Learned associations between drug states: Attempted analysis in Pavlovian terms

SAM REVUSKY, HARALD K. TAUKULIS, and CALVIN PEDDLE
Memorial University of Newfoundland, St. John's, Newfoundland, A1C 5S7, Canada

A sedative dose of pentobarbital was injected into rats 30 min prior to a toxic dose of lithium on a number of occasions. A later test indicated that pentobarbital had lost its normal capacity to produce a mild aversion to previously consumed saccharin solution as a result of these pairings. This "avfail" (aversion failure) effect was opposite to predictions based upon principles of Pavlovian higher order conditioning. Attempts to implicate conditioned inhibition in avfail were unsuccessful, but led to discovery of another effect called conditioned sickness, which also resulted from pairing of pentobarbital with lithium: While the rats were sedated with pentobarbital, they avoided drinking novel saccharin solution. Conditioned sickness looked like straightforward Pavlovian conditioning until it was found not to be obtainable when other mild drugs were substituted for pentobarbital. Thus, neither avfail nor conditioned sickness was congruent with traditional Pavlovian principles of conditioning. Nevertheless, the avfail effect seems to involve learning because of its occurrence when a variety of drugs are substituted for pentobarbital or for lithium. Apparently, then, the learning involving association of feeling states, which probably has an important role in homeostasis, follows laws which are now undiscovered.

The present experiments began as part of a program by which flavor-aversion learning experiments with animals were to be used to supply data relevant to the chemical aversion treatment (CAT) of alcoholism. In this treatment, the consumption of alcoholic beverages by alcoholic patients is made aversive by using sickness as a US. CAT has one serious limitation: It produces aversions only to the flavor of alcohol, not to the alcohol state (Rachman & Teasdale, 1969). Using rats, Revusky, Taukulis, Parker, and Coombes (1979) tried to get around this problem by pairing a mild drug state (called the CS), which many humans would find enjoyable, with intense sickness (called the US); presumably some of the aversiveness of the US drug would transfer to the CS drug. They tested for transferred aversiveness by allowing consumption of saccharin solution prior to injection of the CS drug in order to produce a saccharin aversion. Their results were exactly opposite to expectation. They found that the result of pairing the two drug states (called CS→US pairings) was that the CS drug lost its normal capacity to produce a mild flavor aversion. For instance, if a sedative dose of pentobarbital was injected 30 min prior to a highly toxic dose of lithium on five

occasions spaced 3 days apart, later pairings of saccharin consumption with pentobarbital did not produce a flavor aversion. This loss by pentobarbital of its capacity to produce a flavor aversion could not be attributed to drug habituation (Braveman, 1977; Gamzu, 1977) because it did not occur after pairings of lithium prior to pentobarbital (US→CS pairings), injections of pentobarbital alone (CS alone), or injections of lithium alone (US alone).

This effect was very robust. Four to eight CS→US pairings were capable of preventing as many as 13 successive SAC→Barb pairings from producing a saccharin aversion. In other experiments, Revusky et al. (1979) showed that the effect was not limited to cases in which pentobarbital was the CS and lithium was the US. It can be obtained when a variety of recreational drugs are paired with high doses of lithium or when a sedative dose of pentobarbital is paired with an extremely high dose of d-amphetamine. Since it was not limited to specific combinations of CS and US drugs, it looked like a type of learning involving associations between feeling states. In order not to prejudge the nature of this effect, we have given it the atheoretical label of "avfail" (aversion failure). If avfail involves learning, one would expect its biological role to involve homeostatic regulation in which the animal applies information about its sequence of feeding states to regulate its internal environment. Since there is strong evidence that the rules of Pavlovian conditioning apply to ordinary taste aversions (Revusky, 1977; Taukulis & Revusky, 1975), it was considered possible that they might also apply to the avfail

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effect. Here we describe experimentation designed to investigate this possibility.

Table 1 summarizes the avfail procedure and its various controls for the case in which pentobarbital (called "Barb") was the CS drug and lithium chloride (LiCl) was the US drug. To elucidate our reasoning, the procedures are outlined parenthetically in Pavlovian terms: The CS drug is CS₁ and saccharin is CS₂. These outlines show that the avfail procedure looks like a Pavlovian higher order conditioning procedure: Phase 1 in column 1 of Table 1 consisted of CS₁→US pairings, and Phase 2 consisted of CS₂→CS₁ pairings. For instance, if light→shock pairings were followed by tone→light pairings, we would expect higher order conditioning to the tone. Furthermore, higher order conditioning occurs when CS₁ and CS₂ are different tastes and the US is sickness (Bond & DiGuisto, 1976; Bond & Harland, 1975). For these reasons, we originally expected the avfail procedure to produce higher order conditioning to saccharin and hence lower saccharin preferences than those produced by the control procedures outlined in the second column of Table 1.

Since the avfail results in Table 1 were exactly opposite to those expected on the basis of higher order conditioning, the present series of experiments was designed to evaluate the possibility that conditioned inhibition might be involved. This interpretation is identical to the higher order conditioning interpretation in its assumption that a learned association between pentobarbital and lithium developed during Phase 1 of the avfail procedure as shown in Table 1. However, the interpretation of what happened in Phase 2 is very different. Presumably, when the avfail rats experienced pentobarbital sedation without later lithium sickness in Phase 2, they attributed the nonoccurrence of sickness to the prior consumption of saccharin solution; thus the saccharin solution became a conditioned inhibitor because, in effect, the avfail rats decided that it prevented pentobarbital sedation from resulting in lithium sickness. If so, the saccharin did not

become a conditioned inhibitor for the groups subjected to a Sac→Barb pairing without prior Barb→LiCl pairings (column 2 of Table 1) because these groups did not have a learned expectation that lithium sickness would follow pentobarbital sedation; the lack of such an expectation prevents the development of conditioned inhibition (Best, 1975; Taukulis & Revusky, 1975).

A minor contraindication to the involvement of conditioned inhibition in the avfail effect is the fact that the avfail rats did not have higher saccharin preferences than the baseline controls in column 3 of Table 1. It is known that a conditioned inhibitor tends to function as a reward (Best, 1975; Bolles, 1970; Dinsmoor & Sears, 1973), and this ought to raise saccharin preferences above baseline. However, if a conditioned inhibition explanation of avfail were to be otherwise tenable, the failure of saccharin preferences to rise above baseline could easily be explained. The normal effect of Sac→Barb pairings is to produce a mild saccharin aversion. Presumably this effect might also occur among the avfail rats and counteract the effect of conditioned inhibition so that the net saccharin preference produced by the avfail procedure would be indistinguishable from that produced when saccharin consumption is not paired with pentobarbital.

A more serious objection to a conditioned inhibition explanation of avfail is that it attributes an unreasonably high level of intelligence to the rat. Presumably, as an avfail rat begins to become sedated with pentobarbital after drinking saccharin in Phase 2 (Table 1), it begins to develop a mild saccharin aversion. However, it is also expecting lithium sickness to occur, since, in the past, lithium sickness had occurred about 30 min after pentobarbital sedation. As it becomes clear that the lithium sickness will not occur, the rat must recall that it had consumed saccharin solution well over 30 min earlier, attribute the nonoccurrence of lithium sickness to the saccharin, and reverse its previously developed aversion to the saccharin. Clever rat to do all of this

Table 1
Avfail Effect Summarized for Pentobarbital (Barb) as the CS Drug, Lithium Chloride (LiCl)
as the US Drug, and Saccharin (Sac) as the Test Flavor

Procedure		Control for Aversion Due to Sac→Barb Pairings	Baseline Preference
Phase 1			
Avfail	Barb→LiCl (CS ₁ →US)	Barb Alone, LiCl Alone, or LiCl→Barb Pairings (CS ₁ Alone, US Alone, or US→CS ₁ Pairings)	Irrelevant
Phase 2			
Avfail	Sac→Barb (CS ₂ →CS ₁)	Sac→Barb (CS ₂ →CS ₁)	Sac Alone (CS ₂ Alone)
Avfail	Same as Baseline	Saccharin Preference Mild Aversion	Baseline

in the course of a single Sac→Barb trial! And yet, if conditioned inhibition is involved in avfail, the equivalent of some such process must occur.

This common-sense argument against the involvement of conditioned inhibition in avfail has a Pavlovian counterpart. Pavlov (1927) regarded higher order conditioning as an early stage of the same process which eventually results in conditioned inhibition and insisted that conditioned inhibition would not develop under poor training conditions. The avfail procedure in Table 1 easily met Pavlov's criteria for poor training conditions. Five successive Barb→LiCl (CS_1 →US) pairings preceded a single Sac→Barb (CS_2 → CS_1) trial. In contrast, Pavlov insisted that many CS_1 →US trials must be intermixed with many CS_2 → CS_1 trials if conditioned inhibition is to be obtained. A second feature of the avfail procedure designed to favor higher order conditioning over conditioned inhibition was the lack of a temporal overlap between the saccharin taste and the pentobarbital sedation during the Sac→Barb pairing; indeed, in the Barb→LiCl trials of their first experiment (Table 1), Revusky et al. (1979) did not inject the pentobarbital until 11 min after the saccharin bottle had been removed. According to Pavlov (1927), a temporal gap between CS_2 and CS_1 strengthens higher order conditioning by weakening conditioned inhibition. Thus, it would be clearly contrary to Pavlovian precedents if conditioned inhibition were responsible for the avfail effect.

Nevertheless, the case against a role for conditioned inhibition in the avfail effect is not entirely convincing. A learning process likely to have only a weak effect in traditional experimental situations may have a very strong effect in the feeding situation due to the marked innate propensity to associate feeding CSs with physiological USs. Thus, we deemed the potential role of conditioned inhibition in the avfail effect to be worthy of further investigation.

The strategy underlying the present experiments was to use known principles of Pavlovian conditioning to modify the original avfail procedure so as to strengthen conditioned inhibition at the expense of higher order conditioning. There is now ample evidence that principles derived from traditional learning experiments also apply to feeding, even though the magnitudes of the effects are larger in feeding experiments (Revusky, 1977). Presumably, then, counterparts of Pavlovian procedures which are known to strengthen conditioned inhibition in traditional situations would also strengthen conditioned inhibition in the avfail situation. If so, such a modified avfail procedure would produce higher saccharin preferences than those produced through a baseline preference control procedure

equivalent to that outlined in column 3 of Table 1. If a poor conditioned inhibition procedure like that in column 1 of Table 1 produced saccharin preferences equal to the baseline level, a good procedure ought to produce substantially higher preferences.

EXPERIMENT 1

The procedures for the three treatments of Experiment 1 are outlined in Table 2. Following Pavlov's (1927) rules for strengthening higher order conditioning at the expense of conditioned inhibition, Barb→LiCl pairings had been massed prior to Sac→Barb pairings in the earlier avfail procedure (Table 1). In contrast, we tried to use Pavlov's rules to strengthen conditioned inhibition in Group Barb→LiCl of Table 2 by alternating Barb→LiCl pairings with Sac→Barb pairings. Group LiCl→Barb was treated similarly, except that LiCl→Barb pairings were substituted for the Barb→LiCl pairings so that we would obtain the saccharin aversion usually produced by Sac→Barb pairings as shown in Table 1. Finally, Group Sac-Cont was designed to yield a baseline preference for saccharin.

It was hoped that Group Barb→LiCl would exhibit a higher saccharin preference than the baseline level of Group Sac-Cont. Group LiCl→Barb was expected to exhibit a mild saccharin aversion. The Barb-alone and LiCl-alone procedures mentioned in column 2 of Table 1 were deemed superfluous for this experiment because Revusky et al. (1979) found they yielded results similar to those yielded by Group LiCl→Barb.

A second feature of Experiment 1 was the use of four doses of pentobarbital so that the formal experimental design was 3 by 4 factorial (the three treatments of Table 1 by four pentobarbital doses). The sodium pentobarbital doses were roughly 2.5, 5.0, 10.0, and 20.0 mg/kg; the last of these was the dose which had been used earlier. It was hoped that some lower dose might reduce the aversiveness of the Sac→Barb pairings without an equivalent loss in the capacity of pentobarbital to become a signal for lithium sickness; if so, conditioned inhibition might raise saccharin preferences in Group Barb→LiCl above the baseline level.

Table 2
Procedure of Experiment 1 Outlined

Trials	Groups		
	Barb→LiCl	LiCl→Barb	Sac Cont
Odd	Barb→LiCl	LiCl→Barb	Irrelevant
Even	Sac→Barb	Sac→Barb	Sac Alone

Note—The same groups were used at each of four pentobarbital doses.

Method

The 76 male Wistar rats weighed 210-240 g just before the experiment. They were subjected to 10 5-day cycles. In each cycle, the Day 1 procedure was two injections spaced 30 min apart (odd trial shown in Table 2) and the Day 4 procedure was to allow consumption of saccharin solution for 15 min and then, except for Group Sac-Cont, inject them with pentobarbital (even trial in Table 2). During the first cycle, the rats were maintained on 15 min per day of unflavored water on Days 2, 3, and 5, with no fluid on Day 1. This thirst schedule was too severe, since 3 of 76 rats died. During later cycles, the rats received 24 h of free access to unflavored water beginning 5-6 h after saccharin consumption on Day 4.

Each rat received the same absolute dose of sodium pentobarbital throughout the experiment. The doses were .62, 1.25, 2.5, and 5.0 mg. The lithium dose used throughout was 3.5 ml of a 2.0% (weight/volume) lithium chloride solution. For each pentobarbital dose, there were seven Barb→LiCl rats, seven LiCl→Barb rats, and five Sac-Cont rats. Barb→LiCl rats were then injected with pentobarbital 30 min before injection of lithium on odd trials and drank .5% (w/v) sodium saccharin solution for 15 min just prior to a pentobarbital injection on even trials. LiCl→Barb rats were treated in the same way, except that their lithium injections were 30 min prior to the pentobarbital injections. The five Sac-Cont rats subjected to each pentobarbital dose were split into two subgroups; three rats were treated like the Barb→LiCl rats on odd trials and two rats were treated like the LiCl→Barb rats; on even trials, they drank saccharin solution for 15 min, but were not injected afterward.

Results and Discussion

Even though Barb→LiCl rats were subjected to alternating Barb→LiCl and Sac→Barb trials in order to strengthen the role of conditioned inhibition, at no pentobarbital dose was there any sign that their saccharin preferences were higher than in Group Sac-Cont. Figure 1 shows the results in terms of saccharin preference ratios; these ratios are defined

Figure 1. For each of four doses of pentobarbital, the effects of three treatments on the preference for saccharin solution are shown. Barb→LiCl and LiCl→Barb refer to the sequence of drug-drug pairings which were alternated with Sac→Barb pairings. Group Sac-Cont was not injected with pentobarbital after drinking the saccharin solution.

as the amount, in grams, of saccharin solution consumed on the indicated day divided by the sum of this amount and the amount of unflavored water consumed on the preceding day. The data for Group Sac-Cont in Figure 1 were pooled over all pentobarbital doses, since the different doses did not affect preferences in this group. During early trials, all preferences were below .50, which means that less saccharin solution was consumed than water on the preceding day; this reflects the fact that rats are neophobic for strong novel-flavored solutions. In group Sac-Cont, the preferences soon rose to .50, while in those groups exhibiting saccharin aversions, the rise in preference was less marked. The fact that no preferences in Figure 1 are below .30 points up the mildness of all saccharin aversions exhibited in the present experiment; if the present dose of lithium were to have been directly paired with saccharin consumption even once, the preferences would certainly have dropped to well under .10 after the first cycle (Nachman & Ashe, 1973).

For purposes of statistical inference, the mean saccharin preferences over the last 9 days in Figure 1 were combined. All groups were at the same level, except for the LiCl→Barb groups at 2.5 and 5.0 mg of pentobarbital, which exhibited marked saccharin aversions when compared with Group Sac-Cont [$t(31) > 3.70$, $p < .001$]. In addition, both of these LiCl→Barb groups exhibited reliably lower saccharin preferences than did the corresponding Barb→LiCl groups ($p < .02$). These statistics show that, at the two pentobarbital doses high enough to produce a saccharin aversion, the Barb→LiCl procedure (modified avfail) prevented the aversion from developing.

Since, contrary to expectation, not a single Barb→LiCl group exhibited saccharin preferences higher than those among Group Sac-Cont, the results in Figure 1 failed to support the theory that conditioned inhibition was responsible for the avfail effect.

EXPERIMENT 2

The strategy underlying the present series of experiments was to increase saccharin preferences above baseline by modifying the avfail procedure outlined in Table 1 so that saccharin would become a more potent conditioned inhibitor. Unfortunately, this strategy failed in Experiment 1; a modification of the avfail procedure in which Barb→LiCl pairings ($CS_1 \rightarrow US$) and Sac→Barb pairings ($CS_2 \rightarrow CS_1$) were alternated failed to increase saccharin preferences above baseline. In Experiment 2, we tried another modification of the avfail procedure designed to strengthen conditioned inhibition to saccharin: instead of Sac→Barb pairings in Phase 2, we used Barb→Sac pairings, in which the rat drinks the saccharin

Table 3
The Five Combinations of Phase 1 and Phase 2 Treatments Used in Experiment 2

Phase 1	Barb→LiCl	LiCl→Barb	Barb→LiCl	LiCl→Barb	Irrelevant
Phase 2	Barb→Sac	Barb→Sac	Sac→Barb	Sac→Barb	Sac Alone

solution after pentobarbital sedation has begun to take effect. We expected the switch to Barb→Sac pairings to increase conditioned inhibition to saccharin on the basis of Pavlov's (1927) rule that for strong conditioned inhibition to be obtained, the inhibitory CS (saccharin) must overlap in time with the excitatory CS (pentobarbital). The Barb→Sac pairing also had the advantage that it might be expected to produce a weaker saccharin aversion than the Sac→Barb pairing; when onset of the drug state precedes exposure to a flavor, there is at most a very weak aversion (Boland, 1973; Green & Garcia, 1971).

Table 3 shows the five treatments used in Experiment 2. The two focal groups are those subjected to Barb→Sac pairings in Phase 2 (first and second columns in Table 3); it was expected that after the first Barb→Sac trial, the rats with Barb→LiCl histories would drink more than the rats with LiCl→Barb histories, and that this difference would be more marked than it is after Sac→Barb pairings (third and fourth columns of Table 3). Of course, the fifth column in Table 3 refers to a baseline control group.

There is a methodological problem in this experimental design; pentobarbital produces polydipsia (Schmidt, 1958), and hence it is difficult to compare meaningfully saccharin consumptions in drugged and undrugged rats. One cannot easily circumvent this problem by testing all rats in the same drugged or undrugged state without encountering problems produced by possible drug-dissociated learning (Overton, 1964). It so happened that we were not called upon to deal with this problem, because the pattern of results was not as expected.

The five procedures outlined in Table 3 were administered for different groups at either 1.25 or 2.5 mg of pentobarbital per rat (roughly 5 and 10 mg/kg) for a total of 10 groups. The higher 5-mg dose used in the original avfail experiments (Revusky et al., 1979) was not used because it interferes with measurements of saccharin preference during Barb→Sac pairings; it produces ataxia in some rats and hence results in a great deal of spillage. Although the pentobarbital doses used in Experiment 2 produce polydipsia, they do not produce ataxia severe enough to invalidate a measure of fluid consumption. The 1.25-mg dose of pentobarbital was ineffective in Experiment 1, but we thought it might be effective with the Barb→Sac procedure.

Method

The 90 rats weighed 200-260 g before the experiment and were divided into 10 equal groups based on the factorial combination

of the 1.25- and 2.5-mg pentobarbital doses and the five procedures shown in Table 3.

In Phase 1, the rats were maintained on 24 h of continuous access to water in every 3-day cycle; there were nine such cycles. The Phase 1 injections shown in Table 3 were administered every 3rd day, 30 min apart, while the rats were 1 day thirsty. The lithium dose was 2.5 ml of 2.0% (w/v) solution.

In Phase 2, the rats were maintained on 30 min per day of access to water. Every 3rd day, the water was flavored with saccharin (.5% w/v) for a total of four such trials. On Barb→Sac trials, pentobarbital was injected 15 min before the saccharin solution was presented. On Sac→Barb trials, pentobarbital was injected as the saccharin solution was removed. After these four trials, the Barb→Sac rats received an additional three Barb→Sac trials under the same conditions, except that the saccharin concentration was raised to 2.5% in order to combat ceiling effects caused by the polydipsia.

Results and Discussion

Figure 2 shows mean saccharin preference ratios for each group during the first 4 saccharin drinking days of Phase 2. Since the original avfail effect does not occur until after the first Sac→Barb pairing (Revusky et al., 1979), the concern was with mean saccharin preferences on Days 2-4. A 2 by 2 ANOVA was computed for each pentobarbital dose separately; the factors were Phase 1 procedure (Barb→LiCl vs. LiCl→Barb) and Phase 2 procedure (Barb→Sac vs. Sac→Barb). The theory that Barb→Sac pairings produce more conditioned inhibition than Sac→Barb pairings would have been confirmed by an interaction between these two types of pairings and Barb→LiCl vs. LiCl→Barb histories in their effects on saccharin consumption: The tendency of rats with Barb→LiCl histories to drink more saccharin than rats with LiCl→Barb histories would be more pronounced on Barb→Sac trials than on Sac→Barb

Figure 2. Mean preference during the first 4 test days in Experiment 2 as a function of the Phase 1 procedures (Barb→LiCl vs. LiCl→Barb) and Phase 2 procedures (Barb→H₂O vs. Barb→Sac). Tests conducted in rats sedated with 1.25 or 2.5 mg of pentobarbital.

trials. There was no sign of such an interaction either in the ANOVA for 1.25 mg or in the ANOVA for 2.5 mg ($p > .10$). Furthermore, at neither dose was there an overall higher preference for saccharin among Barb→LiCl than among LiCl→Barb rats ($p > .10$); this means that the original avfail effect was not obtained at either dose, even though it had been obtained at 2.5 mg in the preceding experiment. The only discernible statistical effect was due to the polydipsia produced by pentobarbital; at both doses, saccharin preferences were higher during Barb→Sac trials than during Sac→Barb trials [$F(1,32) = 23.5$ for 1.25 mg; $F(1,32) = 46.7$ for 2.5 mg].

The failure to replicate the avfail effect at 2.5 mg of pentobarbital in the present experiment is not of much theoretical importance. For avfail to occur, a noticeable saccharin aversion must be produced among the LiCl→Barb rats, and this was not present in Figure 2 since their preferences were no lower than in Group Sac-Cont. Since 1.25 mg of pentobarbital was below the threshold for producing an aversion in Experiment 1, we can suppose that 2.5 mg is close to the threshold, even though an aversion was obtained in Experiment 1. In agreement with this conjecture is the fact that the avfail effect was replicated at 2.5 mg of pentobarbital in Experiment 3B, as will be reported later. Hence, we believe it is simply due to a sampling error that we failed to replicate the avfail effect at 2.5 mg in Figure 2.

Although our expectations were wrong, there seemed to be an unexpected effect among the two Barb→Sac groups subjected to 2.5 mg of pentobarbital. Figure 3 shows the results for these groups over all seven exposures to saccharin solution. The impression to be gleaned from this figure is that

Figure 3. Mean preference among rats which consumed saccharin solution while sedated with 2.5 mg of pentobarbital as a function of Barb→LiCl or LiCl→Barb histories. The concentration of saccharin was .5% for Days 1-4 and 2.5% for Days 5-7.

on Day 1, the Barb→LiCl rats drank less saccharin solution than the LiCl→Barb rats. This impression is confirmed by an ex post facto 2 by 3 ANOVA, in which one factor is the two groups subjected to Barb→Sac trials at 2.5 mg of pentobarbital and the second factor consists of the following three within-subject measures: (1) preference during Day 1 of testing; (2) the mean preference during Days 2-4; (3) the mean preference during Days 5-7, when the concentration of saccharin was increased to 2.5%. This F test yielded a significant interaction [$F(2,32) = 14.8$, $p < .0001$]. Hence, the two groups were compared on each of the three measures. On Day 1, the Barb→LiCl history yielded lower preferences than the LiCl→Barb history [$t(16) = 3.38$, $p < .005$]; during Days 2-4, both histories yielded similar preferences [$t(16) = 1.00$]; during Days 5-7, the Barb→LiCl history seemed to yield a higher preference [$t(16) = 2.32$, $p < .05$]. There were no similar effects at the 1.25-mg dose of pentobarbital.

In retrospect, it seems that we ought to have expected the Barb→LiCl history to produce lower preferences on Day 1 in Figure 3 because the procedure fit the paradigm for conditioned suppression. The Barb→LiCl pairings were CS→US pairings, and it should be expected that their subsequent effect would be to suppress consumption in the presence of the pentobarbital CS, just as a tone CS paired with a shock US will later come to suppress ongoing appetitive behavior. Furthermore, there are many precedents for conditioned suppression to CSs paired with sickness (Garcia, McGowan, & Green, 1972; Pavlov, 1927; Zahorik, 1972; Parker, Note 1); for convenience, such suppression may be called "conditioned sickness," although it would be a mistake to suppose that it resembles unconditioned sickness (Parker, Note 1). Of course, conditioned sickness was not obtained among rats with prior LiCl→Barb pairings because these involve backward conditioning.

That saccharin preferences for Group Barb→LiCl were higher than those for Group LiCl→Barb during Days 5-7 suggests that an inhibitory process eventually overcame the conditioned sickness. However, the results for Days 5-7 in Figure 3 were marginally significant and based on an ex post facto analysis; furthermore, they were not replicated in Experiment 3, although the results for Day 1 were. Hence, the conservative decision ought to be that the result for Days 5-7 is a sampling error.

EXPERIMENT 3

Experiments 3A and 3B were run together and involved rats randomly selected from the same batch so that all results would be statistically comparable. They are analyzed as two separate experiments simply for convenience.

Experiment 3A was an attempt to find out more about the conditioned sickness effect apparent in Figure 3 for rats with a Barb→LiCl history subjected to their first Barb→Sac trial. It also was an attempt to find out if the conditioned sickness procedure might eventually yield conditioned inhibition if Barb→LiCl trials were alternated with Barb→Sac trials. The design was 2 by 2 factorial. One factor was whether Barb→LiCl pairings or LiCl→Barb pairings were administered in Phase 1. The second factor was whether the Barb→Sac pairings were used in Phase 2 or whether Barb→H₂O pairings were used instead: in Barb→H₂O pairings, the solution was unflavored water rather than saccharin solution. The saccharin solution used was 2.0% (w/v), which is extremely strong tasting compared to the already strong-tasting .5% saccharin used in Experiment 2; it seemed from Figure 3 that this might possibly result in strengthened conditioned inhibition to saccharin. We had no theoretical rationale worth mentioning for trying Barb→H₂O pairings. After Phase 2 was completed, there were additional procedures designed to foster conditioned inhibition (which, as we will see, was not obtained in Phase 2).

Experiment 3B was an attempt to obtain the original avfall effect with 2.5 mg of pentobarbital under conditions similar in many respects to those of Experiment 3A. We thought its result might prove helpful for the interpretation of the results of Experiment 3A.

Method

Experiment 3A. There were four groups of 13 rats each. Their weights ranged from 215 to 240 g just before the experiment.

In Phase 1, there were five 3-day cycles. On the 1st day of each cycle, water was made available for 24 h. On the 3rd day of each cycle, the rats were subjected to paired injections spaced 30 min apart while they were 24 h thirsty. The two Barb→LiCl groups received 2.5 mg of pentobarbital in 1.0 ml of solute 30 min prior to 2.5 ml of 2.0% (w/v) LiCl; the two LiCl→Barb groups received the same injections in the opposite order.

In Phase 2, the rats had 30 min daily access to water for 9 days. Every 3rd day, all rats were injected with 2.5 mg of pentobarbital 15 min before the drinking period began. For the Barb→Sac groups, the water was flavored with saccharin (2.0%, w/v) on these pentobarbital test days; this was not so for the Barb→H₂O groups.

After Phase 2, the test regimen of Phase 2 was continued for 12 more days (four more tests), except that the Barb→H₂O rats were switched to a Barb→Sac procedure. During the next block of 12 days, the double-injection procedure used in Phase 1 was repeated on Days 3 and 9, while Barb→Sac trials were administered on Days 6 and 12. After that there were still another 12 days in which Barb→LiCl trials were administered every 3rd day under the conditions of Phase 2 except that the concentration of saccharin was raised to 3.0% (w/v).

Experiment 3B. Two groups of 13 rats each were randomly selected from the same batch as those of Experiment 3A. Phase 1 was identical to that in Experiment 3A, with one group subjected to five Barb→LiCl pairings and the other subjected to five LiCl→Barb pairings. For the 21 days of Phase 2, the rats had 30 min daily access to water; every 3rd day, the water was flavored with 2.0% saccharin and the rats were injected with 2.5 mg of sodium pentobarbital as the bottles were removed.

Results and Discussion

Figure 4 shows the preference ratios for each group in Experiment 3A during the 3 test days (while the rats were sedated with pentobarbital). The conditioned sickness effect of Experiment 2 (Figure 3) was obtained with Barb→Sac pairings, but not with Barb→H₂O pairings. However, in contrast to Experiment 2, this conditioned sickness effect was more noticeable on the second Barb→Sac pairing ($t(24) = 3.57$, $p < .005$) than on the first [$t(24) = 1.85$, $p < .05$, one-tail]; we tentatively attribute the weakness of the latter effect to a floor effect which occurred because the rats were neophobic to the very strong-tasting saccharin solution. There was no statistically reliable conditioned sickness effect on Day 3 for the Barb→Sac rats or on any of the 3 pentobarbital test days for the Barb→H₂O rats.

The failure of Figure 4 to reveal a conditioned sickness effect with unflavored water (Barb→H₂O trials) should not be considered definitive, since it is very likely that the effect occurred early in the 30-min drinking period and then dissipated. Usually, conditioned sickness effects last just a very few minutes, and then the rats are likely to compensate for their initial adipsia (Garcia et al., 1972; Parker, Note 1). However, there can be little doubt from the results in Figure 4 that conditioned sickness effects were far more noticeable on Barb→Sac trials, when the appetitive baseline consisted of drinking the novel strong-tasting saccharin solution. This conclusion is in very good agreement with other results (Domjan, 1977; Parker, Note 1).

It will be recalled that, in the previous experiment, after additional Barb→Sac trials, rats with Barb→LiCl histories came to drink more than those with LiCl→Barb histories (Figure 3, Days 5-7); this

Figure 4. Mean saccharin preferences during Phase 2 of Experiment 3A for rats which differed in the sequence of pentobarbital and lithium injections in Phase 1 and in whether the test substance was unflavored water (H₂O) or saccharin solution (Sac). All tests occurred while rats were sedated with 2.5 mg of pentobarbital.

suggested that conditioned inhibition develops later in the course of Barb→Sac pairings. After the results shown in Figure 4 were obtained, we tried to confirm this effect by means of procedures described in the preceding method section. According to Pavlovian precedents, these latter procedures ought to have been more effective than the procedures which seemed to yield conditioned inhibition in Experiment 2 (Figure 3, Days 5-7); for instance, in contrast to Experiment 2, Barb→LiCl trials were interspersed with the later Barb→Sac trials for the groups designed to yield conditioned inhibition. Yet, there was no sign of conditioned inhibition. On each of 10 Barb→Sac test days during these follow-up procedures, we performed two *t* tests to compare Barb→LiCl and LiCl→Barb groups; one test was for rats which had a Barb→Sac history in Phase 1 and the other was for those with a Barb→H₂O history. Each of these 20 *t* tests yielded $p > .10$, and in each case the mean difference between the two preferences was smaller than .038. Careful inspection of the results revealed no trace of any pattern in the results to indicate the presence of conditioned inhibition. Although, according to Pavlovian precedents, the present procedure was better designed to produce conditioned inhibition than was the procedure of Experiment 2 (Days 5-7 in Figure 3), it nevertheless was in Experiment 2 that conditioned inhibition seemed to occur. Hence, we conclude that the result from Experiment 2 is probably a sampling error. If not, the result is obtainable under such special conditions that it still cannot be considered valid evidence for conditioned inhibition.

Experiment 3b confirmed that the original avfail effect could be obtained under the conditions of Experiment 3A. Figure 5 shows that saccharin preferences for rats with a Barb→LiCl history were higher than those for rats with a LiCl→Barb history except during the first Sac→Barb pairing [$t(24) = 2.87, p < .01$, for the mean preference over Days 2-7].

Taken together, Experiments 3A and 3B substantially weaken the case for conditioned inhibition to saccharin as a factor responsible for the avfail effect. Figure 5 shows that the avfail effect was obtained when the original avfail procedure was used; here, as in the experiments by Revusky et al. (1979), the Pavlovian precedents were that conditioned inhibition ought not to be obtained. When the avfail procedure was changed in Experiment 3A in a way which, by Pavlovian precedents, ought to have improved its capacity to produce conditioned inhibition to saccharin, the original avfail effect was lost. Since there is good evidence that conditioned inhibition to feeding stimuli follows the usual Pavlovian rules when it occurs in food aversion learning situations (Best, 1975; Taukulis & Revusky, 1975), it is difficult to see how it could be deemed

Figure 5. Mean preference during Phase 2 of Experiment 3B. That Group Barb→LiCl had higher preferences than Group LiCl→Barb replicates the avfail effect.

responsible for the avfail effect. This conclusion is also supported by the results of Experiment 1 (Figure 1).

EXPERIMENT 4

We were concerned with the effect of the number of Barb→LiCl pairings on the magnitude of the conditioned sickness effect. Revusky et al. (1979) found a pronounced avfail effect with four or eight Barb→LiCl pairings, but no detectable effect with either one or two such pairings.

Method

The 92 male Sprague-Dawley rats weighed from 189 to 220 g just before the experiment. The four experimental groups of 13 rats each received 1, 2, 4, or 8 Barb→LiCl pairings in Phase 1. There were eight control groups of five rats each subjected to 1, 2, 4, or 8 LiCl→Barb pairings or to 1, 2, 4, or 8 pairings of pentobarbital with normal saline. In Phase 2, all of these rats were allowed to drink saccharin solution while sedated with pentobarbital to test for conditioned sickness. The procedural details are as follows.

In Phase 1, all rats were placed on an alternating cycle of 24 h water deprivation and 24 h of free access to water. This cycle was repeated eight times. Rats were 18-19 h thirsty when subjected to their Phase 1 injections. If one pair of injections was to be administered, it was administered during the final cycle; if two pairs, they were administered during the final two cycles; if four pairs, during the final four cycles; if eight pairs, during all eight cycles. As before, the injections were 30 min apart. The pentobarbital dose was 2.5 mg; the lithium chloride dose was 2.5 mg of 2.0% (w/v); and the saline injections were 2.5 ml of normal saline.

About 5 h after the last pair of Phase 1 injections, all rats were given 24 h of free access to water. Then, beginning at 41 h of thirst, 15 min/day of access to water was instituted. On the 3rd, 5th, and 7th days of this regimen, all rats were injected with 2.5 mg of pentobarbital 15 min before the drinking period, and 1.0% (w/v) saccharin solution was made available instead of unflavored water.

Figure 6. Saccharin preference during Barb→Sac trials as a function of number of prior Barb→LiCl pairings. Control level shown as a horizontal line.

Results and Discussion

Figure 6 shows mean preference ratios for each experimental group and for the pooled controls on the first Barb→Sac trial. The controls were pooled into a single group, since a 4 by 2 ANOVA based on number of pairings and the type of control pairing (LiCl→Barb or Barb-alone) yielded $F < 1.0$ on each factor, as well as on the interaction. The eight-trial Barb→LiCl experimental group exhibited conditioned sickness in the form of significantly lower saccharin preferences than the controls [$t(51) = 2.75$] at $p < .01$; the corresponding results for the four-trial and two-trial experimental groups had p s $< .05$, one-tail [$t(51) = 1.73$ and 1.98 , respectively]; for the one-trial experimental group, $t < 1.0$. Confirming that the one-trial experimental group did not exhibit noticeable conditioned sickness were t tests between this group and the other experimental groups; each of these three comparisons had $p < .05$, one-tail. Although statistically reliable, the effects shown in Figure 6 were smaller than we would have liked.

The data for the 2nd and 3rd days of saccharin testing in Phase 2 are not shown because all differences between groups had disappeared with a single minor exception. As in the preceding conditioned sickness experiments, the preference scores increased over days.

EXPERIMENT 5

Although the avfail effect seems to violate all the Pavlovian rules, the fact that it can be obtained with a variety of CS and US drugs (Revusky et al., 1979) seems to put it in the category of learning. In contrast to the avfail effect, the conditioned sickness effect demonstrated in the preceding three

experiments does not seem to violate the rules for conditioning as gleaned from traditional Pavlovian experimentation. Thus, it seemed that conditioned sickness might be a better tool than avfail to study drug-drug associations in the context of a learning methodology. In Experiment 5, we used low doses of d-amphetamine and chlordiazepoxide as CSs in a conditioned sickness paradigm with lithium as the US. If conditioned sickness based on drug-drug pairings is to be attributed to learning, then it ought to be obtained with d-amphetamine and chlordiazepoxide, particularly since the avfail effect is obtained with these drugs (Revusky et al., 1979). In addition, we tried to replicate the conditioned sickness effect with pentobarbital and lithium.

Method

In these experiments, the CS drug doses were .1, .2, .4, and .8 mg/rat of d-amphetamine; 3.0, 6.0, and 12.0 mg of chlordiazepoxide; and the previously used 2.5 mg of pentobarbital. The US was 2.5 ml of 2.0% LiCl. Just before the experiment, the d-amphetamine rats weighed 170-214 g, while the chlordiazepoxide and pentobarbital rats weighed 174-203 g. For each rat, the same CS dose was used throughout the entire experiment. The effects of four CS→US pairings (conditioned sickness training) were compared with two control procedures: four US→CS pairings and four CS-alone presentations.

The Phase 1 procedure was similar to that in Experiment 4 except that only four 2-day deprivation cycles were necessary. For each CS dose, 12 rats were subjected to CS→US pairings, 9 rats were subjected to US→CS pairings, and 9 rats were subjected to the CS alone (with 2.5 ml of normal saline substituted for the lithium injection of the CS→US pairings). The Phase 2 procedure was like that in Experiment 4 with a minimum of 4 1.0% saccharin test days.

Results and Discussion

Table 4 shows the mean saccharin preference ratios obtained on the 1st saccharin test day for each group in the experiment. The $t(28)$ score is the result

Table 4
Saccharin Preference Ratios While in a CS Drug State
as a Function of Type and Dose (in Milligrams)
of CS Drug and Prior History

Dose	CS→US	US→CS	CS Alone	t(28)
d-Amphetamine				
.1	.09	.09	.11	+ .72
.2	.10	.10	.14	+ .52
.4	.09	.07	.07	-1.52
.8	.05	.04	.06	- .11
Chlordiazepoxide				
3.0	.26	.34	.25	+ .76
6.0	.29	.22	.33	-1.13
12.0	.33	.28	.21	- .43
Pentobarbital				
2.5	.13	.15	.24	+1.95*

Note—Values given are the results of a t test ($df = 28$) for conditioned sickness (CS→US vs. Pooled US→CS and CS alone). * $p < .05$ (one-tailed).

of a *t* test for conditioned sickness in which the US→CS and CS-alone controls were pooled; for significance at $p < .05$, one-tail, *t* must be larger than +1.70, where a positive *t* means that the control scores are higher than the CS→US scores. It is apparent that a conditioned sickness effect was obtained only when pentobarbital was the CS; the mean of the remaining *t* scores is negative, although not significantly so. In contrast, there is no difficulty in obtaining an avfail effect with the lowest doses of d-amphetamine and chlordiazepoxide used here. Furthermore, in unpublished work, we have not been able to obtain a conditioned sickness effect with ethanol as the CS and lithium as the US or with pentobarbital as the CS and a very high dose of amphetamine as the US, although we readily obtained the avfail effect with both of these combinations (Revusky et al., 1979). There seems to be no useful purpose in reporting the data from these unpublished experiments here. Suffice it to say that, since the present conditioned sickness effect has only been obtained with pentobarbital and lithium, it may be due to a specific pharmacological interaction between these two drugs rather than due to learning. Still, we have no idea why such an interaction should occur with Barb→LiCl pairings in Phase 1, but not with LiCl→Barb pairings.

This experiment would have been better designed if there had been eight CS→US pairings in Phase 1 instead of four, since the results of Experiment 4 suggest that this would have produced stronger conditioned sickness in the pentobarbital rat. Unfortunately, utilization of this information was impossible because Experiment 4 followed Experiment 5 chronologically and is reported prior to it only for heuristic purposes. However, the weak effect obtained with 2.5 mg of pentobarbital in the present experiment was still larger than any of the other effects shown in Table 1, even though a very low pentobarbital dose was used for the technical reasons described in the introduction to Experiment 2; it may be recalled that we failed to replicate the avfail effect with this dose in Experiment 3, although we have never had such difficulty with the 5.0-mg dose. There were no technical reasons to have a lower dose of chlordiazepoxide or d-amphetamine than had been used to obtain the avfail effect, and, in each case, we have obtained the avfail effect with the lowest dose shown in Table 4 (unpublished work). Thus, it is clear that the conditioned sickness effect cannot be obtained with a Phase 1 procedure which readily produces the avfail effect. In other technical respects, the procedures used in the present experiment were reasonable.

Both amphetamine and chlordiazepoxide affected the rats while they were drinking the saccharin solution during the test. In the case of amphetamine,

this is obvious because it was injected IP 15 min before the test and is known to be fast acting; furthermore, there is an apparent amphetamine-induced adipsia in the amphetamine scores of Table 4, but this is only suggestive evidence, because there is no appropriate control group. In the case of chlordiazepoxide, there is an appropriate control to indicate that it was effective during the test and produced polydipsia. All 30 rats subjected to 3 mg of chlordiazepoxide may be pooled and treated as one group, while the 18 pentobarbital control rats may be treated as a second group; then $t(46) = 2.40$, $p < .025$, for higher ratios among the chlordiazepoxide rats. Pentobarbital is known to produce polydipsia (Schmidt, 1958; Experiment 2 in the present series), and so the saccharin preferences of the pentobarbital rats were higher than normal. The fact that the 3-mg chlordiazepoxide scores were even higher indicates that chlordiazepoxide was effective during the saccharin drinking test and produced even more polydipsia than pentobarbital. Of course, if 3 mg of chlordiazepoxide had an effect, the higher doses must also have had an effect.

The apparent adipsia among the amphetamine rats in Table 4 leaves open the possibility that conditioned sickness might not have been obtained with amphetamine due to a floor effect. Recall, however, that there was a floor effect in Experiment 3 on Day 1, but then, when it dissipated on Day 2, there was clear evidence of conditioned sickness. No similar Day 2 effect occurred here with d-amphetamine. The mean preference on the second day with the .1-mg dose was .18 for the CS→US rats and .17 for the pooled controls; at .2 mg, .16 for CS→US and .12 for pooled controls; at .4 mg, .09 for CS→US and .07 for pooled controls; and at .8 mg, .06 for CS→US and .05 for pooled controls. At least at the lower doses, this floor effect was not pronounced enough to prevent detection of a conditioned sickness effect.

The detailed results of the later saccharin test trials will not be reported since they all were negative. There was no evidence for later emergence of something like a conditioned inhibition effect, in which CS→US rats would have higher preferences than controls. The fact that the trend is in that direction in the examples given in the preceding paragraph is readily attributable to chance.

The failure of anything resembling avfail to occur in the present experiment contradicts the implications of an explanation of avfail in terms of conditioned inhibition. The procedure in Phase 2 of the present experiment followed the Pavlovian method of obtaining conditioned inhibition to saccharin because exposure to saccharin overlapped the CS drug, which presumably was excitatory; yet, this procedure did not yield an avfail effect. The

original procedure did yield an avfail effect with these same drugs, although the method followed ought to have produced an opposite effect according to Pavlov, because the saccharin taste did not overlap with the drug state.

The failure of avfail to develop in the course of later trials, when amphetamine and chlordiazepoxide were the CS drugs, cannot be attributed to masking of the presumed conditioned inhibition effect by an opposite effect, conditioned sickness, for these drugs did not produce conditioned sickness. The net result is that we cannot think of any explanation of the avfail effect in terms of traditional learning theories, and so we are left with a mystery.

GENERAL DISCUSSION

After a number of Barb→LiCl pairings, Sac→Barb pairings lose their normal capacity to produce a saccharin aversion. This puzzling effect, avfail, also occurs when a variety of CS drugs are substituted for the pentobarbital or a very high dose of amphetamine is substituted for the lithium (Revusky et al., 1979). The present series of experiments began as an attempt to explain avfail in terms of known principles of Pavlovian conditioning. The problem was that precedents from the Pavlovian literature implied that the avfail procedure ought to have the opposite of the effect it actually had. It ought to have produced higher order conditioning and hence intensification of the saccharin aversions normally produced by Sac→Barb pairings. Nevertheless, we were ready to conjecture that the same Pavlovian processes could produce effects in the feeding situation different from the effects produced in other situations. There are many findings which show that when learning in the feeding situation superficially appears different from learning in traditional situations, the underlying principles are similar nevertheless (Revusky, 1977).

There also were technical reasons for supposing that an ostensible higher order conditioning procedure might fail to produce higher order conditioning and still adhere to the laws of Pavlovian conditioning. Procedures for obtaining higher order conditioning resemble those for obtaining conditioned inhibition, even though these two processes have opposite effects. In fact, Pavlov (1927) referred to higher order conditioning as an early phase in the same process which produces conditioned inhibition. It is clear that conditioned inhibition occurs in the feeding situation and adheres to the same basic laws which Pavlov delineated for conditioned inhibition in other situations (Best, 1975; Taukulis & Revusky, 1975). This suggested that the conditioned inhibition might have been overcoming the higher order conditioning otherwise to be expected from the avfail procedure. Presumably conditioned inhibition might develop

more rapidly in the avfail situation than in traditional learning situations, but otherwise follow the same laws. If so, it ought to be possible to modify the avfail procedure by following traditional Pavlovian rules for strengthening conditioned inhibition so that pairings of saccharin with pentobarbital might produce a heightened preference for saccharin; this hypothesized effect would be exactly opposite to the saccharin aversion produced by Sac→Barb pairings in rats not subjected to the avfail procedure.

One Pavlovian recipe for strengthening conditioned inhibition to saccharin was to alternate Barb→LiCl pairings with Sac→Barb pairings instead of administering them in successive separate phases as in the original avfail procedure. However, this did not change the original avfail effect. Another Pavlovian recipe for strengthening conditioned inhibition was to change the Sac→Barb pairing to a Barb→Sac pairing, in which the pentobarbital was injected prior to the saccharin drinking session instead of afterward so that the rat would drink while in a pentobarbital state; this would make it easier for the rat to associate the saccharin with the failure of lithium sickness to occur. This second strategy was also ineffective. However, it did yield an interesting unexpected effect: After Barb→LiCl pairings, the rats were loath to drink novel saccharin solution while in a pentobarbital state; there was no similar effect after LiCl→Barb pairings or Barb→Saline pairings. In retrospect, this conditioned sickness effect seemed nicely congruent with Pavlovian theory; the pentobarbital CS had come to produce suppression of appetitive behavior as a result of being paired with the lithium US. Indeed, it seemed conceivable that conditioned sickness might be a better way to study associations between feeling states than the avfail effect. However, such hopes were dashed when we found that conditioned sickness was not obtained with CS drugs which readily yield avfail; as far as we know, it is specific to pentobarbital.

The reasoning by which CS→Sac pairings were expected to produce more conditioned inhibition than Sac→CS pairings seems valid by Pavlovian precedents. Hence, CS→Sac pairings ought to have produced an enhanced avfail effect if conditioned inhibition were responsible for the effect, provided that no other effect masked it. We cannot reasonably attribute such masking to conditioned sickness. First, conditioned sickness is not obtained with amphetamine or chlordiazepoxide, and yet when these CS drugs are used in the avfail procedure with CS→Sac pairings instead of Sac→CS pairings, there is no avfail effect, although avfail is readily obtained with Sac→CS pairings. Furthermore, after the conditioned sickness effect produced by pentobarbital had dissipated, an avfail effect ought to have been apparent if Barb→Sac pairings produced more conditioned inhibition than Sac→Barb pairings. The

reason is that the original avfail effect was much longer lasting than the ephemeral conditioned sickness effect; 4 Barb→LiCl pairings prevented 13 successive Sac→Barb pairings from producing a saccharin aversion (Revusky et al., 1979). But this did not happen even when Barb→LiCl trials were interspersed with the Barb→Sac trials. In short, Pavlovian principles have not helped us understand the avfail effect or, indeed, anything else about these associations between a CS drug state and sickness.

Of course, it is conceivable that our procedures were not adequate to produce Pavlovian conditioning because they violate certain temporal relationships which are important in traditional Pavlovian experiments. On the basis of what we consider more than ample evidence (Revusky, 1977; Taukulis & Revusky, 1975), we believe these relationships are unimportant in the feeding situation. But even if we are wrong, it would not change the implications of the present results; the avfail effect occurs reliably in violation of these temporal relationships, and our question was whether it could be attributed to Pavlovian conditioning. Thus, no matter how we look at things, the failure to explain avfail in terms of generally valid principles of learning is a defeat for a general process approach to flavor aversion learning and a point in favor of the specialized adaptation approach (Rozin & Kalat, 1971). We hasten to add that the general process approach also has had its victories (Revusky, 1977).

Although we cannot explain avfail, we believe it to be important. It seems to be a basic way in which rats react to experiences about sequences of internal states, and it probably has something to do with the regulation of food intake. Certainly, it is hard to imagine that a readily replicable effect involving learning has no relationship to any function in the life of the animal. Some conjectures about its possible role in the aetiology of alcoholism are mentioned by Revusky et al. (1979).

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