness (Lett, 1992). An associative blocking explanation of avfail has some evidentiary basis, albeit indirect and inconsistent, but seems unlikely.

Conditioned Inhibition Explanation of Avfail

The avfail procedure also meets the formal definition of a conditioned inhibition procedure: Lithium-reinforced trials to the pentobarbital CS1 are followed by nonreinforced trials to the saccharin CS2 presented as a compound with CS1 (Pavlov, 1927). Is avfail due to conditioned inhibition?

A conditioned inhibition explanation of avfail complements the blocking interpretation of the CAS/blocking effect outlined in the immediately preceding section. That is, the blocking explanation is not obviously applicable to the avfail effect but provides an alternative, traditional Pavlovian explanation of the CAS/blocking effect. The conditioned inhibition explanation, on the other hand, is not applicable to the CAS/blocking effect but provides an alternative, traditional Pavlovian explanation of the avfail effect based on the more likely assumption that the omission of an expected, high dose of lithium during the second conditioning phase of the avfail procedure is surprising. Presumably, when rats experience pentobarbital sedation without the expected lithium sickness during the second or CTA conditioning phase, they decide, in some sense, that the saccharin must have prevented the pentobarbital from resulting in lithium sickness (Revusky,
Taukulis, & Peddle, 1979). More formally, the avfail procedure presumably endows saccharin with conditioned inhibitory properties as the saccharin comes to signal the omission of expected sickness (Dickinson & Dearing, 1979; Konorski, 1967; Rescorla, 1979; Rescorla & Wagner, 1972). A conditioned inhibition explanation can place the avfail phenomenon within an adaptive evolutionary framework by providing a mechanism whereby individual animals learn to identify medicines or antidotes to sickness (cf. Huffman, 1997), in contrast to the traditional view that "the desire to take medicine is perhaps the greatest feature which distinguishes man from animals" (Osler, 1898, p. 167).

The avfail procedure meets the formal definitions of both the higher-order conditioning and conditioned inhibition paradigms, but on what basis might the same procedure be expected to turn a neutral stimulus into a conditioned excitatory stimulus [by the different rationales presented in the section titled Discovery of the Aversion Failure (Avfail) Phenomenon, pp. 5-11] or a conditioned inhibitory stimulus (by the present reasoning)? Pavlov (1927) regarded higher-order conditioning as an early stage of the same process which eventually results in conditioned inhibition. Conditioned inhibition is presumed to be a more complex form of learning that is preceded by higher-order conditioning until the animal essentially reinterprets the situation. Inhibitory conditioning procedures typically intermix first- and second-order conditioning trials to facilitate the necessary discrimination. Several investigators have shown that excitatory conditioning proceeds rapidly over the first few trials, whereas inhibitory
conditioning typically requires many second-order trials in the context of ongoing excitatory conditioning on the intermixed first-order trials (Holland & Rescorla, 1975; Rizley & Rescorla, 1973; Yin, Barnett, & Miller, 1994). The avfail procedure, by contrast, presents first- and second-order trials sequentially, and the avfail effect commonly occurs after a single second-order pairing of saccharin and pentobarbital (e.g., Revusky, Coombes, & Pohl, 1982b). The avfail procedure is thus poorly designed as a conditioned inhibition procedure. Moreover, the conditioned inhibition explanation of avfail presupposes that the rat makes some remarkable inferences over the course of a single second-order conditioning trial if it is to conclude, in some sense, that saccharin prevented the pentobarbital from resulting in otherwise expected lithium sickness. Notwithstanding the apparent implausibility of the conditioned inhibition explanation, Revusky, Taukulis, and Peddle (1979)—reasoning from one-trial, long-delay CTA precedents that expectations based on traditional precedents might not be entirely convincing—redesigned the avfail procedure to make conditioned inhibition more likely but failed to show that such procedural changes affected saccharin consumption in the expected manner. A conditioned inhibition explanation of avfail thus has no current evidentiary basis and appears unlikely although it has not been ruled out.

**Occasion Setting Explanation of Avfail**

Conditioned inhibition procedures can be couched in the vocabulary of occasion setting (for reviews, see Bouton, 1997; Holland, 1992; Swartzentruber, 1995).
Perhaps the avfail procedure is a kind of occasion-setting procedure, with saccharin acting as a discriminative stimulus or feature that sets the occasion on which pentobarbital is followed by the omission of an otherwise expected lithium reinforcer. This sort of occasion-setting procedure is also called a serial feature-negative discrimination procedure (Jenkins & Sainsbury, 1970) with the discriminative stimulus or feature (i.e., saccharin) present on those trials on which the target stimulus (i.e., pentobarbital) is not reinforced. Occasion setters modulate CS–US associations without themselves entering into association with the US. If saccharin does not acquire conditioned inhibitory properties, perhaps it acquires informational, discriminative stimulus properties that modulate an association between pentobarbital and lithium sickness in a manner consistent with response inhibition or learned safety. The term modulation corresponds to B. F. Skinner's (1938) use of the term occasion setting in the operant conditioning context, that is, to the restriction of responding to particular stimulus situations, and modulators are also called occasion setters in the Pavlovian conditioning context.

Couching avfail in an occasion setting vocabulary is contrived in that the description does not obviously correspond to a naturally occurring situation and moreover does not appear to have received empirical study. But a somewhat similar feature-positive procedure, with a drug state typically serving as the discriminative stimulus or feature and saccharin or other fluid serving as the target, does correspond to naturally occurring situations and has recently received extensive empirical study and application (e.g., Martin et al., 1990; D. M. Skinner &
Martin, 1992; D. M. Skinner, Martin, Howe, Pridgar, & van der Kooy, 1995; D. M. Skinner, Martin, Pridgar, & van der Kooy, 1994; for reviews of the drug discrimination application, and for additional references, see Mastropaolo & Riley, 1990; Riley, 1995, 1997). An early empirical report corresponding to the feature-positive procedure is the direct, historical precursor to avfail (Revusky, Coombes, & Pohl, 1982a; see also Revusky et al., 1980) and was outlined in the section titled Conditioned Taste Aversion (CTA) and Selective Association (pp. 1-5). Martin et al. (1990) and D. M. Skinner et al. (1992, 1994, 1995) have used discrimination procedures corresponding to the avfail procedure but with pentobarbital (or morphine) drug states or a vinegar flavor as modulators of a saccharin–lithium association. Because the procedures are different, the results cannot be said to offer direct support for CAS theory, but they are consistent with CAS theory. For example, drug states acquire discriminative control over fluid consumption more readily than tastes do. D. M. Skinner et al. (1995) argued that this finding is complementary to, and perhaps a consequence of, the selective association of tastes with sickness and drug states with antisickness. In general, conditioned excitatory and inhibitory functions, on the one hand, and discriminative or occasion-setting functions, on the other hand, are acquired under opposing circumstances (e.g., Holland, 1992). By this sort of indirect reasoning, and in the absence of empirical evidence to the contrary, saccharin does not come to modulate a drug—sickness association in the avfail procedure. Moreover, by the sort of reasoning offered in the immediately preceding section for
supposing that conditioned inhibition is unlikely (viz., that it imputes an unreasonably high level of cognitive ability to the rat), saccharin seems unlikely to acquire discriminative control on the basis of a single exposure.

**Validating CAS Theory: Pharmacological Controls**

The avfail phenomenon has previously been obtained by comparison to backward, CS-, and US-only controls, that is, by comparison to Pavlovian controls usually considered appropriate in traditional procedures for ruling out most other sorts of explanation (see Table 1, p. 10). Such controls do not rule out the possibility that avfail is due to some sort of pharmacological drug interaction not involving learning. In the avfail literature, a drug substitution strategy has been used to control for this possibility (Revusky, Coombes, & Pohl, 1982b; Revusky, Taukulis, Parker, & Coombes, 1979). With lithium as the US drug, low doses of ethanol, chlordiazepoxide, morphine, or amphetamine have been substituted for pentobarbital in separate experiments with at least partial success. With pentobarbital as the CS drug, a high dose of amphetamine has been substituted for lithium with partial success: Lithium and amphetamine produce intense sickness at effective doses. Thus, avfail is not due to a pharmacological interaction between specific pairs of drugs. However, it is not obtained using low and high doses of amphetamine as CS and US (cf. Greeley, Lē, Poulos, & Cappell, 1984), nor with substitution of atropine or apomorphine for the pentobarbital.

The pattern of pharmacological generalization for avfail CS drugs is somewhat problematic for CAS theory. Specifically, atropine is highly
discriminable, but neither atropine nor apomorphine is self-administered whereas all drugs that successfully substitute for the pentobarbital in the avfail procedure are self-administered. Within an associative conditioning context, it is puzzling that discriminability of the CS drug state may not be sufficient to determine the effectiveness of avfail CS drugs. But avfail CS drugs are also "US drugs" in the second or CTA phase of the avfail procedure, that is, they induce CTAs in the avfail control groups (see Table 1, p. 10). This invites speculation concerning the nature of the intrinsic reinforcing properties of these drugs during the CTA phase. Specifically, CAS theory presupposes a conditioned sickness model by which drugs and other treatments induce CTAs. Only a conditioned sickness model postulates a common mechanism and places the phenomenon within an adaptive evolutionary framework. If avfail CS drugs are necessarily classed as self-administered drugs, this is inconsistent with CAS theory but consistent with the possibility that avfail is misnamed: So-called taste avoidance or taste "shyness" conditioned with self-administered drugs, and taste aversion conditioned with sickness-inducing drugs, may be based on different underlying mechanisms (e.g., Grigson, 1997; T. Hunt & Amit, 1985; Parker, 1995). But the detailed explanation of the avfail effect outside of the CTA context is unclear.

The pattern of pharmacological generalization thus appears to rule out a pharmacological drug interaction interpretation of avfail, but the validity of the drug substitution strategy as a control will be questioned in the Introduction to Chapter 2 (Antisickness Conditioning Using Rotation and Heat as Nondrug
Stimulus Events, pp. 41–73). The pattern of generalization also suggests that effective avfail CS drugs are necessarily self-administered drugs, contrary to CAS theory. Validating CAS theory requires the conclusive elimination of a pharmacological drug interaction interpretation. It also requires the demonstration that avfail CSs need not be self-administered drugs.

One purpose of the present thesis was to validate CAS theory by substituting nondrug stimulus events for avfail CS drugs. To anticipate the present findings, Experiment 1 (Rotational Stimulation as an Avfail CS, pp. 50–60) and Experiment 2 (Ambient Temperature Increase as an Avfail CS, pp. 61–73) successfully substituted nondrug stimulus events for avfail CS drugs. The nondrug events were assumed to have both internal and external stimulus components, and appropriate steps were taken to demonstrate that the effective stimulus was the internal component in each case, as required by CAS theory. The findings eliminate a pharmacological drug interaction interpretation of avfail and support a conditioned sickness model by which avfail CSs induce taste aversions in the avfail control groups.

Validating CAS Theory: Simple Conditioning Procedures

Using a subsequent conditioning phase as an index of the conditioning that occurs during a previous conditioning phase is common in Pavlovian procedures, including the associative blocking and conditioned inhibition procedures (Mackintosh, 1983, pp. 12–19) in addition to the avfail procedure. An important difference between the CAS and associative blocking explanations of the avfail
phenomenon is that, within CAS theory, the second or CTA conditioning phase of
the avfail procedure does not participate in the phenomenon and is not necessary
for CAS to occur: It is nothing more than an index or measurement of the
conditioning of an antisickness response that occurred during the first or
drug—drug conditioning phase of the procedure. A CAS response could
conceivably be measured against some sickness baseline not involving the
second or CTA phase of the avfail procedure. Within traditional Pavlovian theories,
on the other hand, the second conditioning phase participates in the associative
blocking and conditioned inhibition phenomena by paradigmatic definition.
Procedures that successfully eliminate the second conditioning phase of the avfail
procedure—for example, by using a CS-only or forward pairing test trial—thereby
make Pavlovian alternatives to a CAS explanation of avfail less likely. Procedures
that measure conditioning directly over the course of the drug—drug pairings trials
could eliminate traditional Pavlovian alternatives to a CAS explanation altogether
but raise the question of what to measure and how the measure is related to
avfail.

Revusky, Davey, and Zagorski (1989) reported a preliminary attempt to
cross-validate CAS theory outside of the CTA framework by establishing heart rate
as a physiological index of drug—drug conditioning. Heart rate can be measured
over the course of conditioning and this obviates a blocking interpretation.
Amphetamine rather than lithium was selected as the US drug because it is known
to support conditioning in other heart rate procedures. Pentobarbital was selected
as the CS drug. A putative heart rate CR to pentobarbital was found after four or five pentobarbital—amphetamine pairings. The CR was directionally opposite to the observed effect of the amphetamine. This finding has a certain face validity in terms of a possible homeostatic heart rate conditioning model analogous to the CAS model of avfail, but it does not establish whether the CR compensated for a homeostatic disturbance in heart rate regulation induced by the US drug. Indeed, Revusky et al. tried and failed to demonstrate such compensatory conditioning. Compensatory conditioning, had it been demonstrated to occur, would in any case merely have been consistent with, but would not have established a propensity for, selective association between the pentobarbital drug state CS and a hypothetical homeostatic aftereffect of the amphetamine US. The heart rate effect is, for these reasons, mute with respect to cross-validation of CAS theory. Moreover, although Revusky et al. gave a conditioning interpretation to the heart rate effect, their evidence was unconvincing. V. A. Davey and Biederman (1991) eliminated a confound in the earlier work and demonstrated equivalent heart rate effects in forward and backward groups relative to a long-delayed control group. We argued on empirical and logical grounds that the heart rate effect of Revusky et al. was not due to conditioning but to an uncontrolled pharmacological drug interaction.

Other physiological measures of drug—drug conditioning have also provided results that are inconclusive or inconsistent with respect to the cross-validation of CAS theory. Taukulis (1982, 1986b) found conditioned hyperthermia in response
to a CS drug paired with a hypothermia-inducing US drug but failed to show that the CR compensated for a departure from homeostatic equilibrium induced by the US drug (cf. Taukulis, 1986a; 1993; 1996; Taukulis & Brake, 1989; Taukulis, Fillmore, & Ruggles, 1992). Failure to show compensation implies that the two thermic responses may be unrelated, that is, based on distinct physiological mechanisms. This is inconclusive at best with respect to cross-validation of CAS theory. For example, perhaps anticipation of the US drug induces hyperarousal and hyperactivity which translate into higher body temperatures (Taukulis, 1986b). Wilkin et al. (1982) paired ethanol or saline CSs with a lithium US and found heart rate CRs to the different CSs that were in the same direction as the observed effect of the lithium.

The failure to cross-validate CAS using physiological measures of conditioning does not bring CAS theory into serious question, however. Physiological and CTA measures cannot be presupposed to involve related response systems: Heart rate and body temperature measures have no obvious relation to nausea or sickness, or more generally to the feeding system. Indeed, physiological measures cannot be presupposed to be direct measures of what is learned. An effect of pairings relative to appropriate controls points to a Pavlovian interpretation of Taukulis’ (1982, 1986a, 1986b) conditioned hyperthermia effect, for example, but does not establish its physiological basis. The general strategy illustrated by using physiological measures such as heart rate to cross-validate CAS theory is probably unworkable—judged by the level of methodological and conceptual
complexity in the heart rate studies of Revusky et al. (1989) and V. A. Davey and Biederman (1991)—and was not pursued in the present thesis. But the discussion of heart rate and body temperature measures counterpoints an apparent advantage of the avfail procedure, namely, that it presumably "culls out" responses that are irrelevant to the feeding system. Lithium and amphetamine, for example, have many different physiological effects, but only a common effect of these drugs, and moreover only a sickness-related effect of either drug, is made relevant by the avfail procedure.

Lett's (1986, 1992) stomach emptying and feeding suppression procedures—described in the section titled Associative Blocking Explanation of Avfail (pp. 18-19)—are also simple conditioning procedures. The stomach emptying and feeding suppression measures apparently have one of the advantages of measures such as heart rate and body temperature (i.e., elimination of the second conditioning phase of the avfail procedure) and also one of the advantages of the CTA measure of the avfail procedure (i.e., restriction of what is learned or measured to the feeding system). Lett's findings—consistent with conditioned sickness rather than CAS—thus offer serious challenge to her (1983) CAS hypothesis.

A second purpose of the present thesis was to validate CAS theory using the combination of a suitable simple conditioning procedure and feeding-related measure. To anticipate the present findings, Experiment 3 (Pica as an Index of CAS in Rats, pp. 74-82) uses pica (i.e., dirt or clay consumption) as a measure of
sickness in rats and shows an effect consistent with CAS theory in a simple conditioning procedure. This finding is used as the basis for a reinterpretation of the Lett (1992) feeding suppression finding in a manner consistent with CAS theory. Experiment 4 (Emesis as an Index of CAS in Ferrets, pp. 83-99) presents the first unequivocal confirmation of CAS theory using vomiting in the ferret as a direct measure of sickness in a conditioning context that is not susceptible to a blocking interpretation.

Validating CAS Theory: Selective Association, Response Competition, and Positive Transfer

The avfail procedure and other, similar drug—drug pairings procedures have the advantage of simplifying the study of so-called interoceptive—interoceptive conditioning (i.e., conditioning in which both the CS and the US are perceived in some sense as originating within the animal's body; cf. Razran, 1961) by comparison with traditional procedures typically involving invasive surgery (e.g., Ádám, 1967; Bykov, 1954/1959). But one feature of drug—drug methodology has made a CAS interpretation of avfail difficult to validate. Specifically, conventional analysis of the associative processes that are supposed to mediate avfail is made intractable because, with internal drug states serving as the stimulus events, crucial timing parameters such as stimulus onset and offset are undefined and uncontrolled.

The inability to define or control drug state timing parameters makes any direct, straightforward demonstration of selective association difficult or impossible.
Selective association is a defining feature of the CAS hypothesis: In theory, tastes, and possibly other external cues, are selectively associated with the direct sickness consequences of the avfail US drug, whereas internal cues are selectively associated with homeostatic antisickness. Taste aversion conditioning has been shown to meet the established criteria for selective association [i.e., of tastes with sickness, and environmental cues with pain (Garcia & Koelling, 1966); see LoLordo, 1976, 1979; Testa, 1974], but putative antisickness conditioning has not. Meeting the criteria requires what might be called a "double dissociation" design, similar to the Garcia and Koelling design, for showing that the two sorts of associations postulated by CAS theory can be formed independently and in parallel during the first phase of the avfail procedure. Drug–drug pairings procedures in general—and the avfail procedure in particular—do not readily permit the sorts of event-covariation arrangements required for internal validation of the CAS hypothesis using the double dissociation design.

But suppose that a nondrug compound cue with highly salient internal and external (place) components were to be substituted for pentobarbital in the first phase of the avfail procedure. Pairings of the compound with a lithium US are expected, within CAS theory, to produce independent associations between the external (place) components of the compound and lithium sickness (if they have any effect at all), and between the internal components of the compound and homeostatic antisickness.

How are these independent associations to be measured? CAS theory implies
response competition during the second or CTA phase of the avfail procedure—as a working hypothesis, and in the absence of evidence to the contrary, CAS is presumed to act against generalized sickness-related distress, whether unconditioned or conditioned—and, by this reasoning, removal of the place component of the compound on test is expected to enhance avfail by eliminating a conditioned sickness component of the observed response. Associative blocking (e.g., Rescorla & Wagner, 1972), on the other hand, implies stimulus competition between the external and internal elements of the compound for association with lithium sickness during the first phase of the avfail procedure. The Rescorla-Wagner model—and indeed every other available theory except CAS—predicts that removal of a conditioned place component of the compound on test will diminish avfail by eliminating or reducing the strength of the effective blocking cue. Positive transfer with removal of a component of a compound cue makes no sense in terms other than selective association and CAS. This logic serves to clarify CAS theory and will be revisited in the Discussion section of Experiment 1 (Rotational Stimulation as an Avfail CS, pp. 56-60).

Statement of Purpose

The present experimental series uses several different strategies to validate CAS theory.

Chapter 2 (Antisickness Conditioning Using Rotation and Heat as Nondrug Stimulus Events, pp. 41–73) reports two experiments that successfully substitute the nondrug stimulus events of rotational stimulation (Experiment 1, pp. 50–60)
and an increase in ambient temperature (Experiment 2, pp. 61-73) for avfail CS
drugs in otherwise typical avfail procedures. The findings conclusively eliminate a
pharmacological drug interaction interpretation of avfail. They also eliminate an
alternative to a conditioned sickness interpretation of the CTAs established in avfail
control groups during the second conditioning phase (see Validating CAS Theory:
Pharmacological Controls, pp. 27-29). These experiments also make possible a
crucial experiment to confirm CAS theory—that is, to dissociate CAS and
associative blocking explanations of the avfail effect using the avfail procedure,
rather than some other procedure of potentially questionable relevance—by the
logic outlined in the immediately preceding section and in the Discussion section
of Experiment 1 (pp. 56-60).

Chapter 3 (Food Consumption and Pica as Indices of Antisickness
Conditioning in Rats, pp. 74-82) offers an empirically based reinterpretation of the
Lett (1992) feeding suppression study described earlier (pp. 18-19). Experiment 3
successfully substitutes pica (i.e., dirt or clay consumption) for feeding
suppression as a measure of sickness in a partial procedural replication of Lett
(1992, Experiment 1). The pica study provides an empirically-based alternative to a
conditioned sickness interpretation of the Lett (1986, 1992) results, consistent with
CAS theory, and thereby weakens the empirical basis for an associative blocking
alternative to a CAS explanation of avfail.

All previous studies are indirect tests of CAS—in the sense that nausea or
sickness must be inferred from changes in consummatory behavior in the rat, a
nonvomiting species—and as such are subject to misinterpretation. Chapter 4 (Alleviation of Emesis from the Cancer Chemotherapy Drug Cisplatin by Antisickness Conditioning in Ferrets, pp. 83–99) reports an experiment that successfully eliminates the ambiguity inherent in all indirect, consumption measures—including the feeding suppression (Lett, 1992), stomach emptying time (Lett, 1986), kaolin consumption (Experiment 3), and avfail measures—and suggests the basis for a nondrug conditioning countermeasure to severe nausea in clinical settings. Experiment 4 substitutes the direct sickness measures of retching and vomiting in the ferret, a vomiting species, and demonstrates that a CAS response conditioned with lithium can alleviate not only lithium sickness (on a lithium test trial) but also cisplatin sickness (on a cisplatin test trial). Cisplatin is the most highly emetogenic anticancer drug in common use.

Experiment 3 (Chapter 3, Pica as an Index of CAS in Rats, pp. 74–83) and Experiment 4 (Chapter 4, Emesis as an Index of CAS in Ferrets, pp. 84–99) also make traditional Pavlovian interpretations of avfail other than the CAS interpretation—namely, associative blocking (pp. 16–22) and conditioned inhibition (pp. 22–24)—unlikely by successfully eliminating the second conditioning phase of the avfail procedure (using the logic outlined briefly in the section titled Validating CAS Theory: Simple Conditioning Procedures, pp. 29–34). The findings of Experiments 3 and 4 are within simple conditioning contexts—not obviously susceptible to blocking or conditioned inhibition interpretations—and this obviates
the application of these alternative interpretations to the earlier available literature.

Chapter 5 (pp. 100-115) discusses theoretical implications and practical applications of CAS theory. A crucial theoretical and practical implication of CAS theory mentioned earlier (pp. 15-16) is that CAS is mediated by an endogenously occurring antiemetic substance that has yet to be identified. The finding of Experiment 4 (viz., that a CAS response conditioned with lithium can alleviate cisplatin sickness in the ferret) supports this implication of CAS theory. The section titled The Search for the Endogenous Antiemetic Mediating CAS (Chapter 5, pp. 100-106) develops the argument implying the existence of an endogenous, conditionable antiemetic response and offers an empirical search strategy for showing that such an antiemetic indeed exists. The remaining sections of Chapter 5 develop experimental strategies for determining whether CAS theory is potentially relevant to nausea and vomiting in various clinical situations. Might a CAS response be used to alleviate the unconditioned and conditioned sickness produced by cancer chemotherapy drugs [Application to Unconditioned Nausea and Vomiting in Cancer Chemotherapy (pp. 106-107) and Application to Anticipatory Nausea and Vomiting in Cancer Chemotherapy (pp. 107-108)]? Might it be used to alleviate a component of cancer cachexia in certain cases (Application to Cancer Cachexia Syndrome, pp. 108-111)? Might CTA and CAS theories be used to understand and treat pregnancy sickness? The section in Chapter 5 titled Application to Pregnancy Sickness (pp. 111-115) discusses the possibility that an animal model might be developed: Pregnancy sickness is poorly
understood in part because it currently has no animal model.

Chapter 6 (pp. 116–118) presents a brief, general summary and conclusions.
The homeostatic conditioning model instantiated by CAS theory is based on the special circumstance in which both CS and US are drug states. The paired drug states are assumed to model naturally occurring sequences of internal states: The CS corresponds to naturally occurring internal signals, the US corresponds to naturally occurring aftereffects, and conditioning enables the animal to better regulate its internal environment by anticipating the US. Exploiting drug states in this manner has obvious practical advantages for the study of interoceptive—interoceptive conditioning (cf. Ádám, 1967; Bykov, 1954/1959) but makes CAS theory difficult to validate because the two drug states cannot be thought of as independent events.

A basic problem involves the selection of appropriate controls. Pharmacological drug interactions complicate interpretation in conditioning procedures whenever two drugs are simultaneously present. Pavlovian conditioning controls do not control for pharmacological drug interactions, and a drug substitution strategy has been used for this purpose (see Validating CAS Theory: Pharmacological Controls, pp. 27–29). But is the drug substitution strategy valid? If it is not valid—and I will argue shortly that its validity is questionable—then some other strategy must be devised for providing pharmacological controls and thereby validating CAS theory.

The problem of appropriate Pavlovian and pharmacological controls in
drug–drug conditioning procedures is illustrated by a series of studies using heart rate as the dependent measure. Revusky et al. (1989) examined heart rate in a Pavlovian drug–drug conditioning procedure as a possible second instantiation of Revusky's (1985) homeostatic conditioning theory in a preliminary attempt to cross-validate CAS theory outside of the CTA context. This sort of cross-validation strategy was motivated by the difficulty in dissociating CAS and blocking explanations of avfail described earlier (pp. 18–19). Heart rate can be measured over the course of the drug–drug pairings trials, and this obviates a blocking interpretation. In the Revusky et al. heart rate study, pentobarbital served as the CS and d-amphetamine served as the US: Does the pentobarbital drug state serve as a cue for homeostatic adjustments in heart rate in anticipation of amphetamine's unconditioned effects? In separate experiments, we found higher heart rates in response to pentobarbital by comparison with an unpaired control that received the two drugs 24 hours apart, but not by comparison with a backward control that received the drugs in reverse temporal order. A confounding context change between training and test environments in the latter experiment led us to the erroneous conclusion that external cues (such as handling or heart rate recording cues) participated in conditioning. Specifically, we concluded that environmental stimuli present during training and absent during test participated in heart rate conditioning as a necessary component of the effective CS. But V. A. Davey and Biederman (1991) eliminated the confound and showed consistently higher heart rates in both forward and backward groups by comparison with an
unpaired control. The latter finding calls a conditioning interpretation of the heart rate effect into question. Is the heart rate effect due to some sort of nonassociative phenomenon such as a pharmacological drug interaction, or is one of the two Pavlovian controls invalid in application to the heart rate procedure?

The drug substitution strategy has also been applied to the drug—drug heart rate conditioning procedure. How successful is the strategy in the present application? Although lithium is effective in the avfail procedure and also induces a profound decrease in heart rate, it is not effective when substituted for amphetamine in the heart rate procedure (Revusky et al., 1989). Dose—response characteristics of the pentobarbital—amphetamine combination are also very different for the heart rate and avfail dependent measures (Revusky & Reilly, 1990a). Substitution of nicotine for the amphetamine is effective in the heart rate procedure—indicating some pharmacological generality, consistent with a conditioning interpretation—but substitutions of caffeine, atropine, or footshock are ineffective—indicating that the generality is very limited (Reilly & Revusky, 1992; Revusky, Davey, & Reilly, 1987). A pharmacological drug interaction common to the combination of pentobarbital and amphetamine or nicotine could account for the heart rate effect and is plausible on independent grounds (cf. Hatch, 1973). Moreover, the drug substitution strategy is logically more unconvincing the more limited the demonstration of pharmacological generality.

Notwithstanding the above argument, however, even a total lack of pharmacological generality does not necessarily imply that a putative conditioning
phenomenon is nonassociative in nature. Rather, some strategy other than a drug substitution strategy would have to be used to rule out nonassociative drug interaction effects. How is this so? Within CAS theory, selective association or cue-to-consequence specificity is broadly limited to internal cues and nausea or sickness consequences within an adaptive evolutionary framework.

Pharmacological generality is expected not only to control for nonassociative drug interaction effects but also to conform to theory. Outside of CAS theory, selective association could conceivably be limited to events modeled by only one or a few drug combinations. Notwithstanding the limited pharmacological generality of the heart rate effect, Revusky and coworkers have argued that it is a conditioning phenomenon (Revusky et al., 1989; Revusky & Reilly, 1990a, 1990b, Reilly & Revusky, 1992). V. A. Davey and Biederman (1991), on the other hand, have invalidated most of the conclusions of the initial heart rate demonstration of Revusky et al., either empirically by eliminating a design confound, or logically by illustrating how each point taken by Revusky et al. as evidence of conditioning is consistent with an alternative drug interaction interpretation. The drug substitution strategy does not obviously or unambiguously control for pharmacological drug interaction effects in the heart rate procedure.

Does the drug substitution strategy control for pharmacological drug interaction effects in the avfail procedure? In separate experiments substituting a taste aversion measure for the heart rate measure, V. A. Davey and Biederman (1991) found avfail effects in forward and unpaired (24-hour delayed) groups by
comparison with a backward control whether the US was amphetamine or lithium. The forward group and backward control were similar on the heart rate measure, whereas the forward group and unpaired control were similar on the avfail measure. Is this overall pattern of results reconcilable with a Pavlovian conditioning interpretation of heart rate or avfail phenomena?

The logic of the drug substitution strategy does make unlikely the possibility that one or more functionally similar pharmacological drug interactions have consistently been mistaken for conditioning in the avfail literature. A pharmacological drug interaction is also more likely to be present in forward and backward groups and absent in an unpaired group: This pattern is inconsistent with the finding that avfail is present in forward and unpaired groups and absent in a backward group. The difference between control groups could be due to differential sickness preexposures. That is, on each drug—drug conditioning trial, the forward and backward groups both receive one episode of sickness, whereas the unpaired group receives two episodes on different days. Preexposure habituation to sickness—different from avfail—is known to occur in the avfail procedure and has been assumed to be adequately controlled by the backward control typically used (e.g., Revusky & Coombes, 1982; Revusky, Taukulis, Parker, & Coombes, 1979; see Table 1, p. 10). That is, preexposure habituation to sickness is assumed to be equated in forward and backward groups, and the obtained difference between the groups is attributed to avfail. But it is conceivable that forward and backward pairings could produce functionally different drug
interactions and thus that a drug interaction interpretation has not been entirely ruled out. A conjecture with respect to the pentobarbital—lithium pairings phase of the typical avfail procedure, for example, is that pentobarbital sedates the animal and thereby prevents receipt of and habituation to lithium sickness in the forward but not the backward group. This is a directionally sensitive pharmacological drug interaction of a sort, but one that makes a nominal avfail effect less rather than more likely. The drug substitution strategy is more convincing when applied to the avfail procedure but is not entirely convincing when control problems (V. A. Davey & Biederman, 1991) and anomalies in the pattern of pharmacological generalization (see Validating CAS Theory: Pharmacological Controls, pp. 27–29) are carefully considered.

Partly for the purpose of eliminating a pharmacological drug interaction interpretation of avfail, the first two experiments in the present series substitute nonpharmacological stimulus events (rotational stimulation and an increase in ambient temperature) for the pentobarbital CS typically used in the avfail procedure. Successful substitution would eliminate a drug interaction interpretation in the possibly trivial sense that rotation and heat are not drugs, and in the important sense that the simultaneous presence of rotation or heat and lithium is easily eliminated as a factor in conditioning. Successful substitution would also eliminate speculation based on the presently known pattern of pharmacological generalization that effective avfail CS drugs are necessarily self-administered or positively rewarding (see Validating CAS Theory: Pharmacological Controls.
Drug–drug conditioning methodology makes CAS theory difficult to validate because the paired drug states cannot be thought of as independent events. This introduces the basic problem of appropriate controls for pharmacological drug interactions as discussed in the immediately preceding paragraphs (pp. 41–47). It introduces a second, conceptual or theoretical problem with respect to the distinction between CAS theory and current conditioning theories of drug tolerance, sensitization, and physiological regulation. This distinction was outlined briefly in the section titled *Conditioned Antisickness (CAS) Explanation of Avfail* (pp. 11–16).

Notwithstanding the successful elimination of a pharmacological drug interaction interpretation in drug–drug conditioning procedures using appropriate pharmacological and Pavlovian controls, the pharmacological and physiological interactions between the nominal CS and US drug states must be supposed to change the nature of these stimulus events. Stated plainly, the CS must be supposed to signal not the US alone but rather the interaction between the CS and US. In the pentobarbital–lithium pairings phase of the typical avfail procedure, for example, rats in the forward group are sedated at the time of lithium sickness whereas rats in the backward group are not. Pentobarbital must be presumed to signal the combination of sedation and sickness in the forward group but not in
the backward group. Does a change in the nature of the CS and US events, based on pharmacological and physiological interactions between the nominal CS and US drug states, have important implications for the avfail phenomenon or for CAS theory? With respect to the avfail phenomenon, the literature is consistent for the most part with the assumption that these sorts of complications or dynamic stimulus changes are essentially "culled out" by the avfail procedure as detailed in the section titled Validating CAS Theory: Simple Conditioning Procedures (pp. 29–34). In other words, such changes do not have any obvious functional relevance in a procedure, such as the avfail procedure, that is presumably based on a common sickness effect of the nominal or effective US drug.

The problem is not that such interactions occur—they presumably can and do—but rather that they may make it difficult to argue that the nature of the CS determines the direction of the CR—distinct from its contribution to the effective US—as required by a CAS interpretation. The relevant theories other than CAS theory are based on the assumption that the effective US determines the nature and direction of the CR (e.g., Dworkin, 1993; Eikelboom & Stewart, 1982; Poulos & Cappell, 1991; Ramsay & Woods, 1997). By these other theories, the avfail effect and CAS theory are presumably explained away by supposing that the nature of the CS determines the direction of the CR—consistent with CAS theory—because it

---

* See Dworkin (1993) for detailed characterization of similar issues in the context of the conditioning of physiological responses.
changes the nature or functional significance of the US—consistent with the cited alternatives to CAS theory. But the theoretical basis for supposing that internal stimulus events as a class have a common conditioning effect of the sort proposed is to be found only within CAS theory.

Experiment 1 uses whole-body rotational stimulation as the avfail CS, and Experiment 2 uses an increase in ambient temperature as the avfail CS. These nondrug stimulus events are paired with lithium as the avfail US. Successful substitution of nondrug events for avfail CS drugs is designed to conclusively eliminate a pharmacological drug interaction interpretation of the avfail phenomenon by demonstrating that avfail can be obtained in the absence of a drug interaction. Successful substitution is also designed to militate against the notion that pharmacological or physiological interactions between CS and US stimulus events can change the effective US in a manner that changes the expected direction of the CR. This notion is inconsistent with CAS theory by the reasoning presented in the immediately preceding paragraph. Because the rotation procedure is at least nominally a trace conditioning procedure (Pavlov, 1927), the successful substitution of rotation eliminates physiological interactions in the obvious, and possibly trivial, sense that the rats are not undergoing physical rotation at the time of lithium sickness. Indeed, rotation and its sensory aftereffects are likely to have dissipated by the time of lithium sickness, whereas the memory of such a highly salient event would presumably remain strong.
Experiment 1
Rotational Stimulation as an Avfail CS

Method

Subjects
Male Sprague-Dawley rats were obtained from Charles River (Canada) at a weight range of 190-200 g and weighed 285-428 g at the start of the experiment. They were housed individually in rack-mounted stainless steel wire-mesh cages under continuous lighting conditions and had ad libitum access to Purina Rat Chow. The water deprivation schedule in effect during the rotation—lithium pairings phase consisted of alternating 48-hr deprivation and 24- or 48-hr free access, with the following modification: Rats were allowed an additional 15 min of access 28 hr after the water bottles were removed and each repetition of the deprivation cycle initiated. They were deprived of water for approximately 12-16 hr at the time of rotation or injections. The deprivation schedule in effect for the taste aversion conditioning phase consisted of 15 min of access per day.

Apparatus
The rotational apparatus, described by Harrison and Elkins (1987), permits simultaneous rotation of up to four rats placed in separate housings on a two-tier platform. The housings were sections of ABS Bristolpipe (7.6 cm inside diameter and 20.3 cm inside length) with outside caps for closing both ends. Thirty-six 0.6-cm air holes were drilled in rows along the full length of one side of each cylinder. Rats were placed in the cylinders and the cylinders were mounted on the
rotation platform as appropriate. One rat from each rotated group received simultaneous rotation for each trial throughout the experiment. With each housing assigned a unique position on the platform, groups were counterbalanced for assignment to position, and because positions were filled in sequence, groups were also counterbalanced for minutes in the apparatus prior to rotation. Individual rats were counterbalanced for assignment to position across trials. Rats were placed in the apparatus 1-4 min before rotation and were removed within 1-2 min after rotation.

**Procedure**

Twelve rats were assigned on the basis of weight to three groups of four rats each. During the first phase of the experiment, each group received four training trials that consisted of experimental or control pairings of rotational stimulation and lithium chloride injection. Trials were spaced three or four days apart on a weekly schedule. Rotation was in the horizontal plane at 60 rpm. Lithium (Sigma–Aldrich, St. Louis, MO) was prepared as a 2% weight-to-volume (wt/vol) solution in distilled water and was injected intraperitoneally at a dose of 240 mg/kg. An experimental or forward pairings group received 30 min of rotation followed within 2 min by lithium injection on each trial. A backward pairings group received rotation and lithium in reverse order, that is, the lithium injection was followed 32 min later by 30 min of rotation. An unpaired group received 30 min of rotation followed within 2 min by an equivalent-by-volume injection of normal saline. Approximately 24 hr later, the unpaired group received lithium and the remaining groups received
saline.

For the second phase of the experiment, a fourth group was formed by removing one rat from each of the forward, backward, and unpaired groups whose weight was closest to the mean for the parent group. This fourth group was used to provide a baseline of saccharin consumption in the absence of a rotation-induced CTA. On the day after the fourth rotation—lithium pairings trial and 24-hr drinking period, rats were placed on a schedule of 15 min of access to room-temperature tap water per day. On days 16, 19, 23, and 26 of this schedule, the water was flavored with sodium saccharin (Sigma—Aldrich; 0.75% wt/vol). The parent groups received 30 min of rotation beginning within 4 min after removal of the saccharin bottle. The baseline group received sham rotation. Sham-rotated rats were placed in rotation housings and positioned on the base of the rotation platform but were not rotated.

Saccharin consumption scores were converted to acceptance scores in the form of suppression ratios once it was determined statistically that groups did not differ in their water consumption on any training day. The ratio was $S / (S + W)$, where $S$ is the amount of saccharin consumed on any training day and $W$ is the amount of water consumed on the day before the training day. A ratio below 0.50 indicates lower saccharin consumption on the training day than water consumption on the previous day, that is, a rejection of saccharin relative to tap water. A ratio above 0.50 indicates higher saccharin consumption on the training day than water consumption on the previous day, that is, an acceptance of or
preference for saccharin relative to tap water. Using acceptance or preference scores rather than raw intake scores simplifies the description of results and increases statistical sensitivity by factoring out individual differences in amount of fluid intake without changing the pattern of results. Acceptance scores on the first training day served as the covariate, and the mean of the scores on the remaining three days served as the datum, in an analysis of covariance (ANCOVA). F tests based on the error term and adjusted means of the overall ANCOVA were used for pairwise comparisons. An alpha level of .05 was adopted.

Results

Groups did not differ in their water consumption (all ps > .10), and saccharin consumption scores were converted to acceptance scores for analysis. Groups did not differ in their saccharin acceptances on the first saccharin drinking day, F < 1. The ANCOVA yielded a significant group effect, F (3, 7) = 10.22, p < .01. Pairwise comparisons and inspection of Figure 1 indicate that saccharin acceptances were stronger in the forward group than in the backward control, F (1, 7) = 19.22, p < .01. Stronger acceptances relative to a backward control have been used to define an avfail effect (Revusky, Coombes, & Pohl, 1982b). The effect was complete because the forward group did not differ from the baseline control, F < 1. The pattern of results was similar relative to the unpaired control. That is, saccharin acceptances were stronger in the forward group than in the unpaired control, F (1, 7) = 9.81, p < .05. Backward and unpaired groups did not differ, F < 1. Thus, forward pairings of rotational stimulation and lithium made the
Figure 1. Experiment 1: Unadjusted saccharin acceptance scores across saccharin conditioning days in an avfail procedure using a rotational avfail CS. Rats with histories of forward or control pairings of rotation and lithium toxicosis were given a taste aversion conditioning trial with rotation as the US on each saccharin conditioning day. A mixed-history baseline group received saccharin without rotation exposure. Saccharin consumption scores were converted to acceptance scores equivalent to suppression ratios. The ratio was $\frac{S}{(S + W)}$ where $S$ is the amount of saccharin consumed on any conditioning day and $W$ is the amount of water consumed on the day before the conditioning day. A ratio below 0.50 indicates lower saccharin consumption on the conditioning day than water consumption on the previous day. Plotted points represent group mean saccharin acceptance scores on each conditioning day. Error bars depict standard errors of the means.
rotation less effective in a subsequent CTA procedure by comparison to backward and unpaired control groups.

Discussion

The data illustrate a complete avfail effect (Revusky, 1982b) in the forward group relative to the backward and unpaired groups. The pattern of results appears to be entirely within an associative framework in that the control groups do not differ. Both the unpaired and backward groups show conditioned saccharin aversions, whereas the forward group has been spared an aversion and is statistically indistinguishable from the untrained baseline group.

The drug—drug pairings methodology of the typical avfail procedure has made a CAS interpretation of avfail difficult to validate because the use of internal drug state stimulus events leaves crucial timing parameters undefined and uncontrolled. Rotational was chosen for the present experiment because it (a) can eliminate a drug interaction interpretation of avfail by eliminating drug—drug pairings as such; (b) enables the sorts of parametric manipulations required to validate CAS theory; (c) is known to induce CTAs (e.g., Green & Rachlin, 1976; CTAs were demonstrated in an exploratory procedure using the rotational parameters reported here); (d) has obvious utility as a highly discriminable event; (e) provides a compound cue with prominent, coextensive internal and external (container or place) components; and (f) has useful conditioning possibilities for eventual therapeutic application.

This first demonstration of the use of a nondrug, compound CS in the avfail
procedure opens the avfail phenomenon to manipulation by more usual conditioning techniques. Consider the double dissociation design described earlier (p. 1), namely, the "bright, noisy, and tasty water" experiment of Garcia and Koelling (1966). This experiment provided strong empirical evidence of the selective association of tastes with sickness in the CTA paradigm. How might this logic be applied to avfail? It is not obvious how to establish an external component to an avfail CS drug that is prominent and coextensive with the internal drug state CS. Moreover, establishing such a compound does not address how the postulated parallel associations might be measured, that is, the associations cannot be directly measured by somehow presenting different elements of the presumptive compound US to different groups (cf. Garcia & Koelling). But the rotational cue successfully used as the first nondrug cue in the avfail procedure does have the required prominent, coextensive, and readily dissociable external and internal stimulus components. The independent, parallel, selective associations postulated by CAS theory can also be measured indirectly, as I will shortly argue. The rotation procedure might thus be used to validate a definitive feature of the CAS hypothesis (described in the section titled Stimulus Substitution, Response Competition, and Positive Transfer, pp. 34–36)—that is, whether two sorts of associations can be formed independently and in parallel during the first phase of the avfail procedure.

Suppose that rotation in a distinctive container can successfully be made to serve as a compound cue with highly salient external (place) and internal stimulus
components. Pairings of container rotation and lithium during the first conditioning phase of the avfail procedure are expected to produce independent associations between the external (container or place) components of rotation and lithium sickness, and between the internal components of rotation and homeostatic antisickness. Assuming of course that both components of the rotational cue actually enter into association with lithium or its aftereffects during the first conditioning phase, CAS theory implies response competition during the second, CTA conditioning phase—the conditioned sickness and CAS responses should cancel each other—and removing the external (place) component of the rotational cue during the second phase should therefore enhance avfail by eliminating a conditioned sickness component of the observed response. Associative blocking (e.g., Rescorla & Wagner, 1972), on the other hand, implies stimulus competition between the external (container or place) and internal elements of the compound rotational cue for association with lithium sickness during the first conditioning phase. The Rescorla-Wagner model—and indeed every other available theory except CAS—predicts that removing the external component of the rotational cue during the second conditioning phase will diminish avfail by eliminating or reducing the strength of the effective blocking cue. More generally, CAS theory implies positive transfer between training and test contexts with removal of a component of the training stimulus whereas all other learning theories imply negative transfer or generalization decrement on transfer testing.

Forward and control groups receive rotation and lithium in suitable temporal
arrangements during the first conditioning phase of the avfail procedure, with rotation taking place in special, distinctive containers of the sort used in the present study. The place component of the compound rotational cue is removable at any time by the simple expedient of replacing the platform of the rotational device with a turntable to which the home cages of the rats can be affixed. Rats can be transported and rotated as necessary without removing them from their home cages. During the second conditioning phase, groups are presented with novel saccharin immediately prior to rotation, with rotation taking place in the original containers for half the rats, and in the home cage for the remainder. Traditional associative blocking theories predict stronger avfail in the groups trained and tested in the container, that is, without a container-to-home-cage context shift between the conditioning phases. By these theories, the removal of a component of the compound rotational cue achieved by home cage rotation should produce weaker avfail, if it has any effect. CAS theory makes a unique and counterintuitive prediction: Avfail should be weaker in the groups trained and tested in the container. Removal of the external (place) component of the compound rotational cue should produce stronger avfail, if it has any effect, because it removes a conditioned sickness component of the overall response. This creates the paradox of weaker evidence of conditioning with greater similarity between the training and testing environments. Such a finding would be almost unprecedented.

Validation of the CAS hypothesis may be attempted by several different
strategies. Does the proposed double dissociation strategy have special advantage? A second, simpler strategy might be to substitute a direct sickness measure for the second or taste aversion conditioning phase of the avfail procedure. But sickness is an elusive concept as Experiment 3 (Pica as a Measure of Sickness in Rats, pp. 75–83) will indicate: What appears as conditioned sickness when food is available (Lett, 1992) appears as CAS when kaolin is available. The proposed double dissociation study presents the possibility of an outcome—using the original avfail measure rather than some other measure of possibly questionable relevance—predicted only by CAS and by no other theory. The predicted outcome, if obtained, would be paradoxical to all other conditioning accounts and would provide unique confirmation of CAS theory.

The present demonstration that rotation is effective in the avfail procedure also suggests that the application of antisickness conditioning to human contexts may now be considered. In possible human therapeutic applications (e.g., to reduce sickness from cancer chemotherapy), rotation is inappropriate, but virtual motion (subjective rotation) can produce nausea in a stationary patient (Hu, Stern, & Koch, 1991) and can conceivably serve as the CS in an antisickness conditioning context. In a therapeutic arrangement, perhaps virtual rotation precedes chemotherapy, and, in a higher-order pairing, a tone (or a taste, e.g., a distinctive chewing gum) precedes virtual rotation. The patient, after conditioning, might self-administer the distinctive flavor, and the resultant CAS response might ameliorate the nausea-inducing effects of chemotherapy.
Experiment 2

Ambient Temperature Increase as an Avfail CS

Rotation can be used as an avfail CS but rapidly loses its stimulus effects after rotation ceases. This is an advantage because rotation thereby clearly affords unambiguous operational definition and control, and also thereby clearly minimizes the participation of a direct, physiological interaction between rotation and lithium as described in the Introduction to the present chapter (pp. 47–49). But this is also a disadvantage because trace conditioning is less effective than delay conditioning (Pavlov, 1927). The stimulus effects of heat, however, might be expected to persist for a sufficient period to permit more effective manipulation of temporal parameters, and specifically to permit delay conditioning.

Heat as a conditioning stimulus has additional characteristics that are potentially advantageous from both experimental and theoretical viewpoints. First, changes in ambient temperature afford precise temporal and amplitude control essential for experimental analysis. By contrast, the temporal characteristics of drug onset could, for example, produce unwanted conditioning arrangements whereby a nominal forward pairing sequence is an effective backward pairing sequence (cf. Barker & Smith, 1974). Second, heat has the potential of serving as a stimulus with both external and internal components in contrast to other routinely used conditioning stimuli such as tones or drugs. This property could offer useful control features in complex arrangements such as avfail conditioning.

A third, potentially advantageous characteristic of heat as a conditioning
stimulus is that the toxic effects of heat and their amelioration have a species-relevant history which, from an evolutionary perspective, make it more likely that insight may be gained into putative behaviors such as antisickness responding. The anatomy and evolutionary—phylogenetic history of the physiological and behavioral mechanisms regulating body temperature is intimately interrelated with the anatomy and history of mechanisms of nausea, vomiting, and taste aversion learning. Specifically, Lawes (1990, 1991) hypothesized that mammalian brain mechanisms subserving nausea, emesis, and CTAs on the one hand, and osmoregulation on the other hand, originate with other "antinxious" defenses including thermoregulation from a common system of phylogenetically primitive behavioral escape and avoidance mechanisms subserving analogous functions. An interesting feature of Lawes' theory in the present context is that it offers a framework for understanding how the selective association of external cues with sickness and internal cues with homeostatic antisickness, for example, could be based on the sorts of self versus nonself distinctions defining behavioral versus homeostatic regulation at different levels of phylogenetic organization. The involvement of osmoregulation in this common antinxious defense system will take on greater significance in the section titled The Search for the Endogenous Antiemetic Mediating CAS (pp. 101–107). Indeed, the proposed endogenous antiemetic is arginine vasopressin (AVP), a principal neurohypophyseal osmoregulatory hormone and a close physiological correlate of subjective nausea in humans. What might be called the natural history or adaptive
significance of avfail is presumably more likely to be revealed using stimulus events that are, if not narrowly relevant to the feeding system, then more generally relevant to Lawes' antinoxious defense system. By contrast, whole-body rotation does not occur in nature and is not readily supposed to model naturally occurring events (but cf. Treisman, 1977).

Experiment 2 replicates the avfail procedure with heat as the CS in the first or avfail conditioning phase and as the US in the second or taste aversion conditioning phase: Rats with histories of forward or control pairings of heat and lithium sickness were given saccharin aversion conditioning trials with heat as the US in a standard avfail arrangement. The use of heat in the avfail procedure rests on the assumption that it serves as an effective US in a CTA procedure. This is required if avfail is to be revealed in the forward group by comparison with CTAs in controls during the second phase of the avfail procedure. This assumption is contrary to the existing archival literature in that an increase in ambient temperature failed to support CTAs in a study by Green, Hart, and Hagen (1981). These authors argued that the toxic internal effects of heat are referred to the external environment, that is, that a degree of heat sufficient to make rats nauseous or sick is nevertheless perceived as an external stimulus event. But the failure to show an effect of heat is surprising—lithium intoxication and heat illness symptoms are sufficiently similar in humans that Granoff and Davis (1978) have suggested a unitary mechanism of action. The common assumption that heat is effectively an external stimulus (e.g., Cunningham, Hawks, & Niehus, 1988;
1988; Cunningham, Niehus, & Bachtold, 1992; Green et al., 1981; Holder, Yirmiya, Garcia, & Raizer, 1989; P. S. Hunt, Spear, & Spear, 1991) also rests on a surprisingly narrow database (viz., Green et al., 1981). For these and other reasons, the finding of Green et al. was considered to be inconclusive. To anticipate the present findings, heat does successfully substitute for an avfail CS drug in the avfail procedure and therefore does produce CTAs. Heat-induced CTAs are explored in detail in the Appendices.

Method

Subjects

Subjects were 24 naive female Long-Evans hooded rats weighing 227–304 g at the start of the experiment. The water deprivation schedule in effect during the first conditioning phase of the experiment consisted of 24-hr deprivation and alternating 1- or 24-hr free access. Rats were deprived of water for approximately 20 hr at the time of heating or injections. The deprivation schedule in effect during the second conditioning phase consisted of 15 min of access per day.

Procedure

Rats were assigned by weight to three groups of eight rats each. They were housed in the heat treatment room for the duration of the experiment except as noted below. Room dimensions were 2.41 m x 3.30 m x 2.41 m (l x w x h). Four space heaters were placed in permanent locations on the floor around the periphery of the room. Two of the heaters were forced-air heaters, and their fans remained in continuous operation beginning 24 hr prior to the start of the
experiment. Ventilation was blocked approximately 2 hr before the start of treatment to prevent excessive loss of heat from the room and was unblocked approximately 2 hr after completion of the treatment. Room temperature was measured remotely using a calibrated digital thermometer with a flexible 1.5 m lead. The thermometer’s probe was positioned centrally in the treatment room. Temperature was recorded immediately before the heaters were turned on and every 10 min thereafter until it returned to within 2 °C of the baseline. With the heaters turned on, room temperature was allowed to reach a maximum of 35 °C and was maintained at maximum until the heaters were turned off. The room heated to maximum and cooled to within 2 °C of the baseline in approximately 30–40 min.

During the first phase of the experiment, all groups received four conditioning trials spaced three days apart consisting of experimental or control pairings of heat and lithium. Lithium was prepared as a 2% solution in distilled water and was injected intraperitoneally at a dose of 240 mg/kg. An experimental or forward pairings group received heat exposure followed by lithium injection on each trial. Space heaters were turned on 40 min prior to injection and remained on for a total time of 2 hr. A backward pairings group received heat and lithium in reverse order, that is, the lithium injection was followed 40 min later by heat exposure. An unpaired group received heat followed 40 min later by an equivalent-by-volume injection of saline. Approximately 24 hr later, the unpaired group received lithium and the remaining groups received saline.
For the second phase of the experiment, a fourth group was formed by removing the two rats from each of the forward, backward, and unpaired groups whose weights were closest to the mean for the parent group. This fourth group was used to provide a baseline of saccharin consumption in the absence of a heat-induced CTA. On the day after the fourth heat—lithium conditioning trial and 24-hr drinking period, rats were placed on a schedule of 15 min access to room-temperature tap water per day. Order of placement of drinking bottles on the cages was counterbalanced across groups. On Days 10, 13, 16, and 19 of this schedule, the water was flavored with saccharin (0.75% wt/vol). Immediately upon removal of the saccharin bottles, the heaters were turned on and the parent groups received heat as in the first phase of the experiment. The baseline group was removed from the treatment room during the heating period and was returned at the end of the heating period when the temperature had fallen to within 2 °C of the baseline.

Saccharin consumption scores were converted to acceptance scores in the form of suppression ratios. The ratio was $S / (S + W)$ where $S$ is the amount of saccharin consumed on any conditioning day and $W$ is the amount of water consumed on the day before the conditioning day. Acceptance scores on the first conditioning day served as the covariate, and the mean of the scores on the remaining three days served as the datum, in an ANCOVA. $F$ tests based on the error term and adjusted means of the overall ANCOVA were used for pairwise comparisons.
Results and Discussion

Groups did not differ in their water consumption (all ps > .10), and saccharin consumption scores were converted to acceptance scores for analysis. Groups did not differ in their saccharin acceptances on the first saccharin drinking day, $F < 1$. The ANCOVA yielded a significant group effect, $F (3, 19) = 4.23, p < .05$. Pairwise comparisons and inspection of Figure 2 indicate that saccharin acceptances were stronger in the forward group than in the backward control, $F (1, 19) = 5.42, p < .01$. The avfail effect was complete because the forward group did not differ from the baseline control, $F < 1$. The pattern of results was similar relative to the unpaired control. That is, saccharin acceptances were stronger in the forward group than in the unpaired control, $F (1, 19) = 7.29, p < .01$. Backward and unpaired groups did not differ, $F < 1$. Thus, forward pairings of heat and lithium make the heat ineffective in a subsequent taste aversion procedure by comparison to backward and unpaired control groups. Heat can successfully substitute for an avfail drug CS such as pentobarbital or a nondrug CS such as rotation.

The finding that heat can serve as a first-order CS in the avfail procedure poses a challenge to the view that heat is ineffective as a US in taste aversion conditioning (e.g., Green, et al., 1981). Most obviously, avfail in the forward group is assessed against heat-induced CTAs in Pavlovian controls. Furthermore, CAS theory posits that only internal rather than external cues can become associated with the postulated internal homeostatic response to sickness. If heat were an
Figure 2. Experiment 2: Unadjusted saccharin acceptance scores across saccharin conditioning days in an avail procedure using a heat avail CS. Rats with histories of forward or control pairings of heat and lithium toxicosis were given a taste aversion conditioning trial with heat as the US on each saccharin conditioning day. A mixed-history baseline group received saccharin without heat exposure. Saccharin consumption scores were converted to acceptance scores equivalent to suppression ratios. The ratio was $S / (S + W)$ where $S$ is the amount of saccharin consumed on any conditioning day and $W$ is the amount of water consumed on the day before the conditioning day. A ratio below 0.50 indicates lower saccharin consumption on the conditioning day than water consumption on the previous day. Plotted points represent group mean saccharin acceptance scores on each conditioning day. Error bars depict standard errors of the means.
Baseline
Forward
Backward
Unpaired

Acceptance Score

Saccharin Conditioning Day
external stimulus as the literature contends (e.g., Green et al., 1981), avfail should not have occurred.

**CAS theory requires an internal cue in the first or antisickness conditioning phase of the avfail procedure.** Only an internal cue can become associated with the CAS response, that is, with the hypothetical internal "antidote" to the internally generated sickness produced by the lithium US. Through such association, the heat CS of the present study is endowed with the ability to elicit a conditioned homeostatic antisickness response and consequently, for the forward group only, heat fails as a US in the taste aversion conditioning phase of the avfail procedure. Clearly, this process demands that heat serve an internal function. This theoretical requirement, together with the first demonstration of heat-induced taste aversion conditioning in the complex avfail arrangement, motivated detailed examination of the nature and parametric characteristics of heat-induced aversions in a simple CTA arrangement. This detailed examination in turn can be seen to provide empirical verification of certain assumptions on which interpretation of the avfail effect is based, at least with respect to a heat stimulus, and the studies are thus avfail control studies in each case. These studies are reported in Appendices 1, 2, and 3, and are summarized below.

Appendix 1 (Taste Aversion Conditioning with Heat as the US, pp. 119–140) reports four experiments providing two lines of evidence that heat serves as an internal stimulus, in contrast to the commonly held view (Cunningham et al., 1988, 1992; Cunningham & Niehus, 1989; Green et al., 1981; Holder et al., 1989; P. S.
Hunt et al., 1991). Experiment A (Demonstration of the Phenomenon, pp. 120–125) and Experiment D (Heat Dose Effects, pp. 131–136) serve as straightforward demonstrations that heat induces CTAs in a simple CTA paradigm. This is contrary to the finding of Green et al. (1981) and makes unnecessary their contention that the toxic effects of heat are referred to the external environment. Heat apparently acts as an internal stimulus, as required by CAS theory. Experiment B (The Role of Environmental Context Change, pp. 124–128) and Experiment C (The Role of Abrupt versus Gradual Heating, pp. 129–131) manipulate procedural conditions that could promote an external attribution of the locus of action of heat. Rats in the present procedure were housed in the heat treatment room and exposed to a gradual increase in temperature, whereas rats in the Green et al. study were transported to preheated room and thus exposed to an abrupt increase in temperature together with a correlated context change. Experiments B and C failed to show an effect of context change or abrupt versus gradual heating. Experiments A through D are clearly relevant to the present Experiment 2, which demonstrates that heat is an effective avail CS and is therefore required to be an internal stimulus by CAS theory and to support CTAs.

Appendix 2 (Heat-Induced Taste Aversions: The Role of Taste Intensity and Preexposure, pp. 141–158) further characterizes heat CTAs and explicitly examines an assumption of the avail procedure. The avail procedure uses a highly concentrated saccharin solution to enhance CS salience and thereby facilitate conditioning. [See Mackintosh (1974) for an early review of CS intensity effects in
a conditioning context and Revusky (1985) for a discussion of the logic in the avfail context. The strong saccharin taste initially produces profound neophobia but this becomes attenuated over three or four CTA conditioning trials in the baseline (no aversion) control (see Table 1, p. 10). An assumption of the avfail procedure is that the failure to attenuate neophobia in avfail controls (e.g., backward or unpaired controls) is evidence of a mild taste aversion that has been spared the experimental or forward group. This assumption was explicitly examined in Appendix 2 in the context of heat-induced CTAs. An alternative to a CTA interpretation of the failure to attenuate neophobia is a memory interpretation in which, for example, heat (or an avfail CS drug) interferes with memory for the taste. Finding an absolute decrease in saccharin consumption over trials, rather than a relative decrease or simply a failure to attenuate neophobia, is logically required to eliminate a memory interference interpretation of heat CTAs (or avfail): An absolute decrease directly contradicts the notion that the rat merely fails to remember having had saccharin on a previous occasion. Experiment E (The Role of Taste Intensity, pp. 143–151) minimized neophobia by using a less concentrated saccharin solution but failed to show the required absolute decrease in consumption over trials. Experiment F (The Role of Taste Preexposure, pp. 151–156) minimized neophobia by pre-exposing a highly concentrated saccharin solution and successfully showed the required absolute decrease. These experiments provide the first empirical confirmation of an assumption underlying the CAS interpretation of avfail, at least with respect to a heat stimulus.
Appendix 3 (Heat-Induced Taste Aversions: Unconditioned Effects, Memorial Processes, and the Attenuation of Neophobia, pp. 159-173) uses a retroactive state dependency procedure to determine whether state-dependent memory retrieval failure can account for the heat CTA (and avfail) findings. Richardson, Riccio, and Steele (1986) used this sort of procedure to show state dependency with pentobarbital and footshock stimulus states, but they failed to control for the participation of taste aversion conditioning. State dependency is a somewhat obscure but interesting alternative to CAS theory that was not presented with the other alternatives in Chapter 1 (Historical Background, pp. 1-40) partly because it is not consistent with the pattern of results on the avfail measure when all of the various controls that have been used are brought into consideration (see Table 1). Appendix 3 reports three experiments which fail to show retroactive state dependency with heat (Experiment G, pp. 162-164), pentobarbital (Experiment H, pp. 164-171), or footshock (Experiment I, pp. 171-172) stimulus states, but which provide support for the ability of heat and pentobarbital, but not footshock, to support CTAs consistent with conditioned sickness (in a CTA procedure) and CAS theory.
CHAPTER 3

FOOD CONSUMPTION AND PICA AS INDICES OF

ANTISISICKNESS CONDITIONING IN RATS

Lett (1986, 1992) presented evidence consistent with a necessary component of an associative blocking interpretation of avfail and having at least face validity as a well-controlled challenge to her (1983) hypothesis. These studies were discussed briefly in the sections titled Associative Blocking Explanation of Avfail (pp. 16–22), and Validating CAS Theory: Simple Conditioning Procedures (pp. 29–34).

Specifically, if blocking is to occur during the subsequent taste aversion conditioning phase of the avfail procedure, then the preceding drug–drug pairings phase must endow features of the CS drug with conditioned aversive properties: Blocking implies conditioned sickness rather than antisickness. In separate experiments, Lett (1992) paired pentobarbital, morphine, or place cues with lithium as the US and demonstrated on test that exposure to the CS drug or place suppressed food consumption in a manner consistent with a conditioned sickness interpretation. In Experiment 1, for example, groups of rats received forward or backward pairings of pentobarbital and lithium with an interinjection interval of 30 minutes as in the drug–drug pairings phase of the typical avfail procedure. Rather than using interference with subsequent taste aversion conditioning as the measure of drug–drug conditioning, however, Lett used food consumption on a forward pairing test: Rats were mildly food deprived and given a single forward pairing of pentobarbital and lithium followed by access to food. All rats ate less food on the forward pairing test relative to a baseline test that substituted normal
saline injections for the drug injections. In particular, rats with an experimental or forward pairings history ate less food relative to backward controls. Forward pairings of pentobarbital and lithium thus appear to yield conditioned sickness consistent with a blocking interpretation of avfail, rather than the conditioned antisickness predicted by CAS theory.

I propose that Lett's (1992) finding is nevertheless consistent with CAS theory. Food consumption has face validity as an index of sickness—it seems intuitively unlikely that a nauseated animal will eat food—but rats eat dirt or clay (kaolin) in a response to sickness known as pica (Mitchell, Wells, Hoch, Lind, Woods, & Mitchell, 1976). Pica may serve to dilute toxins in the gastrointestinal tract or to ameliorate the changes in gastrointestinal motility that accompany nausea. Several authors have suggested that rats made sick with a relatively low dose of lithium will adaptively eat small amounts of solid food when dirt or other similar nonnutritive substances are not available (Ervin & Teeter, 1986; Kratz & Levitsky, 1978; Watson, Hawkins, McKinney, Beatey, Bartles, & Rhea, 1987; Watson & Leitner, 1988). Lithium sickness can mask such eating relative to nonsickness baseline. In the Lett (1992) study, a high dose of lithium was used during training but a relatively low dose—within the range known to produce "paradoxical" food consumption and pica—was used on test to prevent a floor effect. I propose that controls ate more food on test because they experienced more rather than less intense sickness and because eating a small amount of solid food is an adaptive response to sickness. Pica is a well-validated and sensitive index of sickness that
overcomes this objection (e.g., McCaffrey, 1985; Mitchell, Krusemark, & Hafner, 1977; Mitchell, Laycock, & Stephens, 1977; Mitchell et al., 1976; Morita, Takeda, Kubo, & Matsunaga, 1988; Takeda, Hasegawa, Morita, & Matsunaga, 1993). And whereas feeding suppression is a passive behavioral measure that could reflect general behavioral suppression of diverse origin in addition to sickness, pica is an active measure that is difficult to interpret in the present context except as an index of gastrointestinal malaise. Finally, using kaolin consumption rather than food consumption as the measure of sickness makes unnecessary the somewhat problematic expedient of reducing the lithium dose on test. Experiment 3 substitutes kaolin for food in a partial procedural replication of Lett's (1992) Experiment 1.

Experiment 3

Pica as an Index of CAS in Rats

Method

Subjects

Sixteen male Sprague-Dawley rats were obtained from Charles River at a weight range of 190–200 g and weighed 363–528 g at the start of the experiment. They had continuous access to Purina Rat Chow and water, and to 45-mg kaolin (hydrated aluminum silicate) pellets (prepared to specification by the P. J. Noyes Company, Lancaster, NH), throughout the experiment. Kaolin was presented in wide-mouth glass jars (height 7.2 cm, diameter 5.4 cm) placed at the rear of the home cage. Each jar was attached to a flat, square base to eliminate spillage; rats
could not approach the jar without standing on the base.

Procedure

Rats were assigned on the basis of weight to two groups of eight rats each. Groups received five training trials spaced two or three days apart on a weekly schedule and consisting of forward or backward pairings of sodium pentobarbital and lithium. Pentobarbital (Somnotol brand) was diluted with normal saline to a concentration of 10 mg/ml and was injected intraperitoneally at a dose of 28 mg/kg. Lithium was prepared as a 2% solution in distilled water and was injected intraperitoneally at a dose of 250 mg/kg. An experimental or forward pairings group received pentobarbital followed 30 min later by lithium on each training trial. A backward pairings group received pentobarbital and lithium in reverse temporal order.

Kaolin pellets were continuously available in the home cage during training. Earlier exploratory work in which kaolin was habituated in the absence of sickness had shown that not all rats could be expected to consume kaolin, and moreover that the rats might consume kaolin hours rather than minutes after lithium when the CAS response is less likely to be present (Musil, 1993). Kaolin availability during training was designed to ensure that all rats had experience with kaolin consumption in the presence of sickness prior to test, and to parallel Lett (1992) who had similarly made food continuously available during training. All rats were observed to eat amounts of kaolin sufficient to form whitened fecal boluses during training, and to approach and eat from the kaolin jars within 20 min of the lithium
injection during the forward pairing test.

Five days intervened between training and testing. All rats were treated identically on each of two test trials spaced two days apart. The first was a baseline trial in which rats received two injections of normal saline with an interinjection interval of 30 min. The second was a forward pairing trial in which rats received pentobarbital followed 30 min later by lithium. The two test trials were identical in all specified respects except for the contents of the syringe. Drug doses were unchanged from training to test, and saline injection volumes on the baseline test were equivalent to the corresponding drug injection volumes on the forward pairing test. Kaolin consumption was measured 1.5, 3, 6, 12, and 24 hr after the second of the two injections on each test day. Jars containing preweighed kaolin were placed at the rear of the cages at the time of the second injection and were replaced with fresh jars at the end of each measurement interval. Although negligible, spillage of the kaolin pellets was assessed by visual inspection and replacement by count.

**Results**

Table 2 shows cumulative kaolin consumption on the baseline (saline—saline) and forward pairing (pentobarbital—lithium) test trials for each measurement interval. By inspection, and in agreement with casual observation during training, the amount of familiarized kaolin eaten on baseline was negligible in the absence of sickness. Both groups increased their kaolin consumption on the forward test relative to baseline, and the increase was less in the forward group relative to the backward
Table 2. Experiment 3: Group mean cumulative kaolin consumption (in grams) for each measurement interval on baseline and forward test trials. Values in parentheses are standard errors of the means.

<table>
<thead>
<tr>
<th>Sample period (time since injection, in hours)</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-1.5</td>
</tr>
<tr>
<td>Baseline (saline–saline) test</td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>0.23 (0.08)</td>
</tr>
<tr>
<td>Backward</td>
<td>0.18 (0.05)</td>
</tr>
<tr>
<td>Forward (pentobarbital–lithium) test</td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>0.95 (0.32)</td>
</tr>
<tr>
<td>Backward</td>
<td>1.84 (0.23)</td>
</tr>
</tbody>
</table>

Note. Rats with histories of forward or backward pairings of pentobarbital and lithium received a baseline consumption test trial—with two normal saline injections substituted for the usual drug injections and spaced 30 min apart as in training—followed two days later by a forward pairing test trial. Kaolin consumption was measured at the specified intervals following the second injection on each test trial.
Data were entered into a 2 (tests) X 2 (groups) X 5 (measurement intervals) ANOVA to confirm the statistical reliability of these observations. A significant main effect of test confirmed that rats in both groups ate more kaolin on the forward test than on baseline, $F(1, 14) = 86.88, p < .01$. This global pattern was analyzed using multiple $t$ tests for each group and measurement interval. The smallest value for a difference between baseline and forward tests was $t(7) = 2.38, p < .05$ for the forward group and $t(7) = 6.48, p < .01$ for the backward group. By this measure, rats in both groups thus experienced at least some degree of sickness for well over 12 hr after the lithium injection.

A significant Test X Group interaction confirmed a global difference in kaolin consumption between groups on the forward test but not on baseline, $F(1, 14) = 8.18, p < .05$. This global pattern was analyzed using multiple $t$ tests for each test day and measurement interval. For the forward test, groups differed on all intervals except the 24-hr interval, with the smallest statistically significant $t(14) = 2.25, p < .05$. Lower consumption in the forward group implies less sickness, consistent with a CAS interpretation. For the baseline test, groups did not differ at any time, all $t$s < 1.

**Discussion**

All rats ate less food (Lett, 1992) and more kaolin on forward test relative to baseline, and rats with a forward pairings history ate less food (Lett) and less kaolin relative to a backward control: Are Lett's (1992, Experiment 1) food...
consumption finding and the present kaolin consumption finding reconcilable?

Lett's finding of lower food consumption in the forward group relative to baseline is consistent with CAS theory. By analogy to conditioned analgesia mediated by endorphins in anticipation of pain, CAS is supposed to be mediated by an endogenously occurring antiemetic substance in anticipation of sickness (Revusky & Harding, 1986). Conditioned anticipatory release of an endogenous antiemetic might be supposed to ameliorate nausea and feelings of sickness but should not enhance appetite: It is reasonable to expect experimental animals not to be sick, and not to be hungry, during a bout of lithium toxicosis. Lett's finding of lower food consumption in the forward group relative to a backward control is also consistent with CAS theory: Rats made sick with lithium are known to eat a small amount of food when nonnutritive dirt or clay is not available, and rats in the backward group may paradoxically have eaten more food because they were more rather than less sick. The present finding of lower kaolin consumption in the forward group relative to a backward control supports this interpretation.

Higher kaolin consumption in both forward and backward groups relative to baseline implies that all animals are made sick in some sense and to some unknown degree by lithium toxicosis regardless of conditioning history. Perhaps the CAS response is strong enough to ameliorate but not to eliminate the intense sickness produced by the very high lithium dose. Alternatively, the putative endogenous antiemetic mediating CAS is supposed to act nonspecifically against the nausea or distress produced in common by a variety of toxins having different
mechanisms of action: Perhaps nausea is at least partly independent of the sorts of gastrointestinal phenomena accompanying toxicosis and for which pica may be the natural remedy. Inhibition of gastric motility—measured as a delay in gastric emptying time—is illustrative. Delayed gastric emptying is closely associated with and commonly supposed to be causally related to nausea and emesis. Lett (1986) paired pentobarbital, morphine, or place cues with lithium toxicosis and demonstrated on test that exposure to the CS drug or place enhanced the slowing of gastric emptying induced by the lithium. Forward pairings of pentobarbital and lithium thus appear to yield conditioned sickness rather than antisickness on this measure as well as on the feeding suppression measure of the 1992 paper. But Lett (1986) suggested as an alternative to a conditioned sickness interpretation the possibility that nausea and inhibition of gastric motility are independent responses mediated by different mechanisms. In support of this alternative, Reid, Grundy, Khan, and Read (1995) demonstrated that nausea and delayed gastric emptying occur independently and argued that a causal relation is therefore unlikely: Perhaps delayed gastric emptying is part of a generalized stress response rather than specific to factors that induce nausea. In the present context, conditioned anticipation of lithium sickness in the forward group might readily be supposed to produce stress with delayed gastric emptying and CAS.
CHAPTER 4
ALLEVIATION OF EMESIS FROM THE CANCER CHEMOTHERAPY DRUG CISPLATIN BY ANTISICKNESS CONDITIONING IN FERRETS

The findings of Experiment 3 using pica as an index of CAS prompt reinterpretation of the Lett (1992, Experiment 1) findings in terms of CAS theory. First, pica has greater face validity than feeding suppression as a measure of sickness in rats because it is a behaviorally active measure that is difficult to interpret in the present context except as a measure of sickness, whereas feeding suppression is a behaviorally passive measure that may reflect response suppression of diverse origin in addition to sickness. Second, a common CAS interpretation of the present finding and those of Lett has the advantage of conceptual parsimony. But the procedural replication of Lett was not exact and does not provide a direct test of the available alternatives. Rather than undertaking such a test, I take the position that the use of rats or any other nonvomiting species in any attempt to validate CAS is inherently problematic in part because all indirect, consummatory measures—including the CTA measure of the avfail procedure as well as the feeding suppression and kaolin consumption measures—are subject to misinterpretation. Experiment 4 uses the ferret—a vomiting species that models human emesis (Florczyk, Schurig, & Bradner, 1982; King, 1990)—to provide a direct measure of sickness and the first unequivocal test of the CAS hypothesis.
Experiment 4

Emesis as an Index of CAS in Ferrets

Method

Subjects

Eleven castrated, descented adult male ferrets (Mustela putorius furo) obtained from Marshall Farms (North Rose, NY) were housed individually in rack-mounted stainless steel rabbit cages (Allentown Caging Equipment, Allentown, NJ) under continuous lighting conditions. Cages were adapted for use with ferrets, and each contained a rectangular plastic basin large enough for the animal to sleep in. Ferrets had ad libitum access to Mazuri ferret food (PMI Feeds, St. Louis, MO) and water. They weighed 1180–2080 g at the start of the experiment.

Apparatus

Four observation boxes each had inside dimensions of 85 x 41 x 39 cm (l x w x h) and were constructed with 2-cm finished plywood on five sides. The sixth side was a long front-facing panel of 0.5-cm transparent Plexiglas with hardware hinge fasteners along the bottom edge and a closure at the top. The floor and sides of the box were fitted with a removable, washable liner of opaque white 0.5-cm Lexan. The front-facing side of the liner was 6.5 cm high and the remaining sides were 23 cm high. An outside-mounted fan provided ventilation through a 6.5-cm circular port in one of the wooden side walls.

Procedure

Beginning 20 weeks prior to the start of the experiment, ferrets were handled daily
and were injected with normal saline every three or four days on a weekly schedule. On the day before the start of the experiment, eleven ferrets were assigned by weight to experimental (n = 5) and control (n = 6) groups.

Place Pairings. In an initial place–drug pairings phase of the experiment, all ferrets were exposed to pairings of observation box cues with lithium sickness on five occasions spaced three or four days apart. Lithium was prepared as a 2% solution in distilled water and was injected intraperitoneally at a dose of 120 mg/kg. On each pairing occasion, the ferret was placed in the box, removed at 20 min after placement for lithium injection, and immediately replaced in the box for an additional 60 min before return to the home cage. The purpose was to reduce the novelty of place cues which could otherwise interfere with testing (Pavlov, 1927) and to look for signs of nausea consistent with conditioned sickness to an external (place) cue (cf. Morrow & Rosenthal, 1996) for contrast with the expected CAS to an internal (drug) cue. All ferrets were treated identically during the place pairings phase.

Videotapes of the ferrets in the boxes were scored for total number of sickness behaviors of gaping, mouth clawing, chin rubbing, and backward walking (J. G. Fox, 1988; King, 1988; Meachum & Bernstein, 1992; Parker, Hills, & Jensen, 1984) occurring prior to the lithium injection on each trial by a rater who was blind to group membership of the ferrets. A gape is a rapid, large-amplitude opening of the mouth with the corners of the mouth retracted. In mouth clawing, front paws rub the snout in a forward and downward direction with a rapid digging or clawing
motion. Chin rubbing involves lowering the head to bring the mandible into direct contact with floor or wall and moving the body forward. Backward walking was counted as a sickness behavior when belly and muzzle were in contact with the floor.

Antisickness Conditioning. Five days intervened between the place pairings and antisickness conditioning phases of the experiment. During the antisickness conditioning phase, ferrets in the experimental group \((n = 5)\) received a forward pairing of pentobarbital followed 30 min later by lithium on each of five training trials spaced three or four days apart. Subgroups of the control group received either backward \((n = 3)\) or unpaired \((n = 3)\) drug–drug arrangements. The backward subgroup received the drugs in reverse temporal order, and the unpaired subgroup received them 24 hr apart. Number and timing of injections were equated for all groups by pairing pentobarbital with saline injection on the training day for the unpaired group and by giving saline injection to subjects in the forward and backward groups on the day after the training day. Ferrets were removed from and immediately returned to the home cage for these injections: They were not placed in the observation boxes at any time during this phase. Pentobarbital was diluted in normal saline to a concentration of 12 mg/ml and was injected intraperitoneally at a dose of 8 mg/kg. The lithium dose was increased from 120 mg/kg to 180 mg/kg to increase the likelihood that it would continue to support conditioning (cf. Cannon, Berman, Baker, & Atkinson, 1975; Klein et al., 1986; Rudy, Iwens, & Best, 1977). Saline injections were equivalent-by-volume to
the lithium. To eliminate any training drug residue, no drugs were given for two weeks immediately prior to test.

**Lithium and Cisplatin Test Trials.** On the first test trial, all ferrets received a forward pairing of pentobarbital followed 30 min later by lithium. On this occasion, the drug–drug pairing occurred in conjunction with placement in the observation boxes. Each ferret was placed in the box, removed at 30 and 60 min for injections, and replaced for an additional 70 min after the second injection. Drug doses were the same as for the antisickness conditioning phase.

Four weeks after the lithium test, all ferrets were given a "reminder" training trial, that is, a forward or control pairing of pentobarbital and lithium as described for the drug–drug pairings phase, followed 10 days later by a second test trial with cisplatin substituted for the lithium. Cisplatin is the most highly emetogenic anticancer drug in common use (McKeage, 1995). Each ferret was injected with cisplatin, placed in the observation box, removed at 30 min after placement for the pentobarbital injection, and returned for an additional 5.5 hr. Timing of the injections was based on evidence that the cisplatin is unlikely to have had its intended effect before the pentobarbital in the present procedure (Rudd, Jordan, & Naylor, 1994). Cisplatin (David Bull Laboratories, Mulgrave, Victoria, Australia) was obtained at a concentration of 1.0 mg/ml in normal saline and was injected intraperitoneally at a dose of 10 mg/kg.

For the scoring of videotapes of the lithium and cisplatin test trials, retching was defined as forceful rhythmic abdominal contractions in association with the
adoption of a characteristic posture with the mouth usually closed and not resulting in the ejection of stomach contents, and emesis was defined as the forcible expulsion of stomach contents when present in association with marked spinal flexion and the mouth wide open (Andrews, Bhandari, Garland, Bingham, Davis, Hawthorn, Davidson, Roylance, & Lane, 1990). The time of the first episode of retching or emesis, the number of discrete episodes, and the total episode duration were recorded from videotapes of the observation period. The onset of retching or emesis following one minute with no visible relevant movements marked the beginning of each discrete episode.

Videotapes were scored by a rater who was blind to the group membership of the ferrets. The rater followed a descriptive protocol for identifying retching or emesis. These behaviors are clearly recognizable as reflexive or species-typical responses to unconditioned sickness involving the entire trunk and culminating in oral expulsion of any stomach contents. The videotapes of the place pairings trials were not scored for retching or emesis because such strong reflexive behaviors were neither expected nor observed as potential conditioned sickness responses to the lithium-paired place cues.

During the period of experimentation, two ferrets (one in the forward group and one in the unpaired group) died of causes unrelated to treatment.

**Results and Discussion**

As can be seen in Figure 3, the number of sickness events increased over trials during the place pairings phase of the experiment, \( F_{\text{linear}} (1, 40) = 37.72, p < .01, \)
Figure 3. Experiment 4: Mean number of sickness events as a function of number of pairings of observation box cues with lithium sickness during the place pairings phase. Error bars depict standard errors of the means. Ferrets in the forward pairings and pooled control groups were treated identically during this phase and did not differ on the dependent measure [F < 1].
consistent with the conditioning of an aversion to the place. The ferrets' sickness behaviors in the place are highly characteristic of nausea (cf. Parker et al., 1984) and may be analogous to anticipatory nausea in humans undergoing cancer chemotherapy (Morrow & Rosenthal, 1996).

For the lithium test trial, the time of the first episode of emesis, and the number and total duration of the episodes, are given for each animal in Table 3. Backward and unpaired controls did not differ on any of these measures, all \( t < 1 \), and were pooled. Ferrets in the forward group differed from pooled controls on all measures. They had significantly delayed onset, \( t (8) = 2.68, p < .05 \), and fewer episodes, \( t (8) = 9.23, p < .01 \), of emesis, and spent significantly less time in emesis, \( t (8) = 4.83, p < .01 \). Figure 4 shows the number of episodes of emesis as a function of time from the lithium injection.

For the cisplatin test trial, the pattern of results was similar. The time of the first episode of emesis, and the number and total duration of the episodes, are given for each animal in Table 4. Backward and unpaired controls did not differ on any measure, largest \( t (3) = 1.59, p > .20 \), and were pooled. Ferrets in the forward group had significantly fewer episodes, \( t (7) = 3.06, p < .02 \), and spent significantly less time in emesis, \( t (7) = 3.96, p < .01 \), but did not differ from controls in time of onset, \( t < 1 \). Figure 5 shows the number of episodes of emesis as a function of time from the cisplatin injection.

Note that the outcome of the cisplatin test depended on selection of an appropriate timing interval between the cisplatin and pentobarbital injections. The
Table 3. Experiment 4: Characteristics of lithium-induced emesis for individual ferrets on test.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Group</th>
<th>Time of First Episode (minutes after lithium injection)</th>
<th>Number of Episodes</th>
<th>Total Episode Duration (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Forward</td>
<td>33</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>Forward</td>
<td>27</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>Forward</td>
<td>23</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>Forward</td>
<td>13</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>Forward</td>
<td>09</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Backward</td>
<td>12</td>
<td>6</td>
<td>180</td>
</tr>
<tr>
<td>8</td>
<td>Backward</td>
<td>06</td>
<td>5</td>
<td>105</td>
</tr>
<tr>
<td>10</td>
<td>Backward</td>
<td>10</td>
<td>6</td>
<td>165</td>
</tr>
<tr>
<td>4</td>
<td>Unpaired</td>
<td>08</td>
<td>5</td>
<td>115</td>
</tr>
<tr>
<td>5</td>
<td>Unpaired</td>
<td>08</td>
<td>6</td>
<td>225</td>
</tr>
</tbody>
</table>

Note. Ferrets had histories of forward place–lithium pairings followed by forward, backward, or 24-hr delayed (unpaired) pentobarbital–lithium pairings. All ferrets received a forward pairing of pentobarbital and lithium on the first test trial. An episode is a discrete period of continuous retching and vomiting separated from other episodes by a period of at least 1 min with no visible relevant movements.
Figure 4. Experiment 4: Mean number of episodes of emesis on lithium test as a function of time from the lithium injection for ferrets with histories of forward (forward pairings group) and backward or unpaired (pooled control group) arrangements of pentobarbital and lithium. All ferrets received pentobarbital followed 30 minutes later by lithium on test. Error bars depict standard errors of the means.
Forward Pairings
Pooled Controls

Group Mean Number of Episodes

Time from Lithium Injection (min)
Table 4. Experiment 4: Characteristics of cisplatin-induced emesis for individual ferrets on test.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Group</th>
<th>Time of First Episode (minutes after lithium injection)</th>
<th>Number of Episodes</th>
<th>Total Episode Duration (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Forward</td>
<td>118</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>Forward</td>
<td>87</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>Forward</td>
<td>114</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Forward</td>
<td>109</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>Backward</td>
<td>122</td>
<td>6</td>
<td>185</td>
</tr>
<tr>
<td>8</td>
<td>Backward</td>
<td>117</td>
<td>6</td>
<td>195</td>
</tr>
<tr>
<td>10</td>
<td>Backward</td>
<td>111</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>Unpaired</td>
<td>101</td>
<td>7</td>
<td>275</td>
</tr>
<tr>
<td>5</td>
<td>Unpaired</td>
<td>95</td>
<td>4</td>
<td>200</td>
</tr>
</tbody>
</table>

Note. Ferrets had histories of forward place—lithium pairings followed by forward, backward, or 24-hr delayed (unpaired) pentobarbital—lithium pairings. All ferrets received a forward pairing of pentobarbital and cisplatin on the second test trial. An episode is a discrete period of continuous retching and vomiting separated from other episodes by a period of at least 1 min with no visible relevant movements.
Figure 5. Experiment 4: Mean number of episodes of emesis on cisplatin test as a function of time from the cisplatin injection for ferrets with histories of forward (forward pairings group) and backward or unpaired (pooled control group) arrangements of pentobarbital and lithium. All ferrets received cisplatin followed 30 min later by pentobarbital on test. As expected, cisplatin-induced emesis was substantially delayed in time by comparison with lithium-induced emesis. Error bars depict standard errors of the means.
Graph showing the group mean number of episodes over time from cisplatin injection.

- **Forward Pairings**
- **Pooled Controls**
nominal CS is the pentobarbital injection per se, but the effective CS is presumed to consist of the conditionable features of the CS drug effect that immediately precede and accompany the lithium sickness US during training. By this reasoning, the cisplatin injection should be timed so that cisplatin sickness coincides with the effective pentobarbital CS. Notwithstanding the fact that experimental and control groups differed significantly and appropriately with respect to confirmation of CAS theory in this first direct test, the timing of the cisplatin injection may not have been optimal. Specifically, cisplatin sickness is evidently delayed by approximately 70 min relative to lithium sickness in this procedure (cf. Figures 4 and 5). Thus, the cisplatin finding might have been stronger had the temporal interval between injections been 60 rather than 30 min, but this is an empirical issue requiring further parametric investigation.

I have confirmed CAS using both drug and nondrug events as avfail CSs and USs: Rotational stimulation (Experiment 1) and high ambient temperature (Experiment 2) can successfully substitute for pentobarbital in the avfail procedure. I have confirmed CAS using the indirect, consummatory measures of CTA (Experiments 1 and 2) and pica (Experiment 3) in rats, and using the direct measures of retching and emesis in ferrets (Experiment 4), and have reconciled Lett’s (1992, Experiment 1) apparently contradictory finding with the CAS interpretation. The elevation of CAS from a possible interpretation of an interesting class of learned behavior in rats to what could prove to be a basic mammalian adaptive response opens even more interesting possibilities for advances in
conditioning.

Scientific discontinuities are often more valuable than confirmation of expected outcomes. The twenty-year-old discontinuity that avfail presents—which could have been a trivial variation of a conventional Pavlovian procedure such as associative blocking—is now attributable to the conditioning of an antisickness response. Empirical examination of the validity issues covered in Chapters 2 through 4 resolves the discontinuity, reveals a form of homeostatic response with broad theoretical implications, and raises the hope of a new weapon in the clinical armamentarium which could positively affect the course of anticancer chemotherapy. Potential theoretical implications and practical applications are discussed in the next chapter (Chapter 5, Theoretical and Practical Implications, pp. 99–114).
CHAPTER 5
THEORETICAL AND PRACTICAL IMPLICATIONS

The Search for the Endogenous Antiemetic Mediating CAS

CAS, in theory, does not depend on the amelioration of specific effects of particular emetogenic agents but rather acts nonspecifically to counteract the nausea or distress produced in common by a variety of agents (Revusky & Harding, 1986). This implies that CAS is mediated by an endogenously occurring antiemetic substance that acts nonspecifically with respect to the emetogenic agent. Experiment 4 (Emesis as an Index of CAS in Ferrets, pp. 84–99) supports the theory in that a CAS response conditioned with lithium alleviates cisplatin-induced sickness (Figure 5, p. 97). Experimental efforts should now be directed at identifying the putative endogenous antiemetic subserving CAS. The present section elaborates on the rationale for supposing that CAS is mediated by an endogenous antiemetic, and develops an empirical strategy or proposal for demonstrating its existence in an animal model.

By heuristic analogy to the search for the humoral mediator for chemotherapy-induced emesis (e.g., Carl, Cubeddu, Lindley, Myers, & Rezvani, 1989; King, 1988), there is a rationale for supposing that CAS is mediated by an endogenous humoral antiemetic. CAS acts nonspecifically with respect to the nausea-inducing agent—CAS conditioned with gamma radiation prevents a lithium-induced CTA (Revusky & Harding, 1986) and CAS conditioned with lithium alleviates cisplatin-induced retching and vomiting (Experiment 4). A candidate antiemetic is arginine vasopressin (AVP). AVP is a close correlate of the subjective
nausea—with or without vomiting—produced by rotation, virtual rotation, lithium, copper sulphate, and several other treatments having very different mechanisms of action (Verbalis, Richardson, & Stricker, 1987; cf. Nussey, Hawthorn, Page, Ang, & Jenkins, 1988). Thus, both CAS and AVP are nonspecific with respect to the nausea-inducing agent.

But is AVP an endogenous antiemetic? The causal role of AVP release in nausea and vomiting is currently under very active investigation. Whether and under what circumstances AVP release alleviates or indeed causes nausea is unknown (e.g., Anonymous, 1991; Kieman, Soykan, Lin, Dale, & McCallum, 1997; Koch, 1991, 1997; cf. Lawes, 1990, 1991). Earlier research suggested that AVP release is a homeostatic response that is preparatory to vomiting in that it leads to water retention by the kidneys and could thereby serve a fluid retention function (e.g., Rowe, Shelton, Helderman, Vestal, & Robertson, 1979; Shelton, Kinney, & Robertson, 1977). But the increase in circulating AVP levels typically accompanying nausea or vomiting is at least an order of magnitude higher than that required to produce maximum antidiuresis (e.g., Anonymous, 1991). Moreover, the detailed interrelations between nausea and vomiting are virtually unknown—Could antiemetic drugs prevent or block objective vomiting responses but thereby actually make subjective nausea worse? R. A. Fox, Keil, Daunton, Crampton, and Lucot (1987) argued that AVP release is a homeostatic response that might alleviate nausea, but Cheung, Kohl, Money, and Kinter (1994) argued that AVP release directly causes nausea and vomiting. Cheung et al. administered
AVP and AVP receptor antagonists to monkeys and showed a pattern of pharmacological results consistent with their interpretation, but of course the pharmacological administration of AVP in sufficient dose would be expected by CTA precedents to cause nausea, and possibly vomiting, as a drug effect, whatever its physiological role. Others have suggested that AVP release is directly related not to nausea or vomiting but rather to physiological and behavioral stress or anxiety (e.g., Kiernan, Soykan, Lin, Dale, & McCallum, 1997; Reid, Grundy, Khan, & Read, 1995). The present working hypothesis is that AVP or glucocorticoids mediate nausea and vomiting or their aftereffects within the causal chain, but whether one or the other is an endogenous emetic or antiemetic entails considerable conceptual ambiguity. Lawes' (1990, 1991) hypothesis is relevant because it illustrates the sort of adaptive evolutionary framework within which this ambiguity is resolved. Indeed, the roles of AVP and glucocorticoid equivalents in the mediation of osmoregulation—possibly related to vomiting?—and behavioral stress responses have been reversed several times within phylogeny, and this reversal of roles should be reflected in reversals within the individual organism at different levels of organization. Glucocorticoids are known to potently inhibit AVP release and AVP to inhibit glucocorticoid release. Glucocorticoids also have antiemetic properties [as shown in a valid CTA interference or antiemetic screening design using dexamethasone (Cairnie & Leach, 1982)] (Raff, 1987) and have been identified as CTA attenuators by Revusky and Martin (1988).

A practical problem in the search for the endogenous antiemetic is where to
look: The evidence proposed in the present thesis for an endogenous antiemetic substance is behavioral. The proposed search strategy is based on the assumption that a humoral mediator exists. A measurable, humoral counterpart to a role for AVP or glucocorticoids in nausea is probable. For example, AVP release in response to nausea in humans (Rowe, Shelton, Helderman, Vestal, & Robertson, 1979) is measurable in plasma by radioimmunoassay where it increases 100- to 1000-fold following administration of lithium, copper sulphate, apomorphine, and several other nausea-inducing treatments (Verbalis et al., 1987).

The proposal for determining whether CAS is mediated by an endogenous antiemetic is an extension of the design used by Garcia, Ervin, and Koelling (1967) to show that radiation-induced CTAs are mediated by elevations in blood histamine levels. The essential logic is to extract blood from trained "donor" rats at the time of elicitation of a CAS response and to test the blood plasma as an antiemetic in a valid CTA interference or antiemetic screening procedure (Cairnie & Leach, 1982). A successful outcome confirms the existence of a humoral antiemetic agent mediating CAS.

In the first phase, one group of rats receives pentobarbital and lithium in a forward-paired arrangement on four or five occasions and a second group receives pentobarbital and lithium in an unpaired or backward-paired arrangement. On a subsequent trial, rats in both groups are injected with the pentobarbital CS and are exsanguinated at a time after injection when the CAS response is expected to be maximal. Plasma is extracted through centrifugation and stored. In
the second phase, experimentally naive rats have brief access to novel saccharin solution followed by lithium injection or some other nausea-inducing treatment. This procedure should result in taste aversion conditioning. For half of the rats, plasma from CAS-conditioned donors is interpolated between saccharin consumption and lithium sickness; for the remaining rats, plasma from control donors is interpolated. A biochemical antisickness agent in plasma from CAS-conditioned donors should interfere with the conditioning of a taste aversion in the experimental group. This design is conceptually similar to the avfail design with the two conditioning phases conducted between- rather than within-subjects. A successful outcome is consistent with CAS theory but not with other theories that require within-subjects physiological or psychological "continuity" between phases.

If this CTA interference or antiemetic screening procedure indicates that CAS is humorally mediated, the next step is direct confirmation of humoral mediation in the avfail context. In the first phase, rats in an experimental group receive forward pairings of pentobarbital and lithium with plasma from CAS-conditioned donors interpolated between pentobarbital and lithium. Control groups receive various combinations of plasma from control or CAS-conditioned donors in conjunction with standard Pavlovian control arrangements of pentobarbital and lithium. All groups are subsequently tested for the CTA-inducing capacity of pentobarbital using saccharin as the novel taste. The group with a history of forward pairings combined with interpolated plasma from
CAS-conditioned donors should show CTA on test because the production and conditioning of an endogenous CAS response has been obviated by exogenous administration of the putative humoral antiemetic mediating CAS; a comparable group given plasma from unconditioned donors should show avfail. The design eliminates alternatives to a CAS interpretation by reversing the paradoxical avfail outcome.

This general strategy, if successful, confirms the existence of a CAS-mediating humoral antiemetic but does not reveal its identity. Whether AVP or glucocorticoids mediate CAS can be determined behaviorally by interpolating an external stressor such as brief inescapable footshock between pentobarbital and lithium in the first phase of the avfail procedure. This is expected to interfere with avfail but different theories postulate very different interference mechanisms. External stressors have obvious conditionable CS or cue properties and also produce massive increases in circulating glucocorticoid levels. By traditional Pavlovian theories, the interpolated stressor should compete with and overshadow the pentobarbital cue for association with the lithium sickness US: "Interference" occurs because the pentobarbital has not become associated with lithium sickness and cannot therefore block a subsequent saccharin—sickness association. By CAS theory, stimulus competition does not occur. An interference effect, if it occurs, can only be mediated by attenuation of the sickness US which thereby obviates the production and conditioning of an antisickness response. Glucocorticoid mediation of CAS provides the mechanism: Stress-induced
glucocorticoid elevation attenuates sickness either directly or by inhibition of AVP release.

If interpolation of an external stressor between pentobarbital and lithium produces the expected "avfail interference effect," how are the various theoretical mechanisms to be dissociated? First, the cue properties of an external stressor are dissociable from its unconditioned properties. For example, placement in a shock box can be established as a cue for shock in rats, and shock can be omitted on a subsequent placement. In the present context, shock administration in a shock box can be interpolated between pentobarbital and lithium in the first phase of the avfail procedure, and placement in the box without shock can be interpolated between saccharin and pentobarbital in the second phase of the avfail procedure. The box cue is a potential blocking cue and may also trigger conditioned glucocorticoid release. Second, the residual cue and unconditioned properties of an external stressor are dissociable from glucocorticoid release by adrenalectomy in rats with or without the maintenance of a baseline level of glucocorticoids by injection. The various theoretical mechanisms mediating the expected avfail interference effect can be dissociated by the combination of adrenalectomy and putative blocking cue presentation in a double dissociation design.

Application to Unconditioned Nausea and Vomiting in Cancer Chemotherapy

One strategy for applying the animal research to sickness alleviation in human clinical settings is to use nausea-ameliorating CSs that can be patient-initiated.
This strategy guides development of an animal therapy model as follows. The logic is to pair an initially neutral stimulus with a CAS-eliciting stimulus in a higher-order conditioning arrangement (cf. Rescorla, 1980) so that the neutral stimulus comes to elicit a CAS response. When the animal subsequently experiences nausea, a voluntary behavioral response can be performed that reinstates the neutral stimulus and thereby alleviates the sickness. In the first conditioning phase, rats receive pairings of rotation with an emetogenic anticancer drug such as cisplatin, and in the second phase, they receive pairings of a neutral stimulus with rotation in a higher-order conditioning arrangement. On test, all rats are housed in Skinner boxes and injected with the emetogenic drug; barpressing produces contingent exposure to the neutral stimulus which should now serve as a second-order antisickness-eliciting CS. The anticancer drug can be administered on a periodic basis in this "continuing treatment" phase (e.g., once every 5 days, mimicking a cancer chemotherapy regimen) with barpressing and pica used as converging measures to assess whether rats barpress more frequently to produce the CAS-eliciting CS and whether this barpressing behavior reduces sickness as indexed by pica.

Application to Anticipatory Nausea and Vomiting in Cancer Chemotherapy

The immediately preceding application, titled Application to Unconditioned Nausea and Vomiting in Cancer Chemotherapy, addresses the alleviation of unconditioned sickness produced by an anticancer drug or tumor burden. The present
application is to the alleviation of conditioned sickness in an animal model of anticipatory nausea and vomiting (ANV) in cancer chemotherapy (e.g., Carey & Burish, 1988; Jacobsen & Redd, 1988; Moher, Arthur, & Pater, 1984; Morrow & Dobkin, 1988; Morrow, Lindke, & Black, 1991). ANV can be as severe and distressing as the sickness produced by the anticancer agent itself, does not respond to and may actually be worsened by standard antiemetic treatments (e.g., LeBaron & Zeltzer, 1984; Morrow, Arseneau, Asbury, Bennett, & Boros, 1982), and once developed is often refractory to treatment (e.g., Carey & Burish, 1988; Redd, 1984).

In the proposed animal model of ANV, an aversion to the novel taste of saccharin is conditioned using pairings of saccharin and lithium (or an anticancer drug). An antisickness response to rotation is also conditioned using pairings of rotation and lithium on alternate trials. Following this phase, all rats receive higher-order pairings of a neutral CS with rotation. On test, rats are given exclusive access to saccharin solution in the home cage; when forced to drink aversive lithium-conditioned saccharin, rats also consume large amounts of kaolin (Mitchell, Winter, & Morisaki, 1975). Kaolin consumption (pica) is measured with the neutral CS present for half of the rats in each group and with the neutral CS absent for the remaining rats. The expectation is that the presence of this CS will reduce pica in rats with a conditioning history that endows the CS with the ability to elicit a CAS response. The CAS response is inferred by measurements of kaolin consumption in the absence of any treatment that produces unconditioned
sickness. This is the first suggested use of pica in an animal model of ANV. The available CTA models (e.g., Bernstein, 1991; Smith, Blumsack, & Bilek, 1985) can be used in attempts to prevent ANV but, unlike the pica model, they cannot be used for determining the efficacy of therapeutic interventions.

Application to Cancer Cachexia Syndrome

If CAS is found as proposed in the section titled Application to Unconditioned Nausea and Vomiting in Cancer Chemotherapy (pp. 106–107), additional steps can be taken to validate the animal therapy model as a promising clinical strategy. A replication using purchased tumor-bearing rats would more closely parallel the projected clinical context and could be used to assess whether tumor-induced nausea or some other tumor effect is likely to interact with the conditioning strategy in expected or unexpected ways. Will a tumor-bearing rat self-administer the CAS-eliciting neutral stimulus and thereby alleviate the sickness produced by a cancer chemotherapy drug, or will the tumor effectively mask the effects of the drug, for example?

A second question is whether a tumor-burdened animal will self-administer the CAS-eliciting neutral stimulus and thereby alleviate the nausea or anorexia component of the syndrome of weight loss and wasting produced directly or indirectly by the tumor itself. Rats with tumor burdens develop CTAs to novel but not to familiar diets, and this has been proposed to model a component of cancer cachexia in an extensive series of investigations by Bernstein and coworkers (e.g., Bernstein, 1983, 1985, 1986, 1991, 1993; Bernstein & Borson, 1986; Bernstein &
Sigmundi, 1980; Bernstein, Treneer, Goehler, & Murowchick, 1985). Some [Leydig-LTW (m) and PW-739] but not other (Walker-256) tumor types induce CTAs, suggesting the possibility of several tumor-specific aversion-inducing agents. For example, estrogen administration induces CTAs in healthy rats (e.g., Wade, 1972) and is secreted by Leydig-LTW (m) tumors. A more recent suggestion is that tumor necrosis factor (TNF) is a common mediator of cancer cachexia and anorexia regardless of tumor type (e.g., Lowry & Moldawer, 1990; Stovroff, Fraker, Swedenborg, & Norton, 1988; Tracey & Cerami, 1992) and moreover that TNF mediates tumor-induced CTAs in rats and therefore presumably induces nausea or sickness (e.g., Bernstein, 1995). Whatever the mechanism, tumor-induced CTAs in rats can be attenuated by lesioning the area postrema (containing the chemoreceptor trigger zone for nausea and vomiting) or by substituting a second novel diet for the conditioned aversive diet (e.g., Bernstein, Courtney, & Braget, 1986).

The proposed experiment uses Bernstein’s paradigm to determine whether CAS can attenuate a component of cancer cachexia involving tumor-induced CTAs. In the first phase, a CAS response is conditioned to an initially neutral stimulus in healthy rats. Half of the rats are subsequently implanted with LTW (m) tumors and the remainder are sham-implanted and pair-fed. When the tumor-bearing rats begin to eat substantially less of the usual diet, all rats are switched to a novel diet. In a factorial design, half of the rats from the tumor- and sham-implanted groups are also given the opportunity to self-administer the
CAS-conditioned neutral CS in a Skinner box, and the remainder are given a similar opportunity to barpress for a stimulus consequence that does not elicit CAS. Barpressing and pica are used to assess whether rats barpress more frequently to produce the CAS-eliciting CS and whether this barpressing behavior reduces sickness as indexed by pica. It may also be feasible to examine the strength and rapidity of development of feeding suppression to the novel diet in the tumor-bearing rats, and perhaps a preference for a second novel diet on a subsequent test day with counterbalancing of the order of introducing the novel diets.

As reviewed in the section titled *The Search for the Endogenous Antiemetic Mediating CAS* (pp. 100-106), a CAS response is effective against the subjective nausea or distress produced in common by a variety of toxins having different mechanisms of action. The expectation is that CAS is also effective against the nausea that may be produced in common by a variety of tumor types. In the event of a successful outcome using LTW (m) tumors, generality can be assessed using a second tumor type. It should be obvious that such generality points to a common mechanism mediating tumor-induced anorexia or nausea but is mute concerning the existence of other mechanisms by which tumors produce anorexia or nausea and other cachexia symptoms. Cancer cachexia is multiply determined.

Application to Pregnancy Sickness

An intriguing possibility is that AVP has parallel roles in CAS and pregnancy sickness. Profet (1992) proposed that pregnancy sickness has evolutionary
adaptive significance in that a pregnancy-induced increase in susceptibility to CTA could subserve the avoidance of toxins to which the fetus might be particularly vulnerable (cf. Deutsch, 1994). By this theory, pregnancy sickness is not restricted to humans, as is almost universally supposed, except by the narrow definition of sickness as vomiting. By any theory, pregnancy sickness is expected to induce CTAs which may be masked by factors such as increased energy and protein requirements that otherwise increase food intake (cf. Wade, 1972). Perhaps its physiological mediation involves changes in AVP homeostasis such as are known to occur in both human and rat pregnancies (Lindheimer, Barron, Dürr, & Davison, 1987; Lindheimer & Davison, 1995). Human pregnancy sickness is common in the first trimester and typically resolves by midpregnancy: Exaggerated AVP release in the first trimester coincides with nausea (Davison, Sheills, Phillips, & Lindheimer, 1988) whereas increased AVP clearance beginning in midpregnancy (Davison, Sheills, Baron, Robinson, & Lindheimer, 1989) coincides with the resolution of pregnancy sickness. Two recent clinical case series reports have shown that glucocorticoid administration is highly effective at controlling severe, intractable pregnancy sickness (Nelson-Piercy & de Swiet, 1994; Taylor, 1996) but whether by a direct effect upon a vomiting center in the brain as is commonly assumed or by the inhibition of AVP secretion is unknown.

A common rejoinder to this argument is that it cannot obviously explain food cravings during pregnancy. But the combination of sickness and cravings is found not only in pregnancy but also in migraine (Blau, 1993) and altitude
sickness (Ward, Milledge, & West, 1989, p. 363). I suspect it would be found in seasickness but for the unusual severity of the sickness and the rapidity of habituation. Cravings are typically for carbohydrates in all cases, the consumption of which may alleviate symptoms secondary to inappetence and low blood sugar. Cravings for unusual foods or food combinations are rare but readily explainable in that such foods have presumably been spared as conditioning targets and do not initially elicit the CTAs that prevent consumption of more familiar foods.

No published studies have explicitly considered pregnancy induction of CTAs but the animal literature is consistent with such a possibility. Menaker and Navia (1973) placed pregnant and nonpregnant rats on isocaloric high- and low-protein diets and showed that pregnant rats on the low-protein (nutritionally inadequate) diet compensated by increasing consumption. Wilson (1987, 1997) failed to replicate this finding; indeed, on the contrary, she showed decreasing consumption consistent with the development of profound and potentially life-threatening aversions to the low-protein diet in pregnant rats. She concluded that the low-protein diet induced sickness and CTA but she failed to consider whether pregnancy itself could induce CTA and did not resolve the discrepancy in findings.

In the Menaker and Navia study both diets were equally novel whereas in the Wilson (1987) study only the low-protein diet was novel: Perhaps pregnancy sickness rather than or in addition to protein deficiency preferentially conditioned an aversion to the novel diet. Protein excess or imbalance rather than deficiency is
more likely to produce sickness, and rats are widely known to adapt to or to compensate for imbalance or deficiency, unless the deficiency is severe (i.e., unless the diet is devoid of one or more essential amino acids; Benevenga & Steele, 1984; Gietzen, 1993; Gietzen, Rogers, & Leung, 1988; Harper, Benevenga, & Wohlhueter, 1970); the low-protein diets in Menaker and Navia and in Wilson (1987) were balanced and at 8% protein they were not severely deficient. Moreover, compensation occurs in the presence of a CTA when rats are forced to consume an unbalanced diet: Given a choice, fully compensated rats will switch from an unbalanced to a protein-free diet (Rogers & Leung, 1977). It is therefore surprising that pregnant rats in the Wilson (1987) study failed to compensate for the relatively mild level of protein deficiency. Using a range of isocaloric low-protein diets equated for novelty, Wilson (1997) also failed to replicate her (1987) finding. Specifically, rats compensated for mild protein deficiency but not for severe deficiency, or for mild deficiency combined with access to novel sucrose solution (cf. Rogers & Leung). Wilson did not address the discrepancy but this can be done by postulating a role for pregnancy sickness, and for differential diet novelty in the (1987) finding.

The absence of an animal model for pregnancy sickness limits understanding and control of this often mild but potentially life-threatening condition and contributes to a pernicious "psychology" that blames the victim when sickness is severe (lancu, Kotler, Spivak, Radwan, & Weizman, 1994; Kaltenbach, 1891). The present proposal substitutes pregnancy for tumor burden
in the procedure outlined in the section titled Application to Cancer Cachexia Syndrome (pp. 109-111) to determine whether rats develop at least a mild CTA when switched to a novel (and nutritionally adequate) diet early in pregnancy. [The sort of equivalence implied by the substitution has possibly profound (Billington, 1989; Sargent, 1993) as well as trivial meaning.] Groups of rats are maintained on a familiar diet or switched to a novel diet at various times after mating. Supposing that the pregnancy state is effective as a means of inducing CTAs, the rats maintained on a familiar diet should be less likely than the rats switched to a novel diet to develop an aversion. Greater aversion to a novel diet relative to a familiar diet is evidence that conditioning has occurred in an appropriately counterbalanced procedure. Groups of rats are switched at various times in the pregnancy to determine when pregnancy sickness might occur. Following Wilson, hormonal differences in successfully versus unsuccessfully impregnated females can be eliminated by randomly assigning the females to males with histories of consistently successful or unsuccessful mating attempts. "Hidden" aversions are unmasked in diet preference tests. Rats with an aversion to their usual diet, for example, should show a stronger preference for a novel diet than otherwise expected. A positive outcome could justify the exploration and cross-validation of a role for AVP in CAS and pregnancy sickness.
CHAPTER 6

SUMMARY AND CONCLUSIONS

The present thesis validates a conditioning phenomenon that has an elegant and compelling theoretical basis as well as potentially important practical or clinical implications. The avfail phenomenon prompted an explanation requiring the selective association of an internal drug state CS with a hypothetical homeostatic or antisickness response to sickness. According to conditioned antisickness (CAS) theory, drug states model naturally occurring sequences of internal states: The CS drug corresponds to naturally occurring internal signals, the US drug to naturally occurring aftereffects, and conditioning enables the animal to better regulate its internal environment by anticipating the US. Drug—drug conditioning provides a general model for the involvement of Pavlovian conditioning in homeostatic regulation.

The drug—drug pairings methodology has made CAS theory difficult to validate because the non-independence of the two drug states invites a pharmacological drug interaction alternative to a conditioning interpretation. The simultaneous presence of particular CS and US drugs in the experimental group but not in Pavlovian controls could produce unique pharmacological effects that somehow mimic avfail. Pharmacological interactions and certain other non-Pavlovian alternative explanations of avfail were ruled out by successfully substituting the nondrug events of rotational stimulation in Experiment 1 (Rotational Stimulation as an Avfail CS, pp. 50–60) and heat in Experiment 2 (Ambient Temperature Increase as an Avfail CS, pp. 61–70) for the usual avfail.
drug CS. Demonstrating avfail in the absence of any drug—drug pairings made a Pavlovian conditioning interpretation more convincing and prompted the further examination of the key theoretical question—whether avfail is due to CAS.

In an indirect test of CAS theory, Lett (1992) paired drug or place cues with lithium and found that rats with an experimental or forward pairings history ate less food on test, consistent with a traditional conditioned sickness account rather than with CAS. But rats eat dirt or clay in response to sickness and adaptively eat small amounts of food when clay is not available: Paradoxically, perhaps rats with a forward pairings history ate less food than controls because they were less rather than more sick. Experiment 3 (Pica as an Index of CAS in Rats, pp. 74–82) substituted clay (kaolin) for food and found that rats with a forward pairings history ate less kaolin, consistent with CAS. The empirical evidence is thus largely consistent with CAS, but all previous studies are indirect tests of CAS—in the sense that nausea or sickness must be inferred from changes in consummatory behavior in the rat, a nonvomiting species—and as such are subject to misinterpretation. In the first direct test with a vomiting species, Experiment 4 (Emesis as an Index of CAS in Ferrets, pp. 83–99) found that ferrets with a forward pairings history had fewer and shorter bouts of retching and vomiting, whether induced by lithium or by the highly emetogenic anticancer drug cisplatin. These findings provided strong support for CAS theory and suggested the basis for a nondrug conditioning countermeasure to severe nausea in clinical settings.

The elevation of CAS from a possible interpretation of an interesting class of
learned behavior in rats to what could prove to be a basic mammalian adaptive response opens even more interesting possibilities for advances in conditioning. Scientific discontinuities are often more valuable than confirmation of expected outcomes. The twenty-year-old discontinuity that avfail presents is finally resolved through empirical examination of the validity issues covered in Chapters 2, 3, and 4. The findings reveal a form of conditionable homeostatic response with broad theoretical implications, and raise the hope of a new weapon in the clinical armamentarium which could positively affect the course of anticancer chemotherapy.
APPENDIX 1

TASTE AVERSION CONDITIONING WITH HEAT AS THE US

Advantages of the drug–drug pairings methodology in modelling homeostatic conditioning are offset by significant disadvantages: Nonindependence of the paired drug states necessitates pharmacological drug interaction controls, and drug states elude the sort of precise temporal control over stimulus events best suited to a Pavlovian analysis. These disadvantages motivated the search for nondrug internal stimulus events that could reliably produce CTAs. An intuitively obvious candidate was an increase in ambient temperature but a literature search revealed several failures to show that heat serves as an effective US for taste aversion conditioning (Cunningham et al., 1988, 1992; Cunningham & Niehus, 1989; Green et al., 1981; Holder et al., 1989; P. S. Hunt et al., 1991). Green et al. reported that toxic heat induced place but not taste aversions and concluded that the effects of toxic heat are referred to the external environment. This is surprising because lithium intoxication and heat illness symptoms are sufficiently similar in humans that Granoff and Davis (1978) have suggested a unitary mechanism of action.

Successful substitution of heat for pentobarbital in the avfail procedure is reported in Experiment 2 (Ambient Temperature Increase as an Avfail CS, pp. 61–73). Appendix 1 reports an experimental series examining selected characteristics of heat as the US in a simple CTA procedure. Experiment A (Demonstration of the Phenomenon, pp. 120–125) demonstrates heat-induced
CTAs in a straightforward CTA paradigm. Experiment B (The Role of Environmental Context Change, pp. 125–129) and Experiment C (The Role of Abrupt versus Gradual Heating, pp. 130–132) examine the soundness of the existing evidence that heat is an external stimulus by manipulating the conditions which should promote an external attribution of the locus of action of heat. Experiment D (Heat Dose Effects, pp. 132–136) examines heat dose characteristics in an effort to gauge the robustness of the CTAs.

Experiment A

Demonstration of the Phenomenon

In this experiment, rats were given forward or control pairings of saccharin and heat in a CTA arrangement. A strong saccharin concentration was used, as in Experiment 2 (Ambient Temperature Increase as an Avfail CS) to maximize the possibility that conditioning would occur.

Method

Subjects

Subjects were 24 naive female Long-Evans hooded rats weighing 198–315 g at the start of the experiment. They were placed on a water deprivation schedule consisting of 15 min of access to room-temperature tap water per day beginning one week prior to the start of the experiment.

Procedure

Rats were assigned by weight to three groups of eight rats each. One week prior to the start of the experiment, each group was placed on a separate cage rack,
and the racks were moved to the heat treatment room for the duration of the experiment except as noted.

Every third day was a conditioning day. On conditioning days, all rats received saccharin solution (0.75% wt/vol) substituted for their usual tap water. Upon removal of the saccharin bottles, two of the three groups, the unpaired and unheated groups, were removed from the heat treatment room and the heaters were turned on; the forward group remained in the treatment room. Room temperature was allowed to reach a maximum of 35 °C and was maintained at maximum until the heaters were turned off 2 hr later. The unpaired and unheated groups were returned to the treatment room once room temperature had fallen to within 2 °C of the baseline.

The procedure on the day after a conditioning day was identical to the procedure on a conditioning day with the following exceptions. First, all rats received their usual tap water. Second, forward and unheated groups were removed from and subsequently returned to the heat treatment room; the unpaired group remained in the treatment room for heat exposure. There were four conditioning trials.

Saccharin consumption scores were converted to acceptance scores in the form of suppression ratios. The ratio was \( \frac{S}{S + W} \) where \( S \) is the amount of saccharin consumed on any training day and \( W \) is the amount of water consumed on the day before the training day. Acceptance scores on the first training day served as the covariate, and the mean of the scores on the remaining three days
served as the datum, in an ANCOVA. $F$ tests based on the error term and adjusted means of the overall ANCOVA were used for pairwise comparisons.

One rat in the unpaired group died. Its data were discarded, and the resulting unequal group sizes were accommodated using an unweighted means analysis.

**Results and Discussion**

Groups did not differ in their water consumption (all $gs > .10$), and saccharin consumption scores were converted to acceptance scores for analysis. Groups did not differ in their saccharin acceptances on the first saccharin drinking day, $F (2, 20) = 1.80$. The ANCOVA yielded a significant group effect, $F (2, 19) = 8.86$, $p < .01$. Pairwise comparisons and inspection of Figure 6 indicate that saccharin consumption was lower in the forward group than in either the unpaired control, $F (1, 19) = 10.11$, $p < .01$, or the unheated control, $F (1,19) = 14.82$, $p < .01$. Unpaired and unheated groups did not differ, $F < 1$. Thus, forward pairings of saccharin and high ambient temperature in a CTA paradigm make the saccharin aversive by comparison to unpaired and unheated controls.

The present finding conflicts with earlier reports in which heat failed to support taste aversion conditioning (Green et al., 1981; Holder et al., 1989; P. S. Hunt et al., 1991). Two procedures used here which depart from those used in the earlier reports, and which may have increased the probability of heat serving as an effective US for taste aversion conditioning, involve gradual heat onset and the absence of a context change correlated with heat exposure. In the previous
Figure 6. Experiment A: Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion conditioning procedure using heat as the nausea-inducing US. An experimental group received forward pairings of saccharin and heat exposure. Control groups received either 24-hour delayed exposures to saccharin and heat (unpaired control), or exposures to saccharin alone (unheated control). Saccharin consumption scores were converted to acceptance scores equivalent to suppression ratios. The ratio was $S / (S + W)$ where $S$ is the amount of saccharin consumed on any conditioning day and $W$ is the amount of water consumed on the day before the conditioning day. A ratio below 0.50 indicates lower saccharin consumption on the conditioning day than water consumption on the previous day. Plotted points represent group mean saccharin acceptance scores on each conditioning day. Error bars depict standard errors of the means.
literature, rats drank a novel taste solution and were then transported to a preheated room or placed in a preheated oven. Perhaps the abrupt change in ambient temperature together with the correlated context change effectively defined heat as an external stimulus. That is, perhaps the internal consequences of toxic heat were attributed to the external environment under conditions in which there was clearly a context change and abrupt onset of heat. As a special adaptation of the temperature system that supports behavioral regulation of body temperature, animals move from a hot environment and successfully reduce the toxic effects of heat. An association between a novel taste and the toxic internal effects of heat would not be expected to occur if animals are biased to treat the heat as purely an external stimulus. In the present conditioning strategy, on the other hand, rats are exposed to a gradual increase in ambient temperature to the literature levels (34 to 38 °C) without removal either from their home cages or from the housing room. Under such circumstances, toxic heat levels equivalent to those used in previous research do support an association between a novel taste and sickness. Experiments B and C focus on these US-related hypotheses in an attempt to resolve the contradictory findings with respect to the status of heat as a US in the CTA context.

Experiment B

The Role of Environmental Context Change

This experiment tested whether a correlated context change would diminish the efficacy of the heat US. The hypothesis is that animals can be biased to treat the
internal heat stimulus as an external stimulus in a manner consistent with Green et al. (1981) showing the conditioning of place but not taste aversions with equivalent heat exposures of 35 °C. Both Green et al. and Holder et al. (1989, Experiment 4) incorporated a context change correlated with heat exposure, that is, rats were transported to a different room or placed in ovens for heat treatment. To provide a context change in the present experiment, rats were housed in a separate room and were moved to the heat treatment room only as required.

**Method**

**Subjects**

Thirty-two male Sprague-Dawley rats were obtained from Charles River at a weight range of 190–200 g and weighed 415–624 g at the start of the experiment.

**Procedure**

Rats were assigned by weight to four groups of eight rats each. Two groups, called replication groups, were housed in the heat treatment room and were used in a replication of Experiment A. Two additional groups, called context change groups, were housed in a room different from the heat treatment room. On conditioning days, all groups received saccharin in the room in which they were housed. Upon removal of the saccharin bottles, the forward context change group was moved to the heat treatment room and received heat exposure along with the forward replication group; the unpaired replication group was removed from the treatment room to the room housing the unpaired context change group. The heaters were then turned on and remained on for 3 hr. Groups were returned to
their home rooms as appropriate at the end of the treatment period when temperature had returned to within 2 °C of the baseline.

The procedure on the day after a conditioning day was identical to the procedure on a conditioning day with the following exceptions. First, all rats received their usual tap water. Second, the unpaired context change group was moved to the heat treatment room and received heat exposure along with the unpaired replication group; the forward replication group was removed from the heat treatment room until the end of the treatment period.

**Results and Discussion**

Groups did not differ in their water consumption (all ps > .10) and saccharin consumption scores were converted to acceptance scores for analysis. Groups did not differ in their saccharin acceptances on the first saccharin drinking day, $F < 1$. A 2 (groups) X 2 (contexts) ANCOVA yielded a significant group effect, $F (1, 27) = 337.89, p < .01$. Neither the main effect of the context manipulation nor the Groups X Contexts interaction were significant, $F < 1$ and $F (1, 27) = 2.80$, respectively. Inspection of Figure 7 indicates that saccharin consumption was lower in the forward groups than in the corresponding unpaired controls. The pattern of results in the present experiment replicates the finding of Experiment A; that is, high ambient temperature successfully conditions saccharin aversions in the forward groups. However, arranging a correlated context change had no effect on saccharin consumption.
Figure 7. Experiment B: Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion conditioning procedure using heat as the US and with or without a context change correlated with heat exposure. Replication groups were housed in the heat treatment room as in Experiment A. Context change groups were transported to the heat treatment room after saccharin consumption in the colony room. Saccharin consumption scores were converted to acceptance scores equivalent to suppression ratios. The ratio was $S / (S + W)$ where $S$ is the amount of saccharin consumed on any conditioning day and $W$ is the amount of water consumed on the day before the conditioning day. A ratio below 0.50 indicates lower saccharin consumption on the conditioning day than water consumption on the previous day. Plotted points represent group mean saccharin acceptance scores on each conditioning day. Error bars depict standard errors of the means.
Replication Forward
Replication Unpaired
Context Change Forward
Context Change Unpaired

Acceptance Score

Saccharin Conditioning Day
Experiment C

The Role of Abrupt versus Gradual Heating

This experiment examined the effect of abrupt versus gradual heat exposure in combination with a correlated context change. Previous researchers placed animals in preheated environments and failed to condition taste aversions with heat exposures equivalent to those used in the present study (e.g., Green et al., 1981; Holder et al., 1989). Does such abrupt heat exposure attenuate the CTA effect, as might be expected if animals are thereby biased to refer the internal consequences of toxic heat to the external environment?

Method

Subjects

Forty-two male Sprague-Dawley rats were obtained from Charles River at a weight range of 190–200 g and weighed 204–294 g at the start of the experiment.

Procedure

Rats were assigned by weight to six groups of seven rats each. All groups were housed in a home room different from the heat treatment room. Two groups, called gradual groups, served to replicate the context groups of Experiment B. They drank saccharin or water and were moved to the treatment room for gradual heat exposure as appropriate immediately after the drinking period. Two groups, called abrupt delay groups, drank at the same time as the gradual groups and were moved to the treatment room 30 min after their drinking bottles were removed, at a time when room temperature was maximal. They experienced an
abrupt transition from normal to hot ambient temperature as well as a longer delay between drinking and heat exposure. The remaining two groups, called abrupt no-delay groups, drank 30 min after the other groups and were moved to the treatment room immediately after the drinking period and at the same time as the abrupt delay groups. The abrupt no-delay groups experienced an abrupt transition from normal to hot ambient temperature but without the delay between drinking and heat exposure experienced by the abrupt delay groups.

On conditioning days, all rats received saccharin, and gradual, abrupt delay, and abrupt no-delay forward pairings groups were moved to the heat treatment room where they remained for 3 hr. On the day after a conditioning day, all rats received water, and gradual, abrupt delay, and abrupt no-delay unpaired groups were moved to the heat treatment room where they remained for 3 hr.

All groups experienced an abrupt transition from hot to normal ambient temperature upon removal from the heat treatment room. Abrupt groups also experienced more total heat because they spent 3 hr at maximum heat whereas gradual groups experienced part of the 3-hr treatment period with gradually increasing heat. This is a conservative procedure because the stronger heat US favors conditioning in the abrupt groups, contrary to the hypothesis under test.

Results and Discussion

Groups did not differ in their water consumption (all ps > .10) and saccharin consumption scores were converted to acceptance scores for analysis. Groups did not differ in their saccharin acceptances on the first saccharin drinking day, all
Whether a 30-min delay was imposed between drinking and heat exposure in the abrupt heat groups had no effect on conditioning, $F < 1$, and the corresponding delay and no-delay groups were pooled for subsequent analysis. A $2 \times 2$ ANCOVA yielded a significant group effect, $F (1, 37) = 223.07, p < .01$. Neither abruptness of heat onset, $F (1, 37) = 2.48$, nor the interaction of group with abruptness, $F < 1$, were significant. Inspection of Figure 8 indicates that saccharin consumption was lower in the forward groups than in the corresponding unpaired controls. Thus, forward pairings of saccharin and high ambient temperature produced a saccharin aversion regardless of whether heat onset was abrupt or gradual and regardless of whether there was or was not a 30-min delay between saccharin consumption and heat exposure.

Experiments B and C investigated context change and abruptness of heat exposure respectively with no evidence of control by these factors of the apparently robust conditioning of a taste aversion with a heat stimulus. These data present the irony of a failure of replication with a positive outcome. It is of course possible that the room change was not sufficiently detectable to the rats to classify as a context change.

Experiment D

Heat Dose Effects

Experiment D examined heat dose in an attempt to assess the apparent robustness of taste aversion conditioning with a heat US. Three groups of rats were given forward pairings of saccharin followed by heat exposure. Heat was low
Figure 8. Experiment C: Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion conditioning procedure using heat as the US and with gradual \( (n = 7) \) or abrupt \( (n = 14) \) heat exposure. All groups were transported to the heat treatment room after saccharin consumption in the colony room. The room was preheated for the abrupt heat groups but not for the gradual heat groups. Saccharin consumption scores were converted to acceptance scores equivalent to suppression ratios. The ratio was \( S / (S + W) \) where \( S \) is the amount of saccharin consumed on any conditioning day and \( W \) is the amount of water consumed on the day before the conditioning day. A ratio below 0.50 indicates lower saccharin consumption on the conditioning day than water consumption on the previous day. Plotted points represent group mean saccharin acceptance scores on each conditioning day. Error bars depict standard errors of the means.
Gradual Forward
Gradual Unpaired
Abrupt Forward
Abrupt Unpaired

Acceptance Score

Saccharin Conditioning Day

1  2  3  4

Gradual Forward
Gradual Unpaired
Abrupt Forward
Abrupt Unpaired
(32 °C), medium (35 °C), or high (38 °C). A fourth or unpaired group was given saccharin access followed 24 hr later by heat exposure. Subgroups of the unpaired group received low-, medium-, or high-dose heat exposure.

**Method**

**Subjects**

Thirty-two male Sprague-Dawley rats were obtained from Charles River at a weight range of 190–200 g and weighed 416–518 g at the start of the experiment.

**Procedure**

Rats were assigned by weight to four groups of eight rats each. All groups were housed in a home room different from the heat treatment room. Three forward groups received saccharin followed immediately by low (32 °C), medium (35 °C), or high (38 °C) heat exposure. Subgroups of a fourth unpaired control group received saccharin followed 24-hr later by low, medium, or high heat exposure. Immediately after the saccharin bottles were removed, corresponding forward and unpaired groups were moved to the treatment room and received simultaneous heat exposure. Heaters were turned on as soon as the groups were placed in the treatment room and were turned off 3 hr later. Rats were returned to the home room as soon as the temperature in the treatment room had returned to within 2 °C of the baseline. In the home room, all rats received 5 min access to water to prevent dehydration. The different forward groups with the corresponding unpaired controls received heat exposure on different days.
Results and Discussion

Groups did not differ in their water consumption (all \( p \)'s > .10), and saccharin consumption scores were converted to acceptance scores for analysis. The unpaired subgroups did not differ, \( F < 1 \), and were pooled for subsequent analysis. Groups did not differ in their saccharin acceptances on the first saccharin drinking day, \( F (3, 28) = 1.41 \). The ANCOVA yielded a significant group effect, \( F (3, 27) = 14.04, \ p < .01 \). Pairwise comparisons and inspection of Figure 9 indicate that saccharin consumption was lower in the high- and medium-heat forward groups \([F (1, 27) = 33.69, \ p < .01 \) and \( F (1, 27) = 25.30, \ p < .01 \), respectively] relative to the unpaired control. High- and medium-heat groups did not differ, \( F < 1 \). The low-heat group was significantly different from both the high- and medium-heat groups \([F (1, 27) = 16.05, \ p < .01 \) and \( F (1, 27) = 10.44, \ p < .01 \), respectively] but did not differ from the unpaired control, \( F (1, 27) = 3.23 \). Taste aversions were obtained with forward pairings of saccharin and high (38 °C) or medium (35 °C) ambient temperatures, but not with forward pairings of saccharin and low (32 °C) ambient temperature. The medium and high heat levels are well within the range used in previous reports of failure to condition taste aversions with toxic heat (e.g., Green et al., 1981, 35 °C; Holder et al., 1989, Experiment 4, 37–38 °C) whereas the low heat level may be outside the range.

General Discussion

The present research provides two lines of evidence suggesting that heat serves as an internal stimulus: Heat is an effective avfail CS (Experiment 2, Ambient...
Figure 9. Experiment D: Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion conditioning procedure using heat as the US in an unheated baseline group and in low (32 °C), medium (35 °C), and high (38 °C) temperature forward pairings groups. Saccharin consumption scores were converted to acceptance scores equivalent to suppression ratios. The ratio was $S / (S + W)$ where $S$ is the amount of saccharin consumed on any conditioning day and $W$ is the amount of water consumed on the day before the conditioning day. A ratio below 0.50 indicates lower saccharin consumption on the conditioning day than water consumption on the previous day. Plotted points represent group mean saccharin acceptance scores on each conditioning day. Error bars depict standard errors of the means.
The graph illustrates the acceptance score over Saccharin Conditioning Day, with conditions differentiated by symbols:

- High: Square (□)
- Medium: Dot (●)
- Low: Cross (✚)
- Unpaired: Box (■)

The x-axis represents theSaccharin Conditioning Day, ranging from 1 to 4, while the y-axis shows the Acceptance Score, ranging from 0.10 to 0.50.
Temperature Increase as an Avfail CS and also supports taste aversion conditioning (Experiments A-D). CAS theory requires an internal cue in the first or antisickness conditioning phase of the avfail procedure. Only an internal cue can become associated with the antisickness response, that is, the hypothetical internal "antidote" to the internally generated sickness produced by the lithium US. Through such association, the heat CS is endowed with the ability to elicit a conditioned homeostatic antisickness response and consequently, for the forward group only, heat fails as a US in the taste aversion conditioning phase of the two-phase avfail procedure. Clearly, this process demands that heat serve an internal function.

Experiments B and C uniformly show the conditioning of a taste aversion with heat as the US despite systematic efforts to diminish its effectiveness when conditions are arranged consistent with the commonplace view (contrary to the one held here) that heat serves as an external cue. Although context change and abruptness of heat exposure appeared as promising avenues of investigation, the evidence indicates that heat-induced CTAs were unaffected by these manipulations. The significance of the finding is highlighted in Holder et al. (1989). These authors report on the effects of stimulating rats' external system, that is, the system that processes external events such as sound and touch. They consider heat as an external event on the basis of the earlier work by Green et al. (1981) in which high ambient temperature supported place but not taste aversion conditioning.
Closer examination of the existing literature suggests, however, that the belief that heat does not serve as an effective US for taste aversion conditioning is based on a surprisingly narrow database. The experiments by P. S. Hunt et al. (1991) and Holder et al. (1989) do not provide Pavlovian controls for determining whether heat-induced conditioned taste aversion has occurred. Although these controls are necessary from the perspective of taste aversion conditioning, it should be noted that these studies, and those of Cunningham and coworkers referred to below, address other issues. In fact, Hunt et al. (Experiment 1) report that subjects in 38 °C groups ingested less sucrose than subjects maintained at either 21 or 34 °C and attribute what could be a heat-induced sucrose aversion to decreased metabolism resulting from the higher ambient temperature.

Cunningham and his associates use a control for assessing whether a heat-induced CTA has occurred in one study only (Cunningham et al., 1992; cf. Cunningham et al., 1988; Cunningham & Niehus, 1989) but use a temperature of 32 °C which was found in the present Experiment D to be marginally below the effective range. It appears that only Green et al. (1981) use Pavlovian controls in directly addressing the utility of heat as a US in the CTA context.

The present experimental series used a concentrated or strong-tasting saccharin solution because the use of a weak CS, such as a less concentrated saccharin solution, would be expected to produce correspondingly weak conditioning (Riley & Clarke, 1977; Riley & Tuck, 1985). However, CS strength is an additional candidate in accounting for the failure of prior research to find
heat-induced CTAs. Paradigmatically, the effect of saccharin—heat pairings on subsequent saccharin drinking shown in the present thesis meets criteria defining taste aversion conditioning. However, failure of attenuation of neophobia provides an alternative view (e.g., Mitchell, Scott, & Mitchell, 1977; see also Garcia, 1978; Mitchell, 1977, 1978; Revusky, 1977a, 1978, 1979; Riley, 1978; Smith, 1978). The intense saccharin concentration used in the present series produces pronounced taste neophobia and drinking suppression in rats. In the absence of an appropriate US, this initial neophobic drinking suppression becomes attenuated with repeated exposure(s) to the taste. The apparent failure of attenuation of neophobia following saccharin—heat pairings is interpreted as a conditioned saccharin aversion but a possible alternative is that taste-paired heating interferes in some way with memory for the taste so that the neophobic response persists. According to this view, the greater saccharin consumption of control groups and the relatively weaker consumption of forward groups in the CTA paradigm do not force the conclusion that CTA has actually been obtained. The only conclusive empirical basis for ruling out such a memory interference interpretation is to show a decrease in saccharin consumption in the forward group over conditioning trials. This strategy is limited because a strong CS may be required for conditioning and yet may produce a floor effect in consumption due to pronounced neophobia. The usual strategies for eliminating such a floor effect, for example by preexposing the taste CS or by making it less intense, will also weaken or eliminate an association between CS and US (Lubow, 1973, 1989; Riley & Clarke, 1977; Riley & Tuck,
The variable of CS strength in the context of a memory interference interpretation of the basis for heat-induced taste aversion conditioning is examined in Appendix 2.

In summary, considering the present series of US-related studies from the perspective of standard Pavlovian conditioning criteria, and using standard Pavlovian controls, all conditions necessary to confirm conditioned taste aversion with a heat US have been met. The avfail Experiment 2 lends additional and unique support to the assertion that heat serves as an internal stimulus under the present conditions; moreover, it provides evidence of antisickness responding in rats which has important theoretical and therapeutic implications. The avfail procedure, freed from the problems inherent in drug—drug pairings and confirming previous work using the more cumbersome rotation arrangements (Experiment 1), is a potential paradigm for an antisickness therapy regime. The prospect of a nondrug treatment for chemotherapy-induced emesis in humans strongly impels the unravelling of the mechanisms of avfail in animals.
APPENDIX 2

HEAT-INDUCED TASTE AVERSIONS:

THE ROLE OF TASTE INTENSITY AND PREEXPOSURE

The finding that high ambient temperature induces CTAs in rats is rendered more salient by the belief that heat acts only as an external stimulus and therefore does not support taste aversion conditioning (Holder et al., 1989; Hunt et al., 1991; Cunningham et al., 1988; Cunningham & Niehus, 1993; Cunningham et al., 1992). This belief is based on the results of a single study that directly examined the efficacy of heat exposure in a CTA context. Green et al. (1981) obtained place but not taste aversion conditioning with a heat US and suggested that the toxic internal effects of heat are referred to the external environment. But the symptoms and physiology of heat illness and lithium toxicosis are so similar in humans that Granoff and Davis (1978) have proposed a common mechanism for these forms of sickness.

Because lithium is in widespread use as an effective stimulus for the induction of CTAs in rats (Riley & Clarke, 1977; Riley & Tuck, 1985), earlier reports of the failure to condition a taste aversion with heat are all the more surprising. Detailed examination of heat as an internal stimulus in the CTA context is warranted because heat may be unique in possessing both external and internal stimulus features in contrast to other routinely used conditioning stimuli such as tones or drugs. This property could offer useful control features in complex arrangements such as avfail conditioning (Revusky, Taukulis, Parker, & Coombes, 1979; Cunningham & Linakis, 1980). In addition, the toxic effects of heat and their
amelioration have a species-relevant history which, from an evolutionary perspective, make insight into putative behaviors such as antisickness responding more likely. The use of a US with species-relevant adaptive consequences represents a significant contrast to more contrived or artificial stimulus arrangements such as rotation and drug pairings.

Using heat as the CS in an avfail procedure (Experiment 2) confirmed a homeostatic antisickness conditioning interpretation of the avfail phenomenon in rats. Experiments A through D (Appendix 1) used a highly concentrated saccharin solution as the taste CS and showed that heat is also an effective US in the CTA context; rats initially displayed intense neophobic drinking suppression to the strong saccharin taste but then increased consumption markedly over trials in the absence of forward pairings of taste and heat exposure. Forward pairings produced relative drinking suppression in that rats failed to increase consumption over trials. It was argued that, from a conditioning perspective, significant relative drinking suppression is sufficient to establish conditioned taste aversion when appropriate Pavlovian controls are used (cf. Revusky, 1977a, 1978, 1979; Riley, 1978; Smith, 1978). It should be remembered, however, that animals exhibit reluctance to accept novel tastes (Domjan, 1977a) and that this unconditional bait shyness or neophobia easily rivals taste aversion conditioning in terms of its potential adaptive significance. There is, in fact, a longstanding literature disagreement about criteria and appropriate controls for distinguishing between CTA and the failure to attenuate neophobia (cf. Mitchell et al., 1977; Garcia, 1978;
Rather than entering the debate on appropriate controls, it is noted that the present work meets paradigmatic criteria defining Pavlovian conditioning and that any definitional ambiguity is not unique to the use of heat as a US in the CTA context.

The observed failure of attenuation of neophobia is also consistent with a memorial interpretation couched in terms of consolidation or retrieval failure. By this theory, perhaps rats fail to increase saccharin consumption over trials because heat exposure interferes with memory for the taste. This sort of interpretation is obviously ruled out by showing an absolute decrease in consumption over conditioning trials. It is also addressed separately in Appendix 3. The present appendix reports the results of two strategies designed to distinguish between memory interference and taste aversion conditioning interpretations of the relative drinking suppression found in Experiments 2 and A through D, and to provide the first unequivocal evidence for taste aversion conditioning with a heat US. In Experiment E, a mild-tasting saccharin solution is substituted for the strong-tasting solution used previously, and in Experiment F, a strong-tasting, highly concentrated saccharin solution is preexposed prior to the taste aversion conditioning trials.

Experiment E-1 and E-2
The Role of Taste Intensity at 35 °C and 38 °C
The earlier experiments used a highly concentrated 0.75% saccharin solution to
enhance CS salience and thereby facilitate conditioning. [See Mackintosh (1974) for an early review of CS intensity effects in a conditioning context and Revusky (1985) for a discussion of the logic in the avfail context.] At the same time, profound neophobia produced by the strong saccharin taste makes interpretation problematic because the absolute decrease in consumption that would logically rule out a memory interference interpretation is thereby made difficult to obtain. Experiment E reports one strategy for resolving this problem by using a weak saccharin taste to minimize neophobia. Earlier experiments also used ambient temperatures of 35 or 38 °C as the US. Temperature selection was based in part on the knowledge that rats exposed to ambient temperatures above 30 or 31 °C show increases in core body temperature, and moreover that male Sprague-Dawley rats exposed above 32 °C become markedly hyperthermic (Gordon, 1987, 1990, 1993; Hainsworth, 1967; Herrington, 1940; Poole & Stephenson, 1977).

Method

Subjects

Male Sprague Dawley rats were obtained from Charles River at a weight range of 190–200 g and weighed 195–227 g at the start of the experiment. A water deprivation schedule was in effect beginning one week prior to the start of the experiment and consisted of 15 min of access to room-temperature tap water per day.
Procedure

In Experiment E-1, twenty-four rats were assigned by weight to three groups of eight rats each and received four training trials using an ambient temperature maximum of 35 °C. In Experiment E-2, an additional 24 rats served in an otherwise exact replication with eight training trials and a temperature maximum of 38 °C. One week prior to the start of the experiment, each group was placed on a separate cage rack, and the racks were moved to the heat treatment room for the duration of the experiment except as noted below.

**Experiment E-1.** On each of four training days spaced three days apart, rats received 15 min access to saccharin solution (0.10% wt/vol) substituted for their usual tap water. Upon removal of the saccharin bottles, two of the three groups, the unpaired and unheated groups, were removed from the heat treatment room and the heaters were turned on; the forward group remained in the treatment room. Temperature in the treatment room was allowed to reach a maximum of 35 °C and was maintained at maximum until the heaters were turned off 2 hr later. The unpaired and unheated groups were returned to the treatment room once room temperature had fallen to within 2 °C of the baseline. The procedure on the day after a training day was identical to the procedure on a training day with the following exceptions. First, all rats received their usual tap water. Second, forward and unheated groups were removed from and subsequently returned to the heat treatment room; the unpaired group remained in the treatment room for heat exposure.
Experiment E-2. Rats received eight training trials using an ambient temperature maximum of 38 °C in a procedure that was otherwise identical to Experiment E-1.

Saccharin consumption scores were converted to acceptance scores in the form of suppression ratios. The ratio was \( S \) / \( (S + W) \) where \( S \) is the amount of saccharin consumed on any training day and \( W \) is the amount of water consumed on the day before the training day. Acceptance scores were entered into a two-factor (groups X days) mixed ANOVA. \( F \) tests were evaluated both in the conventional manner and also using a corrected degrees of freedom test which conservatively assumes maximum violation of the required pattern of variances and covariances within and across groups. The test divides the degrees of freedom with which the \( F \) table is entered by a factor equal to the degrees of freedom associated with the repeated factor. In the event of a mismatch on these tests, the degrees of freedom were corrected to reflect the degree of heterogeneity actually present in the data (Greenhouse & Geisser, 1959; see Keppel, 1982, pp. 468-472). Error terms for all within-subjects tests were based on data entering into the particular analysis.

Results and Discussion

Experiment E-1. Figure 10 shows group saccharin acceptance scores over the four training days using a temperature maximum of 35 °C. By inspection, and in contrast to the finding of Experiment B using a 0.75% saccharin solution, an increase in ambient temperature to 35 °C for 2 hours is not sufficient to suppress
Figure 10. Experiment E-1: Unadjusted saccharin acceptance scores across saccharin conditioning days in a taste aversion conditioning procedure with 0.10% saccharin solution as the CS and 35 °C heat exposure as the US. Saccharin consumption scores were converted to acceptance scores equivalent to suppression ratios. The ratio was $S / (S + W)$ where $S$ is the amount of saccharin consumed on any conditioning day and $W$ is the amount of water consumed on the day before the conditioning day. A ratio below 0.50 indicates lower saccharin consumption on the conditioning day than water consumption on the previous day. Plotted points represent group mean saccharin acceptance scores on each conditioning day. Error bars depict standard errors of the means.
drinking of a 0.10% saccharin solution in a CTA procedure. Acceptance scores were entered into a 3 (groups) X 4 (days) ANOVA once it had been determined by ANOVAs that groups did not differ on water consumption on any conditioning day, $F (2, 21) < 2.10$. The main effect of groups was not significant, $F (2, 21) = 1.66$, $p > .20$, but the corrected Groups X Days interaction approached significance, $F (1.9, 40.8) = 3.15$. The interaction suggests a tendency for the forward group to drink relatively less saccharin after three or four training trials, but the difference may be spurious and is not significant at the .05 level in any case. All rats were observed to have become wet from saliva spreading by the end of the heating period (cf., Hainsworth, 1967).

**Experiment E-2.** Figure 11 shows group acceptance scores over eight training days using a 0.10% saccharin concentration and 38 °C heat exposure. By inspection, relative drinking suppression was obtained with forward pairings of saccharin and heat relative to unpaired and unheated controls. Rats in the forward group failed to increase their saccharin consumption over days, whereas those in the control groups showed a gradual increase in consumption.

Acceptance scores were entered into a 3 (groups) X 8 (days) ANOVA to confirm the statistical reliability of these observations, once it had been determined by ANOVAs that groups did not differ on their water consumption on any training day [$F s < 1.25$]. The ANOVA yielded a significant groups effect, $F (2, 21) = 11.63$, $p < .01$, as well as a significant corrected Groups X Days interaction, $F (5.7, 60.7) = 4.36$, $p < .01$. The significant interaction indicates that the global
Figure 11. Experiment E-2: Saccharin acceptance scores across saccharin conditioning days with 0.10% saccharin solution as the CS and 38 °C heat exposure as the US. Saccharin consumption scores were converted to acceptance scores equivalent to suppression ratios. The ratio was \( \frac{S}{S + W} \) where \( S \) is the amount of saccharin consumed on any conditioning day and \( W \) is the amount of water consumed on the day before the conditioning day. A ratio below 0.50 indicates lower saccharin consumption on the conditioning day than water consumption on the previous day. Plotted points represent group mean saccharin acceptance scores on each conditioning day. Error bars depict standard errors of the means.
trend among means over training days differed as a function of group membership. Separate two-factor ANOVAs for pairs of groups over training days indicated that the forward group differs from both the unpaired control, $F(1, 21) = 8.98, p < .01$, and the unheated control, $F(1, 21) = 10.12, p < .01$, on linear trend. Unpaired and unheated controls did not differ, $F < 1$. Follow-up analyses of the simple main effects of days for each group confirmed that saccharin consumption was a linear function of training day in the unpaired and unheated groups, $F(7, 63) = 5.15$ and $5.95$, respectively, $p < .01$, but not in the forward group, $F < 1$. These analyses confirm the initial observations. By inspection of Figure 11, saccharin consumption increased linearly over saccharin drinking days in the unpaired and unheated control groups but it did not change over days in the forward group. Thus, forward pairings of a 0.10% saccharin solution with 38 °C heat exposure produced only relative drinking suppression but not the absolute decrease in consumption required to rule out a neophobia interpretation. I turned to a saccharin preexposure strategy in Experiment F.

Experiment F

The Role of Taste Preexposure

Pairings of a mild saccharin taste and exposure to 38 °C heat produced drinking suppression in the forward group relative to controls (Experiment E-2) but did not produce the absolute suppression required to rule out a memory interference interpretation. This failure motivated use of a second independent strategy for minimizing neophobia, that is, to preexpose a highly concentrated saccharin
solution prior to its pairings with high ambient temperature.

Method

Subjects
Thirty male Sprague Dawley rats were obtained from Charles River at a weight range of 190–200 g and weighed 310–418 g at the start of the experiment.

Procedure
Rats were assigned by weight to three groups of 10 rats each. Every third day was a preexposure or training day. All rats received 15 min of access to saccharin solution (0.75% wt/vol) substituted for their usual tap water on each of four preexposure and eight training days. On preexposure days, groups received saccharin access with no other treatment. On training days, the unpaired and unheated control groups were removed from the heat treatment room immediately after the saccharin drinking period; the forward group remained in the room for heat exposure. The unpaired group received heat exposure on the day after the training day. Ambient temperature in the treatment room reached a maximum of 38 °C.

Results and Discussion
Figure 12 shows group acceptance scores over saccharin preexposure and training days using a 0.75% saccharin concentration and 38 °C heat exposure. By inspection, rats initially showed intense neophobic drinking suppression to the strong saccharin taste but increased consumption markedly over preexposure days. Three or four preexposures minimized the contribution of neophobia
Figure 12. Experiment F: Saccharin acceptance scores across saccharin preexposure and conditioning days with 0.75% saccharin solution as the CS and 38 °C heat exposure as the US. Saccharin consumption scores were converted to acceptance scores equivalent to suppression ratios. The ratio was $S / (S + W)$ where $S$ is the amount of saccharin consumed on any conditioning day and $W$ is the amount of water consumed on the day before the conditioning day. A ratio below 0.50 indicates lower saccharin consumption on the conditioning day than water consumption on the previous day. Plotted points represent group mean saccharin acceptance scores on each conditioning day. Error bars depict standard errors of the means.
attenuation to subsequent saccharin drinking in that consumption did not increase over conditioning days in unpaired and unheated controls. The forward group drank less overall than did controls and also reduced their consumption over training days.

Saccharin consumption scores were converted to acceptance scores after it was determined by ANOVAs that groups did not differ in their water consumption, $F_s < 1$, and acceptance scores for preexposure and training days were entered into independent mixed two-factor ANOVAs to confirm the statistical reliability of the above observations. For preexposure days, the ANOVA yielded a significant main effect of days, $F(3, 81) = 196.45, p < .01$. The linear and quadratic components of the main effect of days were significant, $F(1, 27) = 468.50$ and $40.10$, respectively, $p < .01$, confirming the observation that a linear increase in saccharin consumption over preexposure days slows toward the end of the preexposure period.

For training days, the main effect of groups, $F(2, 27) = 9.63, p < .01$, and the Groups X Days interaction, $F(14, 189) = 4.55, p < .05$, were both significant. The significant interaction indicates that the global trend among means over days differed as a function of group membership. Separate two-factor ANOVAs for pairs of groups over days indicated that the forward group differed from both the unpaired control, $F(1, 27) = 23.64, p < .01$, and the unheated control, $F(1, 27) = 20.14, p < .01$, on linear trend. Unpaired and unheated controls did not differ, $F < 1$. Follow-up analyses of the simple main effects of days for each
group confirmed that saccharin consumption was a linear function of training day in the forward group, \( F(7, 63) = 5.69, p < .01 \), but not in the unpaired or unheated controls, \( F_s < 1 \). These analyses confirm the initial observations. By inspection of Figure 12, saccharin consumption decreased linearly over saccharin conditioning days in the forward group but was essentially unchanged in unpaired and unheated controls. Decreased consumption in the forward group is not susceptible to a neophobia interpretation and confirms that taste aversion conditioning was obtained.

**General Discussion**

The relative drinking suppression obtained in the earlier experiments and in the present Experiment E-2 increases the viability of an alternative to a taste aversion conditioning interpretation couched in terms of the failure of attenuation of neophobia. Bait shyness is an adaptive response within a functional evolutionary context, and the notion that poisoning following the consumption of a novel food can result in sensitization or enhancement of neophobia is certainly plausible. Domjan (1977a) reviews the evidence for poison-induced enhancement of taste neophobia but the phenomenon may be limited to short-term effects (e.g., Best & Domjan, 1979; Domjan & Best, 1980; Domjan & Gemberling, 1980) and is distinct from taste aversion conditioning in any case (e.g., Franchina & Gilley, 1986). The obtained drinking suppression meets paradigmatic criteria for Pavlovian conditioning.

A second alternative to a taste aversion conditioning interpretation of the
obtained relative drinking suppression is that heat exposure interferes with
memory for the taste. By this reasoning, taste-paired heat exposure does not
make the taste aversive but rather prevents consolidation of the memory of the
taste experience (cf. Duncan, 1949) or possibly interferes with retrieval of the
memory of previous taste exposure(s) as a consequence of the disparity between
encoding and retrieval contexts (e.g., Overton, 1991; Richardson, Riccio, & Steele,
1986). The animal does not remember earlier exposures to the taste and therefore
continues to respond as if the taste were completely novel. Perhaps drug state
cues coincident with the processing of the gustatory memory provide retrieval
cues that facilitate memory for the previous taste exposure on subsequent
exposure. The possibility is that a retrograde effect on memory of introducing a US
such as heat exposure could retard the attenuation of neophobia to a novel taste
in a nominal CTA procedure. As unlikely as this appears to be on a priori grounds,
Appendix 3 nevertheless reports a direct empirical test.

The present experiments were designed to demonstrate an absolute
decrease in the consumption of a taste solution in rats with a history of forward
pairings of taste and heat exposure which could not logically be attributed to a
memorial interpretation of the failure to attenuate neophobia. The decline in
drinking over trials in the forward group found in Experiment F both eliminates
alternative memorial explanations and confirms that heat-induced relative drinking
suppression in the CTA context must be attributed to taste aversion conditioning in
the absence of a confirmed amnestic process that could account for the
phenomenon.

The conditioning of an aversion using a highly concentrated taste CS (Experiment F) prompts the speculation that there may be a threshold governing attribution of heat symptoms to external or internal factors; intense tastes are associated with the sickness arising from external heat, as if the source of the distress were internal. It may be that an ambient temperature increase is effectively an external event unless the animal experiences an ingestion-related stimulus of sufficient salience followed by the sickness arising from heat. The attribution is that the taste CS has caused the sickness and that both sickness and hyperthermia are the result of poisoning. Using weak taste CSs (as in Green et al., 1981) makes it less likely that external heat will be attributed to ingestion of the taste CS.

In conclusion, Experiments E and F provide further evidence that the CAS interpretation of the avfail phenomenon offered earlier is not subject to an alternative interpretation couched in terms of failure of attenuation of neophobia. Showing an unequivocal CTA to heat both validates the CAS interpretation and provides direct evidence that heat acts as an internal stimulus in the present context.
APPENDIX 3

HEAT-INDUCED TASTE AVersions:
UNCONDITIONED EFFECTS, MEMORIAL PROCESSES,
AND THE ATTENUATION OF NEOPHOBIA

High ambient temperature is effective as a US in a CTA procedure using a highly concentrated saccharin solution as the CS. In Experiment A (Appendix 1, pp. 120-124), for example, rats showed intense neophobic drinking suppression to the strong-tasting saccharin solution. This drinking suppression appeared to persist over putative conditioning trials in those receiving forward pairings of saccharin followed shortly thereafter by heat exposure relative to unpaired and unheated controls.

The phenomenon of failure of attenuation of neophobia in the forward pairings group has been interpreted in the CTA and avfail literatures as evidence of a mild CTA. Historically, however, one of two sorts of alternatives to a conditioning interpretation has also been applied to the phenomenon. The first (e.g., Mitchell et al., 1977; see also Garcia, 1978; Mitchell, 1977, 1978; Revusky, 1977a, 1978, 1979; Riley, 1978; Smith, 1978) is that the neophobic hesitancy to consume a novel-tasting food can be enhanced or sensitized by the experience of nausea or sickness which heightens the perceptual effects of novelty per se. Sensitization of neophobia probably occurs only in the immediate presence of sickness (e.g., Domjan, 1977b; but cf. Carroll, Dinc, Levy, & Smith, 1975) and is eliminated in any case by the use of standard Pavlovian controls.

The second sort of alternative interpretation is that taste-paired US exposure
interferes with memory consolidation or retrieval. Perhaps heat exposure during the period immediately following the drinking of a novel taste solution effectively interferes with consolidation of the gustatory memory trace (cf. Duncan, 1949; Green & Parker, 1975; Nachman, 1970). By this reasoning, the obtained drinking suppression occurs not because the taste becomes aversive but because it effectively retains its novelty over putative conditioning trials. Or perhaps retrieval of the memory of the taste on test depends on reinstatement of the stimulus conditions present during consolidation.

Consistent with the possible interpretation that taste-paired US exposure interferes with retrieval, Richardson, Riccio, and Steele (1986) reported state-dependent retrieval in an attenuation of neophobia procedure. Rats were injected with pentobarbital or normal saline immediately after drinking novel apple juice on the training day and again, in a 2 X 2 design, shortly before juice was made available on the test day. Only the group that received pentobarbital on training and saline on test showed drinking suppression consistent with the interpretation of asymmetrical retrograde state dependency of memory for the taste. Gridshock substitution for pentobarbital yielded similar results in a separate experiment. Rats apparently fail to remember previous exposure to a novel taste unless the drug state accompanying initial taste processing is reinstated as a retrieval cue at the time of test.

Can such a mismatch between taste consolidation and retrieval states explain the drinking suppression obtained in the present experimental series?
Green and Parker (1975) reported postingestional interference with gustatory memory over the sort of relatively brief delay likely to have been experienced by rats in the forward taste–heat group of Experiment A. Moreover, Mactutus, Ferek, and Riccio (1980) reported profound but reversible hyperthermia-induced retrograde amnesia for a passive avoidance task that survived multiple test trials. Hyperthermia-induced retrograde amnesia in the multiple-trial procedure of Experiment A is therefore a plausible alternative to a CTA interpretation, notwithstanding the presence of a delay of many minutes between saccharin consumption and heat exposure in the forward group.

An explanation based on retrieval deficit for memory of the taste could potentially explain particular features of the nominal heat-induced CTA phenomenon, such as its dependence on the use of a relatively intense and therefore highly salient or memorable taste CS. Earlier attempts by other investigators to condition taste aversions with heat may have failed because the taste was not sufficiently intense (e.g., Green et al., 1981). It could also potentially supersede the theoretical antisickness conditioning account of the avfail finding reported in Experiment 2 based on the elicitation and conditioning of an internal heat-compensatory response (cf. Lett, 1982). Finally, it could potentially be extended to explain other selected putative CTA phenomena, in particular those in which the US is highly effective at inducing state dependency. The retrograde state dependency (2 X 2) design is used with heat as the putative amnestic treatment in Experiment G (State Dependency Design with Heat, pp. 165–168),
and with pentobarbital or shock in Experiments H (State Dependency Design with Pentobarbital, pp. 169-174), and I (State Dependency Design with Footshock, pp. 174-176) in a more direct attempt to assess the retrieval deficit interpretation.

Experiment G

State Dependency Design with Heat

Experiment G uses a retrograde state dependency design and substitutes an increase in ambient temperature for the pentobarbital or shock used by Richardson et al. (1986). Heat parameters were the same as those used successfully in the experiments reported earlier, whereas taste parameters were those used by Richardson et al.

Method

Subjects

Thirty-two naive male Sprague Dawley rats were obtained from Charles River at a weight range of 170–180 g and weighed 199–222 g at the start of the experiment. They had ad libitum access to water and Purina Rat Chow except as noted.

Procedure

On the day before the training day, rats were assigned by weight to four groups of eight rats each. Each group was transferred to a separate transportation rack for the duration of the experiment. All experimental procedures were conducted in the colony room except as noted. Groups received one brief 5-min presentation of apple juice (Allen's brand) on the training day and a second 5-min presentation on the test day. Water bottles were removed 24 hr before each of the juice
presentation periods. Food was removed 1 hr before the start of training or testing; food and water were returned 1–2 hr after the end of any training or testing procedure. Forty-eight hr intervened between training and test.

On the training day, all groups were presented with apple juice in standard glass drinking bottles. Immediately following removal of the drinking bottles, two groups, called Heat groups, were transported approximately 2.5–3.0 m to an adjacent room preheated to 38 °C, and the remaining two groups, called Sham groups, were transported approximately the same distance to a second room maintained at the usual temperature of the colony room (20–22 °C). Temperature in the heat treatment room was maintained at a maximum of 38 °C until the heaters were turned off 2 hr after the two Heat groups had been placed in the room. All four groups were returned to the colony room approximately 30–40 min after the heaters were turned off, at a time when the heat treatment room had cooled to within 2 °C of the colony room temperature.

On the test day, one Heat group, called the Heat–Heat group, and one Sham group, called the Sham–Heat group, were transported to the heat treatment room and received heat exposure as for the training day. The remaining groups, called the Heat–Sham and the Sham–Sham groups, were transported to an adjacent room maintained at the colony temperature as for the training day. The first term in the group name refers to the training treatment and the second term refers to the test treatment. Groups received a second 5-min apple juice presentation during the final 15 min of the 2-hr heat or sham treatment period.
Heaters were turned off and groups were returned to the colony room at the end of the drinking period.

The weight of apple juice voluntarily consumed was recorded for each rat on each of the training and test days. Juice consumption scores were converted to acceptance scores in the form of suppression ratios. The ratio was Test / (Training + Test), where Training is the amount of juice consumed on the training day and Test is the amount consumed on the test day. A ratio above 0.50 indicates higher juice consumption on the test day than on the training day.

Acceptance scores were entered into a 2 (training treatment) x 2 (test treatment) ANOVA.

Results and Discussion

All rats were observed to sample novel apple juice on the training day; the lowest consumption score for any rat was 2.4 g. This obviated the giving of 1 ml of juice intraorally by syringe to any rat that had been found to consume less than 1 g as had been planned (using the procedure of V. A. Davey & Revusky, 1987) to ensure receipt of the taste. A one-way ANOVA on training day consumption scores failed to yield statistically reliable group differences, $F < 1.09$, and consumption scores were converted to acceptance scores for analysis. A 2 (training state) X 2 (test state) ANOVA on acceptance scores yielded a significant main effect of training treatment, $F (1, 28) = 16.64, p < .01$. Neither the main effect of test treatment nor the Training X Test interaction were significant, $F s < 1$. Group mean acceptance scores are shown in Table 5. By inspection, consumption increased
Table 5. Experiment G: Apple juice consumption in a retroactive state dependency (2 x 2) design using 38 °C heat exposure. Values in parentheses are standard errors of the means.

<table>
<thead>
<tr>
<th>Juice Consumption</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heat–Heat</td>
</tr>
<tr>
<td>Training (g)</td>
<td>4.7 (0.2)</td>
</tr>
<tr>
<td>Test (g)</td>
<td>5.3 (0.2)</td>
</tr>
<tr>
<td>Acceptance Score</td>
<td>0.53 (0.01)</td>
</tr>
</tbody>
</table>

Note. Independent groups received the factorial combinations of heat or sham treatment following juice exposure on the training day and heat or sham treatment preceding juice exposure on the test day. The first term in the group name refers to training treatment and the second term refers to test treatment. Entries are juice consumption scores on training and test days and acceptance scores in the form of suppression ratios. The ratio was Test / (Training + Test), where Training is the amount of juice consumed on the training day and Test is the amount consumed on the test day. A ratio above 0.50 indicates higher juice consumption on the test day than on the training day.
less on the test day in groups that had been heated immediately following consumption on the training day, consistent with the conditioning of a mild CTA in these groups. No other effects are evident; in particular, the nonsignificant interaction indicates that state dependency was not obtained.

Experiment H

State Dependency Design with Pentobarbital

The failure to obtain retroactive state-dependent retention using heat and the lack of published independent confirmatory evidence for the retrieval deficit effect impel a more direct attempt at replication. Experiment H uses pentobarbital as in Richardson et al. (1986, Experiment 1). Additional Pavlovian controls are incorporated to assess the possibility that taste aversion conditioning with pentobarbital (Taukulis, 1983; Vogel & Nathan, 1975) in combination with an unconditioned pharmacological dipsogenic effect of pentobarbital on test (Schmidt, 1958; Schmidt & Moak, 1959; Watson & Cox, 1976) could account for the retrieval deficit effect.

Method

Subjects

Forty-eight naive male Sprague Dawley rats weighing 491–715 g at the start of the experiment were assigned by weight to six groups of eight rats each.

Procedure

On the training day, rats were given 5 min access to apple juice. Upon removal of the juice bottles, they were injected intraperitoneally with either pentobarbital
(1 ml/kg of a solution containing 12.5 mg/ml in normal saline) or saline (equivalent-by-volume). On the test day, rats were injected with pentobarbital or saline 15 min before 5-min access to apple juice. Forty-eight hr intervened between training and test.

Four groups were used in a retrograde state dependency design. On the training day, two of these groups received juice followed by pentobarbital and two received juice followed by saline. On the test day, the four groups received pentobarbital or saline before juice presentation in a factorial design. Group designations are Pent-Pent, Pent-Sal, Sal-Pent, and Sal-Sal, where Pent is pentobarbital, Sal is saline, the first term of the group name refers to the training treatment, and the second term refers to the test treatment.

The Pent-Pent and Pent-Sal groups of the above state dependency design both received a nominal forward pairing of juice followed by pentobarbital on the training day. A CTA design was organized around one of these two groups. Specifically, whether taste aversion conditioning occurred in the Pent-Pent group was assessed by comparison with CS-only and unpaired controls. The Sal-Pent group of the state dependency design served as the CS-only control. An additional fifth and sixth group provided unpaired controls. On the training day, both of these groups received saline immediately following juice consumption. One group received pentobarbital approximately 12 hr after juice consumption in an explicitly unpaired procedure. Because forward conditioning is unlikely but possible with a 12-hr delay between taste and toxicosis, and moreover because...
pentobarbital could conceivably have pharmacological effects of sufficient duration to unconditionally affect drinking on the test day, a second group received pentobarbital approximately 12 hr prior to juice consumption on the training day. On the test day, both groups received pentobarbital 15 min before juice presentation. The groups are designated AdPent—Pent and PentdA—Pent, where A is apple juice, d is a 12-hr delay between pentobarbital injection and juice consumption on the training day, the first term of the group name refers to the training treatment, and the second term refers to the test treatment. Because all groups in the CTA design received pentobarbital prior to juice consumption on the test day, any group differences in acceptance scores are attributable to differences in treatment on the training day.

The Pent—Sal group of the state dependency design also received a nominal forward pairing of juice and pentobarbital on the training day, but whether taste aversion conditioning also occurred in this group was not assessed. I reasoned that a combination of taste aversion conditioning and an unconditioned dipsogenic effect of pentobarbital on test could mimic state dependency in the 2 X 2 design; the forward group that received pentobarbital on test—that is, the Pent—Pent group—was therefore favored.

Acceptance scores for all six groups were entered into a one-way ANOVA. In the event of a significant omnibus F, groups were pooled as required and pairs of pooled or unpooled groups were entered into ANOVAs to yield comparison Fs based on the error term and per comparison error rate of the overall ANOVA.
Results and Discussion

All rats were observed to sample novel apple juice on the training day. Groups did not differ in their juice consumption on the training day, $F(5, 42) = 1.42, p > .20$, and consumption scores were converted to acceptance scores for analysis. A one-way ANOVA on acceptance scores was significant, $F(5, 42) = 4.43, p < .01$, indicating global differences among groups on juice consumption.

Retrograde state dependency (2 X 2) design. The groups in this analysis are Pent–Pent, Pent–Sal, Sal–Pent, and Sal–Sal. The main effect of training was arrived at by pooling the pairs of groups that were treated the same on the training day and then entering the pooled groups into a one-way ANOVA. The ANOVA yielded a significant effect of training, $F(1, 42) = 12.26, p < .01$. The main effect of testing, arrived at by pooling the pairs of groups that were treated the same on the test day, was not significant, $F < 1$. The interaction, arrived at by pooling the pair of groups that was treated the same on training and test and the pair that was treated differently on training and test, was not significant, $F < 1$.

Inspection of the acceptance scores in Table 6 shows that juice consumption on the test day was lower in the groups that had received pentobarbital immediately after juice consumption on the training day. This pattern of results is consistent with the conditioning of a mild CTA in groups receiving pentobarbital immediately following juice consumption on the training day. No other effects are evident. Pentobarbital was not dipsogenic when administered prior to juice consumption on the test day, and juice consumption on test did not depend on reinstatement of
Table 6. Experiment H: Apple juice consumption in a retroactive state dependency (2 x 2) design using pentobarbital. Values in parentheses are standard errors of the means.

<table>
<thead>
<tr>
<th>Juice Consumption</th>
<th>Group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pent–Pent</td>
<td>Pent–Sal</td>
<td>Sal–Pent</td>
<td>Sal–Sal</td>
</tr>
<tr>
<td>Training (g)</td>
<td>5.3 (0.2)</td>
<td>5.6 (0.2)</td>
<td>5.7 (0.2)</td>
<td>5.5 (0.3)</td>
</tr>
<tr>
<td>Test (g)</td>
<td>5.0 (0.2)</td>
<td>5.6 (0.4)</td>
<td>8.2 (1.1)</td>
<td>8.1 (0.8)</td>
</tr>
<tr>
<td>Acceptance Score</td>
<td>0.49 (0.02)</td>
<td>0.50 (0.02)</td>
<td>0.57 (0.03)</td>
<td>0.59 (0.02)</td>
</tr>
</tbody>
</table>

Note. Independent groups received the factorial combinations of pentobarbital or sham treatment following juice exposure on the training day and pentobarbital or sham treatment preceding juice exposure on the test day. The first term in the group name refers to training treatment and the second term to test treatment. Pent is pentobarbital and Sal is saline. Entries are juice consumption scores on training and test days and acceptance scores in the form of suppression ratios. The ratio was Test / (Training + Test), where Training is the amount of juice consumed on the training day and Test is the amount consumed on the test day. A ratio above 0.50 indicates higher juice consumption on the test day than on the training day.
the training day drug state.

**CTA design.** The groups in this analysis are Pent—Pent, Sal—Pent, AdPent—Pent, and PentdA—Pent. The unpaired control groups AdPent—Pent and PentdA—Pent did not differ, $F < 1$, and were pooled for subsequent analyses. Group Pent—Pent differed from the pooled unpaired groups, $F (1, 42) = 14.06$, $p < .01$, and from group Sal—Pent, $F (1, 42) = 5.44$, $p < .05$. The Sal—Pent and pooled unpaired groups did not differ, $F < 1$. Group mean acceptance scores are shown in Table 7. By inspection, juice consumption on the test day was lower in the group that received pentobarbital immediately after juice consumption on the training day relative to groups that received pentobarbital unpaired with juice or to the group that did not receive pentobarbital on the training day. This pattern of results is consistent with the conditioning of a mild CTA in groups receiving pentobarbital immediately following juice consumption on the training day. No other effects are evident.

**Experiment I**

**State Dependency Design with Footshock**

Richardson et al. (1986, Experiment 2) reported that subconvulsive footshock successfully substituted for pentobarbital in the retrograde state dependency procedure. This finding is made more salient in the present context by the fact that shock is not normally considered a candidate as an inducer of CTAs (e.g., Garcia & Koelling, 1966; Nachman, 1970). In Experiment I of this thesis, footshock is also substituted for pentobarbital in an attempt at replication.
Table 7. Experiment H: Apple juice consumption in a taste aversion conditioning design using pentobarbital. Values in parentheses are standard errors of the means.

<table>
<thead>
<tr>
<th>Juice Consumption</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pent</td>
</tr>
<tr>
<td>Training (g)</td>
<td>5.3  (0.2)</td>
</tr>
<tr>
<td>Test (g)</td>
<td>5.0  (0.2)</td>
</tr>
<tr>
<td>Acceptance Score</td>
<td>0.49 (0.02)</td>
</tr>
</tbody>
</table>

Note. Pent is pentobarbital, Sal is saline, A is apple juice, and d is a 12-hr delay between pentobarbital injection and juice consumption on the training day. All groups received pentobarbital before juice consumption on the test day. Entries are juice consumption scores on training and test days and acceptance scores in the form of suppression ratios. The ratio was Test / (Training + Test), where Training is the amount of juice consumed on the training day and Test is the amount consumed on the test day. A ratio above 0.50 indicates higher juice consumption on the test day than on the training day.
Method

Subjects
Thirty-two naive male Sprague Dawley rats weighing 163–186 g at the start of the experiment were assigned by weight to four groups of eight rats each.

Procedure
On the training day, rats were given 5 min access to apple juice. Two groups, called Shock groups, were then immediately placed in shock boxes and received scrambled shock (1 mA). Shocks were 2 sec in duration with one shock every 15 sec for a total of 40 shocks over a 10-min exposure period. The remaining two groups, called Sham groups, were placed in shock boxes for 10 min but did not receive shock. Rats were removed immediately after the 10-min shock period.

One day intervened between training and test. On the test day, one Shock group, called the Shock–Shock group, and one Sham group, called the Sham–Shock group, received shock as on the training day. The remaining groups, called the Shock–Sham and the Sham–Sham groups, were placed in the shock box but did not receive shock. The first term in the group name refers to the training treatment and the second term refers to the test treatment. Rats were returned to their home cages immediately after the shock period and were left undisturbed for 2 min prior to the 5 min juice presentation period.

Results and Discussion
All rats were observed to sample novel apple juice on the training day. Groups did not differ by one-way ANOVA on training day juice consumption, F < 1, and
consumption scores were converted to acceptance scores for analysis. Neither the main effects nor the interaction effect of a 2 X 2 ANOVA reached significance, $F_s < 1.14$. Failure to find relative drinking suppression on test in groups that received shock on the training day is consistent with the interpretation given in Experiments G and H. That is, drinking suppression consistent with the conditioning of a mild CTA is found with heat and pentobarbital (Experiments G and H) but not with footshock (Experiment I).

General Discussion

The present results provide no support for retroactive state dependency with heat, pentobarbital, or shock, but on the contrary provide uniform support for CTA with heat and pentobarbital. Mactutus et al. (1980) and Misanin, Vonheyn, Bartelt, and Boulden (1979) reported that heat exposure interfered with memory for a one-trial passive avoidance task when rats were placed in restrainers and immersed in hot water. Mactutus et al. failed to find an effect unless at least some rats showed heat-induced convulsions whereas Misanin et al. obtained an effect without convulsions but not in a CTA context. By contrast, Green et al. (1981) used a heating procedure similar to the one used here and reported success with place but not taste aversion conditioning; there is no reason to suppose that a state-related memorial process would eliminate memory for taste and spare memory for place. Invoking state dependency to explain the relative drinking suppression reported in the present experimental series is unwarranted in the absence of confirmation of the state dependency hypothesis.
References
Budapest: Akadémiai Kiadó.
Andrews, P. L. R., Bhandari, P., Garland, S., Bingham, S., Davis, C. J., Hawthorn,
J., Davidson, H. I. M., Roylance, R., & Lane, S. (1990). Does retching have
a function?: An experimental study in the ferret. Pharmacodynamics and
Therapeutics (Life Science Advances). 9, 135–152.
failure: Reactivation of associations to a blocked stimulus. Quarterly Journal
radiation and lithium chloride in CS–US and US–CS paradigms. Journal of
Comparative and Physiological Psychology. 87, 644–654.
Bernstein, I. L. (1983). Learned food aversions: Heterogeneity of animal models of
tumor-induced anorexia. Appetite. 4, 79–86.


Cairnie, A. B., & Leach, K. E. (1982). Dexamethasone: A potent blocker of
radiation-induced taste aversions in rats. *Pharmacology, Biochemistry, and
Behavior, 17*, 305–312.

preconditioning unconditioned stimulus experience on learned taste
aversions. *Journal of Experimental Psychology: Animal Behavior Processes, 1*,
270–284.

side effects associated with cancer chemotherapy: A critical review and

humoral factors mediate cancer chemotherapy-induced emesis? *Drug Metabolism Reviews, 12*,
319–333.

neophobia and enhanced neophobia in the albino rat. *Journal of
Comparative and Physiological Psychology, 89*, 457–467.

significance of arginine vasopressin in motion sickness. *Journal of Clinical

Cunningham, C. L. (1978). Alcohol interacts with flavor during extinction of

ethanol-induced conditioned taste aversion. *Psychopharmacology, 95*. 


Investigation, 83, 1313-1318.


nonassociative aspects. Learning and Motivation, 11, 522-537.


Febiger.


cues in the conditional control of tolerance to alcohol. *Psychopharmacology, 83*, 159-162.


Hatch, R. C. (1973). Experiments on antagonism of barbiturate anesthesia with


Jones (Ed.), *Miami symposium on the prediction of behavior: Aversive stimulation* (pp. 9-33). Coral Gables, FL: University of Miami Press.


homeostasis and vasopressin release during rodent and human gestation.

American Journal of Kidney Diseases. 9, 270-275.


Martin, G. M. (1982). Examination of factors which might disrupt a learned association between pentobarbital and LiCl. Learning and Motivation, 13, 185-199.


Weizman (Eds.), Application of basic neuroscience to child psychiatry (pp. 125-140). New York: Plenum.


injection: Relative effectiveness of apomorphine, emetine, and lithium.


Revusky, S., & Reilly, S. (1990a). Dose effects on heart rate conditioning when pentobarbital is the CS and amphetamine is the US. *Pharmacology, Biochemistry, and Behavior, 36*, 933–936.


343–369.


Tarr, L. (1933). The circulation time in various clinical conditions determined by the
use of sodium dehydrocholate. American Heart Journal, 8, 766-785.


changes in the anxiolytic and myorelaxant properties of diazepam in the rat. 
Pharmacology, Biochemistry, and Behavior, 41, 13-21.


