Physiological Psychology
1980, Vol. 8 (4), 437-443

Postnatal alcohol exposure in the rat: Its effects on avoidance conditioning, Hebb-Williams maze performance, maternal behavior, and pup development

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In Experiment 1, lactating Wistar rats consumed a liquid diet containing ethanol during Days 0-17 of the nursing period. Control dams were pair-fed an identical liquid diet containing isocaloric sucrose or received chow and water ad lib. At 75 days of age, offspring were tested on a two-way shock avoidance task and, at 150 days of age, were tested on a Hebb-Williams maze. The offspring of ethanol-fed dams were found to be impaired on the shock-avoidance task when compared with both control groups but did not differ from controls on the Hebb-Williams maze task. Experiment 2 employed repeated time-lapse photographic observations to examine the behavioral development of pups of ethanol-fed mothers and pair-fed control mothers. The behavioral changes observed were restricted to Day 17, during the period immediately following the withdrawal of the ethanol diet. Specifically, dams previously exposed to the ethanol diet spent less time in the nest area with their pups and more time lying outside the nest area and engaged in locomotor activity. Pups whose mothers consumed the ethanol diet displayed increased litter fragmentation and spent more time rearing. Given the transient nature of the observed behavioral changes, it was concluded that the learning deficit observed in Experiment 1 was not mediated via alterations in maternal behavior and was probably due to a direct effect of ethanol on the central nervous system of the developing rat pup.

It has now been clearly demonstrated that a variety of treatments, including drugs, malnutrition, and stress, imposed on the neonatal organism can have profound and permanent effects on subsequent behavioral and physiological processes (Gottlieb, 1978). Despite this, very little is known about the effects of alcohol on the developing organism (Hollstedt, Olsson, & Rydberg, 1977). Recently, a number of studies have reported that the offspring of chronic alcoholic women exhibit a distinct pattern of craniofacial, limb, and cardiovascular defects associated with growth deficiencies and mental retardation (Jones, Smith, Ulleland, & Streissguth, 1973; Jones & Smith, 1973). Following the discovery of this "fetal alcohol syndrome," there has been an increase of interest in the effects of prenatal alcohol exposure on offspring behavior, but the same enthusiasm has not encompassed the study of the effects of alcohol on the neonatal organism. This is important because much research into the fetal alcohol syndrome has employed the rat and the mouse as possible models. Both of these animals differ from man in that their whole-brain growth spurts are postnatal whereas in man the spurt is perinatal (Dobbing & Smart, 1973). Thus, if one is interested in the effects of alcohol during the period of maximal brain growth, one should study the postnatal period in the rat and mouse.

Very few studies have restricted alcohol exposure to the postnatal period. However, those that have seem to indicate that the effects of alcohol on the neonatal organism are at least as profound as the effects on the fetus. Thus, exposure during the postnatal period leads to higher infant mortality, growth retardation, and developmental delays in rats (Martin, Martin, Sigman, & Radow, 1977), emotional reactivity in female rats (Abel, 1975), increased seizure susceptibility in C57 and DBA mice (Yanai & Ginsburg, 1976), and decreases in aggressive behavior in male C57 and DBA mice (Yanai & Ginsburg, 1977). Furthermore, Bauer-Moffett and Altman (1977) have demonstrated that rats exposed to alcohol postnatally evidence retarded growth in a variety of brain regions, and Rawat (1975) has observed that pups suckling on ethanol-fed mothers had significantly lower levels of cerebral DNA and RNA.

In all of the above studies, with the exception of Bauer-Moffett and Altman (1977), the experimental offspring were exposed to alcohol via their mother's

The research reported was supported by a Macquarie University research grant. Thanks are due to Len Glue for his technical assistance. Experiment 2 formed part of a paper presented to the 7th annual meeting of the Australian Society for the Study of Animal Behaviour held at Narooma, N.S.W.

0090-5046/80/040437-07$00.95/0

milk, and pair-fed controls were employed to determine that the deficits observed could not be attributed to malnutrition. Thus, given that alcohol occurs in the breast milk in concentrations higher than in the mother's blood (Matzdorff, 1942) and that it is excreted in the milk (Lehman, Schwerma, & Rickards, 1945), it seems reasonable to attribute the physical and behavioral changes to the alcohol exposure per se.

Missing from the above list of behaviors studied is performance on learning tasks. This lack is especially noteworthy given the morphological and biochemical changes that have been reported following postnatal alcohol exposure (Bauer-Moffett & Altman, 1977; Rawat, 1975). Therefore, the first experiment sought to examine the effects of postnatal alcohol exposure on offspring performance on two learning tasks, shuttlebox avoidance and the Hebb-Williams maze. These tasks were chosen because they have been shown to be sensitive to the performance deficits displayed by the offspring of rats exposed to alcohol prenatally (Abel, 1979; Bond & Di Giusto, 1978).

EXPERIMENT 1

Method

Subjects. Fifteen 100-day-old pregnant rats were used. They were housed individually in plastic cages measuring 23 × 38 × 15 cm, kept in a sound-attenuated temperature-controlled room on a 12-h light/dark cycle with lights on at 0600 h. Nesting material (shredded paper) was provided.

Drug administration. On the day of birth, the litters were culled to eight pups per dam and the dams were divided into three groups of five each matched on the basis of body weight. The experimental group received a liquid diet containing 6.5% ethanol (95% v/v), 3% sucrose (87% w/v), 87.5% Sustagen (.95 Cal/ml), and 3% water. One control group received an identical liquid diet except for isocaloric substitution of sucrose for the ethanol. Each dam in this control group was pair-fed the amount consumed by the corresponding experimental dam on the previous day. The diets were prepared fresh daily and presented in graduated Richter tubes inserted into the side of the cage. The dams were fed their respective diets for Days 1-17 after parturition and were then placed on laboratory chow and water ad lib. The average dose of ethanol consumed by the experimental dams during the last 24 h was 13.8 g/kg. A second group received laboratory chow and water ad lib throughout.

The dams and their offspring were weighed on Days 1, 17, and 28. The offspring were weaned on Day 28 and housed in same-sex pairs in wire cages measuring 15 × 24 × 20 cm.

Shuttlebox avoidance. At 75 days of age, one male and one female from each of the 15 litters were tested on the shuttlebox avoidance task. The shuttlebox was identical to that described in detail by Chesher (1974). It was fully automated, and response latencies were recorded by means of automatic printout timers. All equipment was situated in a darkened, temperature-controlled, sound-attenuated cubicle. At the beginning of the session, a rat was placed in one compartment of the shuttlebox with the guillotine door closed. Each trial began with the raising of the guillotine door and the presentation of a 2,800-Hz tone. If the rat had not moved to the other side after 5 sec of the tone, a 1-mA scrambled shock was delivered to the floor of the compartment in which the animal was standing. Both the tone and the shock then remained on for a maximum of 25 sec or until the animal crossed into the other compartment. At the same time, the guillotine door was lowered. The intertrial interval was 30 sec, and each animal received 50 trials in one complete session. An avoidance response was recorded if the animal moved to the other side of the shuttlebox during the 5-sec warning period preceding the shock.

Hebb-Williams maze. At 150 days of age, a different male and a different female from each of the 15 litters was tested in the Hebb-Williams maze. The Hebb-Williams maze was a completely automated unit identical to that described by Giulian, Snowdon, and Krom (1974). The animals were reduced to 80% of their free-feeding weights and then trained to run from one end box to the other with no barriers present. Barriers were then introduced in a series of six training problems, one problem per day, eight trials per problem. Once the animals completed their eight daily trials in less than 5 min, they received a series of six test problems, one problem per day. The session criterion for each problem was either four errorless runs out of 5 consecutive trials or a total of 48 trials. Errors were scored as in Giulian et al. (1974). Deprivation weights were maintained throughout training and testing, and reinforcement consisted of one 45-mg Noyes food pellet per trial. The performance index consisted of the total trials to criterion summed over the six test problems.

Results

Maternal weights. Maternal weights are summarized in Table 1. A two-way analysis of variance with repeated measures on days yielded a significant diet effect [$F(2,6) = 27.0$, $p < .001$], days effect [$F(2,30) = 20.6$, $p < .001$], and Diet by Days interaction [$F(4,30) = 18.0$, $p < .001$]. As indicated by t tests on repeated and independent means, both the experimental group and the pair-fed control group were significantly lighter than the chow-fed control group on Day 17 ($p < .01$, in both cases) but not on Day 28. This indicates that the experimental group and the pair-fed control group lost weight compared with the chow-fed control group while on their respective liquid diets but recouped the weight lost when again placed on laboratory chow and water.

Table 1
Weights of Dams and Their Litters in Experiment 1

	Pups						Dams					
	Experimentals (N = 5)		Controls				Experimentals (N = 5)		Controls			
			Pair-Fed (N = 5)		Chow-Fed (N = 5)				Pair-Fed (N = 5)		Chow-Fed (N = 5)	
Day	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
1	6.2	.2	5.8	.1	6.1	.3	313.1	5.7	316.6	4.7	322.6	9.1
17	18.3	.9	20.1	.5	29.6	1.3	261.8	10.4	258.6	3.6	350.8	8.4
28	44.8	2.9	50.6	1.8	66.1	3.6	325.0	7.6	315.8	1.8	331.2	6.5

Offspring weight. The weights of the three groups of offspring are summarized in Table 1. Since measures within litters could have been correlated, a two-way analysis of variance with repeated measures on days was carried out on the mean litter weights. This yielded a significant diet effect [$F(2,6) = 18.8$, $p < .001$], days effect [$F(2,30) = 792.2$, $p < .001$], and Diet by Days interaction [$F(4,30) = 16.9$, $p < .001$]. As indicated by t tests on repeated and independent means, the chow-fed control group were heavier than either of the two groups exposed to the liquid diets ($p < .01$, in all cases). The latter did not differ from each other. On Day 28, 95% of the experimental offspring, 92% of the pair-fed controls, and 82% of the chow-fed controls remained alive.

Shuttlebox avoidance. A two-way analysis of variance on the weights of the animals tested in the shuttlebox yielded effects of diet [$F(2,24) = 31.4$, $p < .001$], sex [$F(1,24) = 614.4$, $p < .001$], and a Diet by Sex interaction [$F(2,24) = 11.1$, $p < .001$]. At this age, the three groups of females were similar in weight, but the males of the two groups previously exposed to the liquid diets were significantly lighter than their chow-fed counterparts.

Figure 1 shows the mean avoidance responses in 10-trial blocks for each of the three groups. A two-way analysis of variance with repeated measures on trials yielded significant effects of diet [$F(2,27) = 11.7$, $p < .001$] and trials [$F(4,108) = 47.6$, $p < .001$]. Newman-Keuls tests revealed that the experimental group made fewer avoidance responses over the 50 trials than did either the pair-fed or chow-fed control groups ($p < .01$, in both cases). The two control groups did not differ from each other.

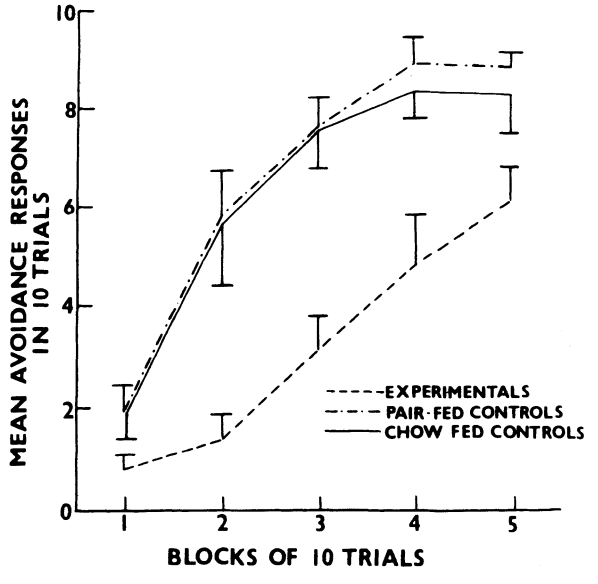

Figure 1. Mean avoidance responses in 10-trial blocks for each of the three groups of offspring. (Vertical bars indicate SE.)

Table 2
Trials to Criterion Totaled Over the Six Problems in the Hebb-Williams Maze

Experimentals (N = 10)		Controls			
		Pair-Fed (N = 10)		Chow-Fed (N = 10)	
Mean	SE	Mean	SE	Mean	SE
112.0	9.1	89.2	7.6	120.9	10.0

Hebb-Williams maze. A two-way analysis of variance on the weights of the animals tested in the Hebb-Williams maze yielded only an effect of sex [$F(1,24) = 269.8$, $p < .001$], indicating that the three groups were similar in weight.

Table 2 summarizes for each of the three groups the total trials to criterion summed over the six test problems in the Hebb-Williams maze. A one-way analysis of variance on these data was significant [$F(2,27) = 3.4$, $p < .05$]. However, Newman-Keuls tests failed to reveal any differences between the groups.

Discussion

The present results indicate that the pups of ethanol-fed mothers are impaired on a shuttlebox avoidance task; they provide more evidence of the profound influence of early ethanol exposure. Importantly, this cannot be attributed to malnutrition. As shown in Table 1, the pair-feeding technique was successful in matching the weights of both groups of nursing mothers and their offspring, albeit at levels lower than those observed in the chow-fed control group. Yet, the experimental pups were impaired in comparison with the pair-fed controls on the shuttlebox avoidance task. Clearly, this deficit cannot be attributed to nutritional deficiencies in the experimental offspring.

The behavioral changes reported in the present experiment bear some similarity to those observed in offspring following prenatal alcohol exposure (Abel, 1979; Bond & Di Giusto, 1978). Shuttlebox avoidance performance is affected by ethanol treatment at both periods (Abel, 1979; Bond & Di Giusto, 1978). Prenatal alcohol exposure has little effect on offspring performance in the Hebb-Williams maze (Bond & Di-Giusto, 1978). Similarly, in the present study, postnatally exposed offspring did not differ from the offspring of either group of control mothers in performance in the Hebb-Williams maze. The reason for this anomaly is unclear, although it may be related to the fact that the animals in the present study and those in Bond and Di Giusto (1978) were tested on shuttlebox avoidance at 75 days, whereas the animals tested on the Hebb-Williams maze were 150 days of age. Thus, the effect on learning may disappear with age. However, it is noteworthy that, while a number of investigators have found changes

in aversively motivated behaviors following prenatal alcohol exposure (Abel, 1979; Bond & Di Giusto, 1978; Riley, Lochry, & Shapiro, 1979), there are few published reports of deficits on appetitively motivated tasks (Abel, 1979; Bond & Di Giusto, 1978; Martin et al., 1977). It may be that the systems controlling aversively motivated behavior are more sensitive to early ethanol exposure than are those controlling appetitively motivated behavior.

The low incidence of mortality and the success of the pair-feeding technique are especially interesting because some previous authors have found that if ethanol is given to mothers while they are lactating, the young lose weight regardless of the mother's nutritional state (Martin et al., 1977; Pilstrom & Kiessling, 1967). These findings have been attributed to the fact that acute injections of ethanol at doses greater then 1.0 g/kg can depress the milk ejection reflex in nursing mothers through the inhibition of oxytocin release (Fuchs, 1969). However, while the experimental dams in the present study consumed large quantities of ethanol, it is important to note that they consumed the ethanol throughout the day. It is, therefore, possible that under these conditions of chronic exposure no inhibition of milk release occurs. Further research is clearly indicated.

It would be tempting to attribute the learning deficit observed following postnatal ethanol exposure to the morphological and biochemical changes reported previously (Bauer-Moffett & Altman, 1977; Rawat, 1975). However, it is also possible that the effect of the ethanol was mediated via changes in maternal behavior (Abel, 1975; Yanai & Ginsburg, 1977). For example, Baer and Crumpacker (1977) have reported increased cannibalism in the mothers of long-sleep (LS) mice forced to drink alcohol during lactation and have suggested that part of the effect of the drug on progeny survival is due to deleterious alterations in maternal-care behavior. Given the profound influence of the early environment on offspring behavior, such an alteration in the mother-pup interaction might account for the long-term changes seen in the pups' behavior (Denenberg, 1964).

EXPERIMENT 2

The present experiment was undertaken to observe systematically the manner in which postnatal alcohol affects both maternal behavior and pup development. The technique chosen was the "automated Peeping Tom" method described by Massaro, Levitsky, and Barnes (1974). Briefly, the technique involves mounting two subject cages, one experimental and one control, in front of a camera and, by means of electronic timing equipment, taking individual frames at set intervals. Subsequently, each frame can be scored for the occurence of a variety of behaviors. The technique is extremely useful because it provides for a large number of observations without any experimenter-subject interaction. Certainly, it has proved sensitive enough to demonstrate the profound influence of both prenatal and postnatal undernutrition on maternal behavior and pup development (Massaro et al., 1974, 1977).

Method

Subjects. Eight 100-day-old pregnant Wistar rats were used. They were housed individually in plastic cages measuring 23 × 38 × 15 cm high and kept in a sound-attenuated temperature-controlled room on a 12-h light/dark cycle with lights on at 0600 h. Nesting material (shredded paper) was provided throughout the experiment.

Apparatus. Time-lapse photographic observations were made with a Eumig 65-XLS Super 8 movie camera mounted on a tripod and programmed to take a frame automatically once every 3 min over a 12-h period. The camera was fixed at a distance of 1.5 m above the cages, both of which were photographed simultaneously. Three 15-W red light bulbs provided illumination.

Drug administration. On the day of parturition, each litter was reduced to eight pups. One of a matched pair of dams was placed on the liquid diet containing Sustagen and ethanol, and the other dam received the liquid diet containing isocalorically substituted sucrose. The control dam was pair-fed the amount consumed by the experimental dam on the previous day. The females were fed their respective diets until 1400 h on Day 17, when they were placed on laboratory chow and water ad lib. The average dose of ethanol consumed by the experimental dams during the final 24 h was 15.4 g/kg. The weights of the two groups of dams did not differ throughout the experiment, nor did the mean weights of their respective litters. One pup was lost from each of three experimental litters and one from each of two control litters.

Photographic observations and behavioral classifications. Photographic observations were begun on the day of parturition at the onset of the 12-h dark period of the cycle. This was Observation Day 1. Subsequent observations of each of the four experimental litters and their corresponding control litter were performed on Days 6, 12, 17, 23, and 28. Each frame was observed and rated according to the behavioral classification system outlined by Massaro et al. (1974). All ratings were made by one observer who was blind as to the group of origin of each frame.

Results

Dam behavior. The two groups of dams did not differ significantly in the frequency of observed self-grooming, feeding, drinking, or "other" behavior. However, significant differences were observed in the time spent in the nest with the pups [$F(1,6) = 12.5$, $p < .02$], time lying outside the nest away from the pups [$F(1,6) = 7.3$, $p < .05$], and locomotor activity [$F(1,6) = 7.6$, $p < .05$]. As shown in Figure 2 and confirmed by t tests for repeated and independent means, on Day 17 the experimental dams spent significantly less time in the nest with their pups ($p < .01$) and significantly more time both lying outside the nest ($p < .05$) and engaged in locomotor activity ($p < .05$).

Pup behavior. The frequences of the major pup behaviors are illustrated in Figure 3. There were no significant differences between the two groups in the observed frequencies of feeding, drinking , or "other" behavior. However, there were significant differences in litter fragmentation [$F(1,6) = 9.7$, $p < .025$] and in

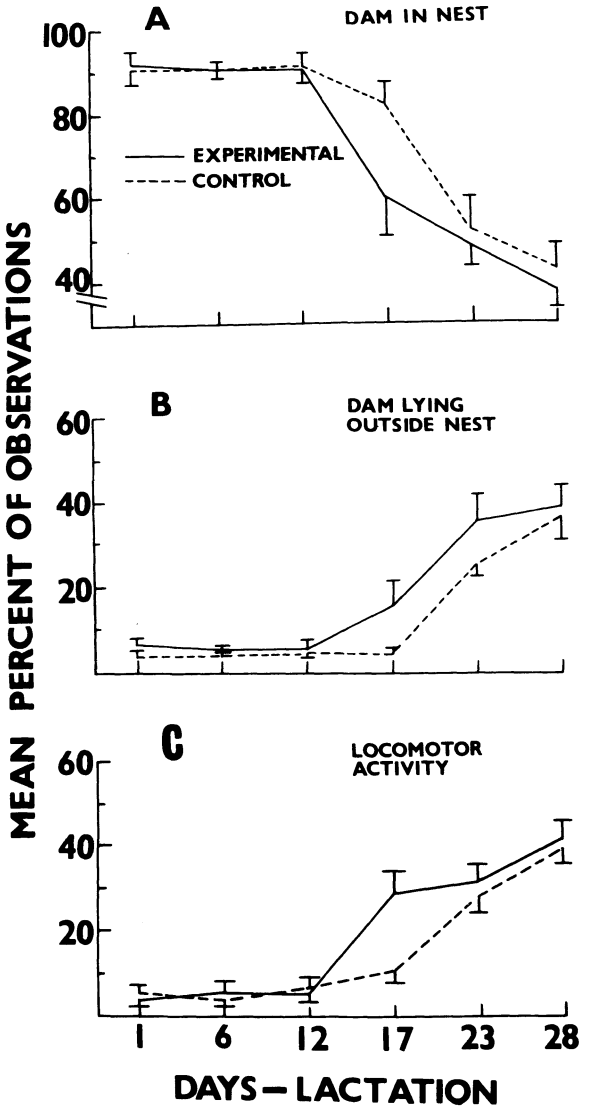

Figure 2. Mean percent of time during a 12-h observation period that dams maintained on liquid diets containing either ethanol (experimentals) or sucrose (controls): (a) spent in the nest area with their litters; (b) spent lying outside the nest area away from direct contact with their litters; (c) were observed in a quadrant different from that of the previous frame. (Each point is the mean of four litters and the vertical bars indicate SE.)

rearing activity [$F(1,6) = 6.8$, $p < .05$]. As shown in Figures 3A and 3B and confirmed by t tests for repeated and independent means, on Day 17 the experimental pups spent significantly more time in groups of fewer than four ($p < .05$) and more time engaged in rearing activity ($p < .05$).

GENERAL DISCUSSION

The present results indicate that the effects of the ethanol treatment on a variety of maternal behaviors were restricted to Observation Day 17. The significance of this finding is that the observations on Day 17 covered the period 4-16 h following the transition from the ethanol liquid diet to the laboratory chow diet. Given the behaviors that were affected, that is, time spent on the nest decreased and both time lying outside the nest and locomotor activity increased, it is possible that the observed changes in behavior were due to the withdrawal of the ethanol. That is, they reflected a transient hyperexcitability akin to a mild alcohol withdrawal syndrome (Majchrowicz, 1975). When ethanol is presented in liquid diet form, as in the present study, an animal would not normally display any symptoms of alcohol withdrawal unless food-deprived or subjected to cold stress (Freund, 1971). Despite the fact that the experimental dams had free access to the ethanol diet, they did lose considerable weight (cf. Experiment 1). Since an equivalent weight loss is experienced by the pair-fed dams, the changes in the behavior of the experimental dams must be attributed to their consumption of ethanol. Thus, the most parsimonious explanation for the observed changes is that the experimental females evidenced a mild form of the alcohol withdrawal syndrome.

As with maternal behavior, the effect of the ethanol treatment on pup behavior was restricted to Observation Day 17. Again, given the behavioral categories affected, that is, litter fragmentation and rearing, and given the fact that the observations on

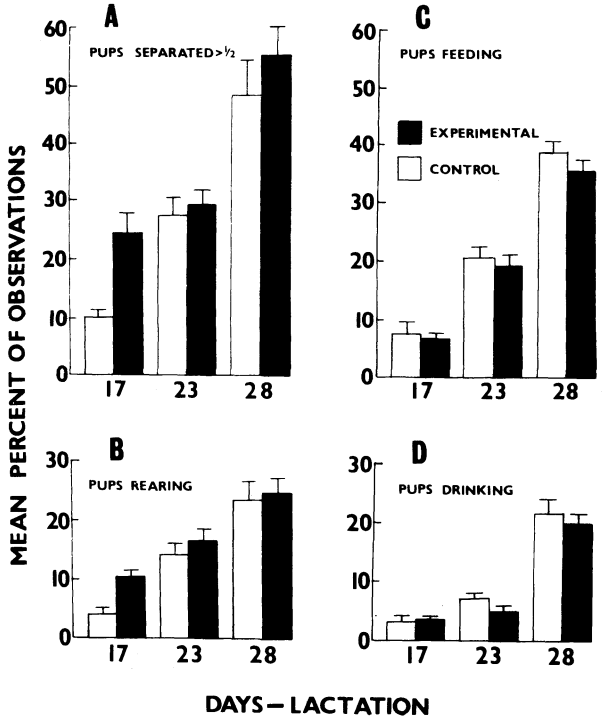

Figure 3. Mean percent of time during a 12-h observation period that the experimental and control pups: (a) spent out of the nest area (four or more pups were dispersed throughout the housing area); (b) spent in rearing activity; (c) spent in feeding activity; (d) were observed to drink. (Each column is the mean of four litters and the vertical bars indicate SE.)

Day 17 followed shortly after the removal of the ethanol diet, it is reasonable to suggest that the changes were due to alcohol withdrawal. However, at present it is difficult to determine whether the changes in the pups' behavior were due to the withdrawal of the ethanol diet or due indirectly to the changes in the mothers' behavior that resulted from her being withdrawn. (Alternatively, the changes in the mothers' behavior might be due to the changes in the pups' behavior).

The failure to observe behavioral changes in the experimental dams and their litters is in accord with the findings of a recent paper by Ewart and Cutler (1979). These authors used mice and carried out observations of alcohol-treated and control and their litters for short periods on Days 1, 5-7, and 12-14 postpartum. There were few significant differences between the treated and control dams and pups. However, employing automated nesting boxes which allowed for the continuous monitoring of maternal nesting behavior, Bond (1979) found significant differences between alcohol-fed and pair-fed control dams in the time spent nursing, the alcohol-fed dams displaying an increase in time over Days 6-12. Unfortunately, the observations carried out in the present study and those performed by Ewart and Cutler (1979) did not encompass this particular period. However, even if such an increase in nesting time did occur unobserved in the present study, it clearly had no permanent effects on the behavior of the offspring, because there were no differences between the experimental and pair-fed control offspring on Observation Days 23 and 28 (cf. Figure 3). In the only other related study, Baer and Crumpacker (1977) observed that increased cannibalism of pups by mothers forced to drink alcohol during lactation was restricted to the alcohol-sensitive LS (long-sleep) strain. The relatively insensitive SS (short-sleep) strain showed no effect of the treatment. Given these strain differences, further work is required to determine under what conditions ethanol might influence maternal behavior.

The main purpose of the present study was to determine if postnatal ethanol exposure brings about changes in maternal behavior or pup development to which the learning deficit observed in Experiment 1 might be attributed. The behavioral changes observed were restricted to Day 17 and appear to be due to alcohol withdrawal. It is unlikely that these transient changes in behavior or the alcohol withdrawal per se could bring about the learning deficit observed (cf. Freund, 1971).

Given the previous findings of morphological and biochemical changes following postnatal alcohol exposure (Bauer-Moffett & Altman, 1977; Rawat, 1975), it would appear that the learning deficit observed in Experiment 1 might be attributable to a direct effect of alcohol on the central nervous system of the developing rat pup.

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(Received for publication March 6, 1980;
accepted May 23, 1980.)