in their movements—especially movements involving the hind limbs—throughout the study.

Whereas the administration of ethanol for only 4 days during the brain growth spurt did not interfere with body growth, it had a marked effect on brain growth, particularly that of the cerebellum. The cerebellum grows at a faster rate than the rest of the brain during the spurt; cerebellar development consequently tends to be particularly vulnerable to insults during this period (*14*). [Our results confirm those of another experiment, in which ethanol was administered to rats by inhalation throughout the preweaning period (*15*).] However, the fact that ethanol administration produces substantial growth deficits in other brain areas during the brain growth spurt should not be ignored. This is especially important when accounting for the observed behavioral deficits.

Whether or not the developing CNS would compensate, given time, for the brain growth and behavioral deficits seen by GD 40 remains to be determined. Although there was gradual improvement of motor coordination in the experimental animals, the hyperreactivity showed no indication of change.

Blood ethanol levels induced in these rats were high, but still within the range seen in human female chronic alcoholics (*16*). Since alcohol passes the placenta easily, and since fetal blood ethanol levels approximate those of the mother (*17*), it is likely that the fetus of a drinking mother would experience these levels of exposure.

It is clear that while ethanol may act as a teratogen early in an organism's development (*18*), there are critical periods later in development that may also be vulnerable to the influence of ethanol. Although it is difficult to make direct comparisons between species, the present data suggest that ethanol could have a toxic effect on the development of the human CNS relatively late in gestation, particularly during the third trimester. In fact, clinical studies have reported that when mothers who are heavy drinkers abstain or reduce their alcohol intake during the third trimester, fewer abnormalities occur in their offspring than in those of mothers who continue heavy alcohol consumption (*19*). The present study has added to the evidence by demonstrating that ethanol exposure relatively late in development can cause microcephaly, one of the three major components of FAS.

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Flavor-Illness Aversions: The Peculiar Roles of Odor and Taste in Memory for Poison

Abstract. *When either taste or odor alone was followed by poison, rats acquired a strong aversion for the taste but not for odor, especially if poison was delayed. When odor-taste combinations were poisoned, however, odor aversions were potentiated, as if odor could gain the enduring memorial property of taste by associative contiguity.*

Strong associations are formed when consumption of a distinctive flavor is followed by visceral feedback on a single occasion. Flavor aversions have been acquired by human patients eating ice cream before undergoing chemotherapy, by wild predators eating the flesh of their prey tainted with toxic lithium, and by laboratory rats drinking saccharin water before being injected with noxious substances; flavor preferences have been acquired when saccharin water is followed by recuperation from illness or thiamine deficiency (*1*). This associative process resembles classical conditioning, with the flavor acting as the conditioned stimulus (CS) and the visceral feedback acting as the unconditioned stimulus (UCS); it differs in that the flavor CS is selected over other stimuli in the feeding situation and in that long CS-UCS intervals can be spanned with ease.

There are other differences. In classical conditioning, when strong and weak stimuli are combined into a compound CS, the strong component overshadows or blocks conditioning to the weak component. In flavor-visceral conditioning the opposite is true for laboratory rats; strong taste stimuli facilitate conditioning to odors which are weak signals for slow-acting poison when used alone (*2*). Wild predators show a similar effect. Coyotes that feed on the tainted flesh of their prey and become ill quickly learn to avoid live prey without biting, as if the odor were a sufficient signal for poison. Of course, the predators we tested had prior experience with prey, which suggests that prior associations of prey odor with prey taste might facilitate the potentiation of odor by taste at the time of poi-

soning. To examine the role of prior experience with odor and taste, we (i) exposed rats to novel odor and taste stimuli for one or two trials, then (ii) paired the same stimulus with poison on a single trial, and finally (iii) tested aversive reactions of animals to odor and taste alone in separate tests.

Adult male Sprague-Dawley rats were maintained on freely available laboratory chow. For a 10-day period, they were deprived of water for 22 hours and habituated to drinking for a 5-minute trial each day in the conditioning chamber (15 by 20 by 25 cm, plastic) (*3*). On each trial, distilled water was available at a single stainless steel tube protruding 1.0 cm from the center of an inverted bottle cap (3.0 cm in diameter, 1.5 cm deep). The rat had to thrust its muzzle into the cap to lick the end of the water tube (Fig. 1). Licks were counted by a drinkometer (Grason-Stadler). The taste CS was 0.1 percent sodium saccharin in water. The odor CS was 0.2 ml of almond extract (Schillings) on filter paper behind a wire mesh at the back of the bottle cap. The poison UCS was an intragastric intubation of 0.15*M* lithium chloride (190 mg per kilogram of body weight) delivered shortly (< 5 minutes) after the animal was removed from the chamber. Rats became lethargic after about 5 minutes and recovered about 2 hours after intubation.

Preliminary exposure and poisoning conditions for all groups are shown along the abscissa of Fig. 1. For prior experience, some rats were exposed to odor (O), taste (T), or the compound stimulus (OT) on a single day. Other rats were exposed to each stimulus sequentially (O/T) in counterbalanced order on successive days. On the poisoning trial 2 days later, animals received O, T, or OT. Two days later, all animals were tested with O and T separately on successive days (*4*).

The overall pattern of results indicated the potentiation of odor by taste (Fig. 1). In general, during odor tests (Fig. 1B), drinking decrements depended primarily upon an OT association on the poisoning trial. Condition O alone on the poisoning trial was not sufficient (*5*). In contrast, during the taste tests (Fig. 1A), comparable decrements occurred whenever T was present on the poisoning trial, regardless of any association with O on either the poisoning or the preliminary exposure trial.

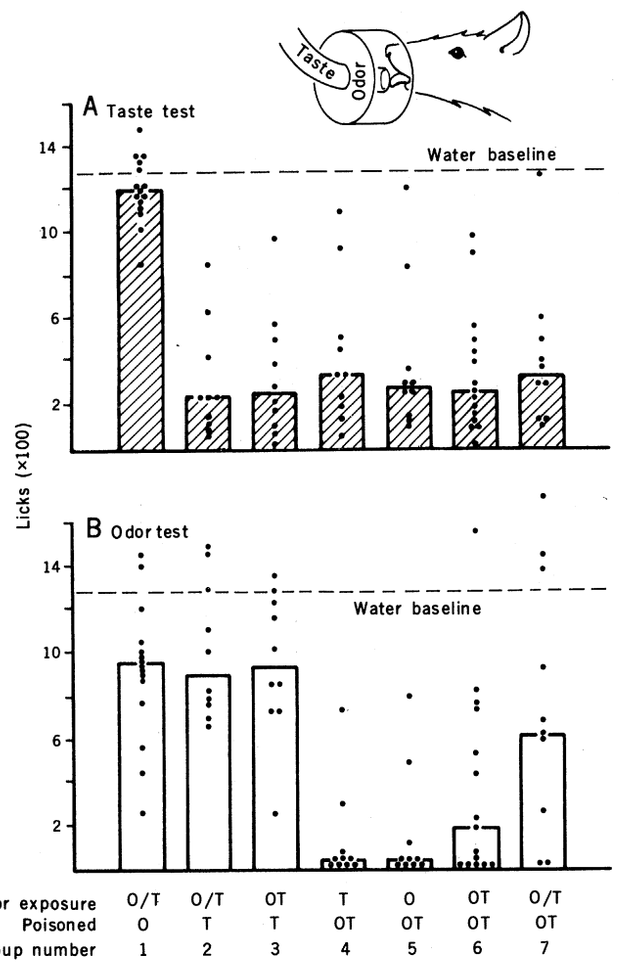

Fig. 1. Potentiation of odor by taste. Seven groups of rats were given almond odor (*O*) and saccharin taste (*T*) separately (*O/T*) or as a compound stimulus (*OT*) during the preliminary exposure trial and then again on the poisoning trial. Each group was then tested with taste alone (A) and odor alone (B); bars represent group medians and dots represent individual lick scores. Water baseline is the median number of licks on the 2 days before the preliminary trial; the baseline remained constant over the experiment. In (A), group 1 was the control group; in (B), group 2 was the control group.

Now examine the differential effects on the odor tests (Fig. 1B). Odor alone was ineffective as a single CS whether O (group 1) or T (group 2) had been poisoned. However, taste alone was effective as a single CS (group 2 in Fig. 1A). On the taste test, drinking was depressed when T had been poisoned (group 2) but not when O had been (group 1).

An association with taste on the poisoning trial seems to be a necessary condition for odor potentiation. In group 3, a single OT association prior to the presentation of T on the poisoning trial did not result in a decrement on the odor test. But for groups 4 and 5, for which OT had been poisoned, an odor aversion was evident. The aversions of groups 4 and 5 to the odor component (Fig. 1B) were stronger ($P < .01$) than single O conditioning (group 1 in Fig. 1B) and also stronger ($P < .05$) than single T conditioning (group 2 in Fig 1A). Thus, the weak odor signal was potentiated, not overshadowed, by the stronger taste signal.

Prior experience with odor and taste on separate occasions disrupted the potentiation effect. For group 7, the stimuli were dissociated (O/T) during the preliminary trial but associated during the poisoning trial; under these conditions, the group as a whole did not differ statistically from the group conditioned to O alone, although two animals did acquire very strong odor aversions. For group 6, in which the stimuli were associated (OT) on both preliminary exposure and poisoning trials, potentiation was not disrupted; component O was stronger ($P < .01$) than single O (group 1). The effect may have been weakened somewhat, however, in that component O was not stronger than single T conditioning (group 6 in Fig. 1B versus group 2 in Fig. 1A). Thus, it appears that the association of odor and taste at the time of poisoning is more important than prior association.

In many learning situations, the CS must be followed immediately by the UCS if the organism is to acquire an association. When the CS-UCS interval is extended by delaying the UCS, associative learning is disrupted. There are two traditional explanations. (i) The memory trace of the signaling CS rapidly decays with time and is not available for associative reinforcement by the delayed UCS, and (ii) distracting events occur during the extended CS-UCS interval and interfere with the association of the target CS with the UCS. Most theorists emphasize interference (*6*). Because eating and drinking occur in discrete bouts spaced by periods of satiation, taste can be con-

sidered an intermittent information channel, characterized by low interference over extended periods. In contrast, olfaction is a busy channel, as the rat is constantly sniffing a variety of odor cues in the environment. According to this view, taste may be a more effective CS than odor for a delayed poison UCS because it is protected from interference during the CS-UCS interval. To determine if potentiated food odors were also protected from interference, we examined the effect of varied CS-UCS intervals on an odor CS conditioned either alone or with taste.

The procedures were those shown in Fig. 1, except (i) there was no preliminary exposure to either O or T and (ii) the zero delay rats received lithium immediately upon being removed from the conditioning chamber. Independent groups received O, T, or OT; then they were intubed with the lithium UCS at various delays (Fig. 2) ($N = 5$ per group except for the zero delay groups, where $N = 13$) (*7*).

The CS-UCS delay gradients during extinction for O and T tested alone are illustrated in Fig. 2. The gradient for single O conditioning (O-O) was steep; the zero delay group acquired a clear aversion, but the conditioning was attenuated in the group delayed by 0.25 hour and completely abolished thereafter. In contrast, the aversion for component O after compound OT conditioning (OT-O) was not attenuated until the CS-UCS delay reached 4 hours. The 0-, 0.5-, and 2-hour groups all displayed significant ($P < .05$) decrements and did not differ from one another. The 4- and 6-hour delay groups showed less aversion, drinking more than each of the earlier groups ($P < .05$) and less than the 20-hour group ($P < .05$) (*8*). Furthermore, the absence of differences between OT-O groups and the T-T or OT-T groups indicates that potentiated odor had the same prolonged delay gradient as taste.

At zero delay, conditioning to odor alone (O-O) appeared as effective as conditioning to potentiated odor (OT-O), in apparent contrast to effects shown in Fig. 1B (group 1 versus groups 4 and 5). Two procedural differences are relevant. In the delay study, (i) there was no preliminary exposure, so a novel CS was used on the poisoning trial; and (ii) the UCS injection was given immediately upon termination of the CS. A novel odor CS and prompt poison UCS can produce an odor aversion without taste potentiation, but when odor is familiar and illness delayed (as might be expected

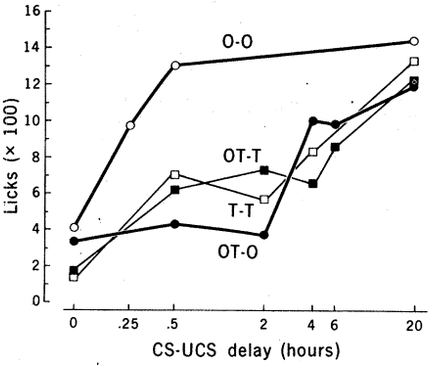

Fig. 2. Delay of poison gradients for odor (almond) and taste (saccharin). Mean licks are shown for the extinction tests from groups of animals poisoned at various CS-UCS delays (log scale). Group O-O was poisoned after O alone and tested with O alone; group T-T was poisoned after T alone and tested with T alone; group OT was poisoned after compound almond-scented saccharin and then tested with almond (*OT-O*) and saccharin (*OT-T*) separately.

in nature), odor aversions are strongly facilitated by taste mediation.

The peculiar interaction between odor and taste may be due to the different roles played by the two chemical analyzers in mammalian evolution. Olfaction is a busy multipurpose information channel: receptors in the respiratory system extract information from the atmosphere by constant sniffing. The olfactory fibers project to the olfactory bulb and become so entwined with the limbic system that the entire system has been called the "nose brain." This system has been implicated in a wide variety of emotions ranging from fear, rage, reproduction, and territoriality to hunting and feeding (*9*). If a meal contains a slow-acting poison, the mammal must retrieve the memory of the poisoned food odor from a stream of recent odor memories that signify not only food but also danger, rivals, and mates. Thus, recency, primacy, and salience of odors may be misleading; a specific indexing system is required.

Taste is ideally suited to index attendant odors as food-related cues. Taste receptors in the oral region extract information from food and water and have a special relationship with visceral monitors of the digestive system. Taste fibers project to the same brainstem area that receives visceral feedback via the vagus and the area postrema. This area plays a part in ejecting the poisoned meal from the stomach by vomiting and establishing an aversion for the taste of that meal. Pontine cells respond to both taste and hepatic-portal stimulation, further illustrating the convergence of these two systems onto the same central mechanisms (*10*).

Our data demonstrate that when an odor is accompanied by taste and followed by visceral feedback from a toxin, the odor acquires some of the memorial properties of a taste, as if a neural "and-gate" allowed the odor information into the central mechanisms specialized to handle taste and visceral feedback. There, odor categorized as a food stimulus is protected from interference by other odors subsequently sniffed by the animal and remains available for conditioning by food effects over long CS-UCS intervals.

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3. Approximately 90 minutes after each trial, rats had access to water in their home cage for 8 minutes; thus, rats could refuse water during the trial and drink later. Our rats drank at a rate of six licks per second; a score of 1800 was thus possible but never achieved.
4. Pilot studies showed no test order effect.
5. We used Wilcoxon ranks tests on raw scores, with $\alpha = .05$ and group 1 (single O) and group 2 (single T) designated a priori as conditioning baselines for statistical comparisons. In the second study, the 20-hour groups were designated baseline.
6. For example, see J. P. Houston, *Fundamentals in Learning* (Academic Press, New York, 1976), pp. 28 and 239–243; S. H. Revusky, in *Animal Memory*, W. Honig and H. James, Eds. (Academic Press, New York, 1971).
7. The experiment was conducted in explorative series, using the information from each step to select delay intervals for the next step as follows: step 1, OT, O, T at CS-UCS delays of 0 and 0.5 hour; step 2, O reduced to 0.25 hour, OT and T extended to 2 hours; step 3, OT delay sequence at 0, 4, and 6 hours; 20-hour delay controls, which provided the conditioning baseline, were also run in each step.
8. Scores for the tests not shown in Fig. 2 are T-O, 1241 (0 hour), 1236 (0.5 hour), 956 (2 hours), 1114 (4 hours), and 1261 (20 hours); O-T, 1333 (0 hour), 1133 (0.25 hour), 1309 (0.5 hour), and 1553 (20 hours).
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