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Nose-poking and Head-dipping Behaviors in Rats Prenatally Exposed to Alcohol[1]

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RILEY, E. P., N. R. SHAPIRO AND E. A. LOCHRY. *Nose-poking and head-dipping behaviors in rats prenatally exposed to alcohol.* PHARMAC. BIOCHEM. BEHAV. 11(5) 513–519, 1979.—In three experiments pregnant female rats consumed liquid diets containing various amounts of the total calories in the form of ethanol. In the first study, offspring of these females were tested in a nose-poking paradigm. The frequency of this response was found to be a direct function of the level of alcohol exposure *in utero*. In a second study when nose poking produced the onset of a dim light, animals prenatally exposed to alcohol were again found to poke more often, and this effect was not attenuated by preweanling handling. Finally, the generality of these findings became evident when head dipping rather than nose poking was examined; head-dip frequency was higher in alcohol-exposed offspring, and this effect was independent of stimulus complexity. Additionally, offspring body weights and survival rates following this prenatal alcohol exposure are presented.

Ethanol Prenatal Fetal alcohol syndrome Nose poke Hole poke Inhibition Rats

SEVERAL studies have substantiated that alcohol can act as a behavioral teratogen. For example, animals exposed to alcohol prenatally have been found to be impaired in T-maze learning and shuttle avoidance [5,17]; to perform poorly on several operant schedules [12]; and to evidence heightened open-field activity [3, 4, 6, 17]. Recently it has been suggested that rats exposed to alcohol *in utero* have difficulty withholding a response as evidenced by performance deficits in conventional shock motivated passive avoidance and in a taste aversion paradigm [14]. In this latter paradigm the alcohol-exposed animals appeared less able to inhibit ingestion of an illness-inducing fluid. In each case the inhibition deficit was a direct function of the amount of maternal alcohol consumption.

Further evidence that prenatal alcohol exposure results in an inhibition deficit was derived from the perseverative behavior of alcohol-treated rats in a T-maze [15]. These offspring made a greater number of mistakes during the reversal learning of a discriminated escape response. It was also shown that prenatally-exposed animals evidenced less of a tendency to spontaneously alternate in a T-maze when no extrinsic rewards were present. The tendency to spontaneously alternate develops at about the same time as a central cholinergic inhibitory system and is thought to reflect such development [8]. Again, in both of these paradigms linear dose-response functions were obtained.

An animal which has difficulty withholding responses might be expected to respond more in situations where normal animals show response habituation, since such an animal would be slower in the reduction of response rates. Indeed, certain surgical and pharmacological manipulations which presumably disinhibit behavior have been shown to prolong the habituation process in a nose-poke paradigm [21]. The present investigation thus examined the effect of prenatal alcohol exposure on exploratory nose-poking and head-dipping behaviors under various conditions.

EXPERIMENT 1

METHOD

Animals

Parent animals were Long-Evans hooded rats obtained from Blue Spruce Farms, Altamont, NY. Following acclimation to the laboratory, females were individually placed with males each evening until a vaginal smear taken the following morning was sperm positive indicating Day 1 of pregnancy. Pregnant females were then weighed and housed in standard plastic breeding cages where they remained until their pups were weaned at 21 days of age. Lab chow and water were freely available except as noted under a 12-hr light-dark cycle.

From Day 5 through and including Day 20 of pregnancy, 10 animals were given free access to a liquid diet containing 35% ethanol-derived calories (EDC). Additional females were provided with diets containing 23.3, 11.7, and 0% EDC (n's=7, 8, and 7, respectively) during this same gestation

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TABLE 1

LIQUID DIET COMPOSITION (per 100 ml)*

	Experiment 1 (1 Kcal/ml)				Experiment 2 (1.3 Kcal/ml)		Experiment 3 (1 Kcal/ml)		
	35%	23.3%	11.7%	0%	32%	0%	35%	17%	0%
ml Nutrament	64.10	64.10	64.10	64.10	87.17	87.17	64.10	64.10	64.10
ml 95% EtOH	6.67	4.44	2.23	0.00	7.93	0.00	6.67	3.34	0.00
grams sucrose	0.00	2.93	5.83	8.75	0.00	10.40	0.00	4.38	8.75
grams vitamins	0.25	0.25	0.25	0.25	0.34	0.34	0.24	0.24	0.24

*Water added for total volume of 100 ml.

period. The compositions of these diets are presented in Table 1 and it can be seen that the 23, 11, and 0% diets provide sucrose instead of or in conjunction with the alcohol, making all diets isocaloric (1 Kcal/ml). To assess the effects of liquid diet administration, a group of six females were maintained on lab chow and water throughout pregnancy.

In order to manipulate only the prenatal dose of alcohol, while keeping caloric intake relatively equal, a pair-feeding procedure was used. Each animal in the 23, 11, and 0% groups was matched to one in the 35% group which had free access to its diet. For any specified day of pregnancy matched animals were fed the amount consumed by this 35% animal on a ml/kg body-weight basis. Thus, all animals in a yoked group received the same volume of diet, and hence the same number of calories per gram body weight, with only the dose of alcohol varied. Maternal weights were monitored at five-day intervals for more precise pair-feeding control. Blood alcohol levels were assessed on Days 10 and 15 of gestation using a relatively nontraumatic method. Briefly, about 10 ml of air was injected subcutaneously into the back of each animal's neck. Ten min later, 0.25 ml of this air was withdrawn in an air-tight syringe and injected into a nitrogen stream leading to a Galvanic cell of Berton. By measuring the difference between the alcohol content of this sample and standards of known concentrations, blood alcohol levels were estimated [11].

Just prior to the expected parturition, breeding cages were checked three times daily. Newborn pups were weighed, measured, and inspected for any gross anomalies. At this time litters were randomly culled to 10 with the exception that equal numbers of each sex were maintained where possible. Offspring were again weighed at 10 and 20 days of age. At approximately 29 days of age, eight male offspring from each treatment condition were tested in the nose-poke apparatus. Selection was random with the exception that each litter was represented.

Apparatus and Procedure

Testing was conducted in two Plexiglas chambers, each 19×21×27.5 cm. Each chamber was made lightproof by applying heavy opaque black enamel paint and by sealing the corners with opaque cement. Furthermore, the chambers were enclosed in a sound-attenuating cubicle which also helped to prevent light from entering the test chamber. On the 21 cm wall of each chamber a hole, 3 cm in diameter, was centered horizontally and aligned with the opening of a 6.5 cm long, 3.5 cm diameter, opaque Plexiglas cylinder. If the animal poked its head 1 cm into the tube it broke an infrared photobeam and activated a counter and timer located in an adjacent room. Frequency and total duration of photobeam interruptions were recorded in four 15-min blocks during a 60-min test session. White masking noise was continually present during the course of the experiment. All animals were weighed prior to being placed in the chamber.

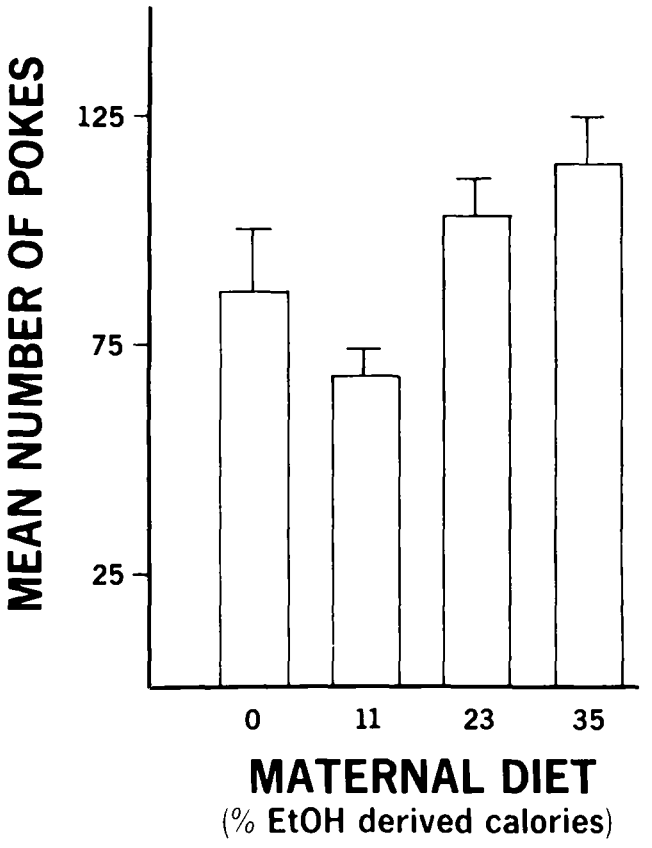

FIG. 1. Mean number of nose pokes (± SE) for offspring in each maternal diet group.

RESULTS

Mean poke frequency as a function of maternal diet is presented in Figure 1. As can be seen, with the exception of the 11% group, alcohol exposure *in utero* appears to result in increased responding. An analysis of variance on poke frequency with maternal diet as a between-subject factor and 15-min blocks as a within-subject factor, indicated a signifi-

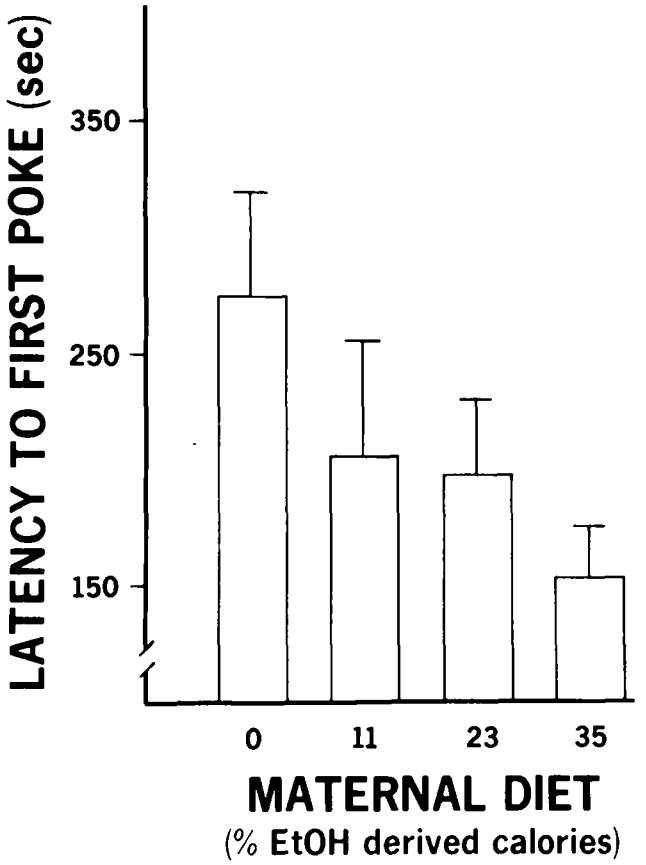

FIG. 2. Mean latency (± SE) to perform the first nose poke for offspring in each maternal diet group.

cant effect of maternal diet, $F(3,28)=4.01$, $p<0.025$. Decomposition of this effect into its trend components indicated a significant linear increase in responding with an increase in EDC, $F(1,28)=6.89$, $p<0.025$. The 11% group did not deviate significantly from this linear fit in that significant quadratic and cubic trend components were absent. Furthermore, there was an overall decrease in frequency of poking, evidenced by a significant linear effect of blocks, $F(1,28)=119.48$, $p<0.001$. However, all groups decreased similarly across blocks as indicated by the lack of a significant blocks × maternal diet interaction, $F(9,84)=1.24$, $p>0.05$.

The total duration of photobeam interruptions for each 15 min block was divided by the number of pokes during that same period to provide an estimate of the average poke duration. An analysis of variance on these data failed to reveal any significant differences among the groups, $F<1$. Average poke durations also remained relatively constant across blocks since this effect as well as the blocks × maternal diet interaction failed to reach significance, $F(3,84)=1.81$, $p>0.05$, and $F<1$, respectively.

An additional dependent measure, which was automatically recorded, was the latency to the initial poke following placement in the chamber. These data are depicted in Fig. 2. There appears to be an inverse monotonic relation between the percent EDC in the diet and first-poke latency. An analysis of variance and subsequent decomposition revealed a significant linear trend, $F(1,28)=4.81$, $p<0.05$, accounting for 92% of the variance between groups.

Separate analyses were performed to assess the effects of the liquid diet by comparing the 0% and lab chow control groups. The lab chow group was not included in the original analyses because this group is not on the quantitative continuum which defines the liquid diet groups, and thus its inclusion would have precluded the possibility of conducting trend decomposition. In no instance did these two groups differ significantly from each other.

The average daily alcohol consumption on a gram per kilogram body weight basis for mothers in the 35, 23, and 11% EDC groups was 12.82 (SE ± 0.26), 8.26 (SE ± 0.16), and 4.18 (SE ± 0.08) respectively, while mean blood alcohol concentrations were 0.11 (SE ± 0.03), 0.06 (SE ± 0.02), and 0.03 (SE ± 0.01)%. Average percent weight gain was 37.6, 35.2, 35.1, and 37.4% for the 35, 23, 11, and 0% groups respectively, $F<1$, while the lab chow group averaged 63.2%. The difference between the lab chow and the 0% group was highly significant, $F(1,11)=57.1$, $p<0.001$. Significant differences in body weight and length were evident for offspring in the liquid diet groups, with the alcohol-exposed progeny showing growth deficits directly proportional to the amount of EDC consumed by the mother during pregnancy. These data, as well as offspring survival rates to weaning are presented in detail elsewhere (Lochry *et al.*, manuscript in submission).

It should be noted, however, that the growth deficiencies evidenced in the alcohol-treated offspring were not longer statistically significant at the time of behavioral testing, $F(3,28)=1.63$, $p>0.05$, although a linear trend was still evident. Mean body weights for the 35, 23, 11, and 0% groups were 80.6, 84.6, 87.4, and 91.5 g while the lab chow group averaged 90.8 g.

EXPERIMENT 2

The results of the previous study indicated that animals exposed to alcohol *in utero* have a higher response rate than controls in a simple nose-poke paradigm. This second study was conducted to determine if this relation would also be present when nose-poking produced a consequence—the onset of a dim light. Generally, response-produced feedback of this type results in greater response rates than when feedback is minimal [21]. Furthermore, since hole-poking behavior is affected by early handling experiences [9,20], this variable was also manipulated to determine if the effects of maternal alcohol consumption might be ameliorated by early postnatal experiences.

METHOD

Animals

Parent animals and the mating procedure were similar to that described previously. However, in this experiment diets provided either 32 or 0% EDC (n's=7). As before, these diets were isocaloric (1.3 Kcal/ml) since the 0% diet provided sucrose instead of alcohol. The compositions of the diets are presented in Table 1. Diets were available from Day 6–16 of gestation and a pair-feeding procedure was used. Blood alcohol levels were assessed on Days 10 and 15 of gestation as described in Experiment 1. Newborn litters were randomly assigned to either a handled (H) or non-handled (NH) condition and litters were culled randomly to 10 pups. At this time each pup in the handled condition was held by an experimenter for approximately five min; this handling period was

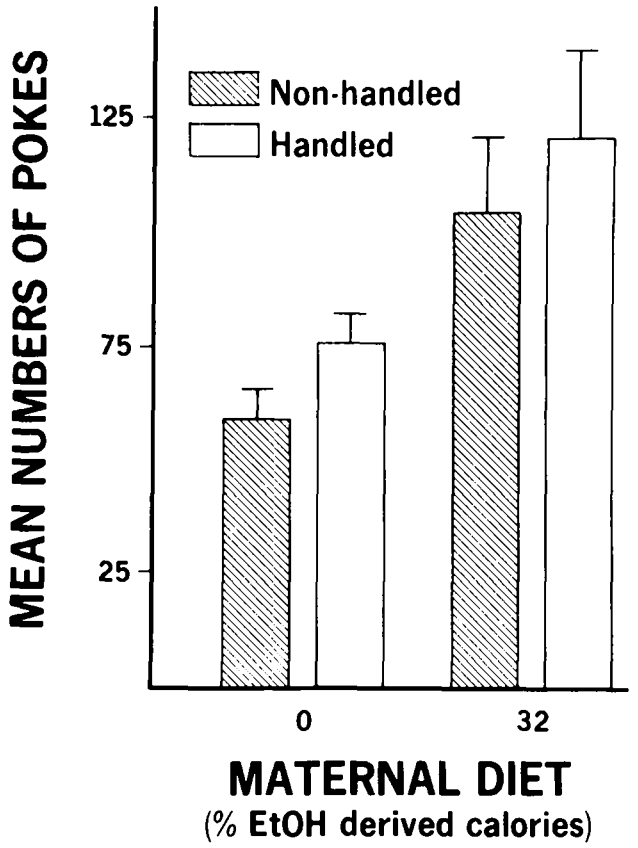

FIG. 3. Mean number of nose pokes for offspring in each maternal diet group and handling condition.

repeated twice more at five-day intervals. Following culling the non-handled animals were left undisturbed for 15 days. At this time all rats were weighed and the groups were found to be equivalent. Eight male rats from each of the four groups defined by maternal diet and postnatal handling condition, 32% H, 32% NH, 0% H, and 0% NH, were tested at approximately 34 days of age.

Apparatus and Procedure

The apparatus and procedure were the same as described previously with the following exceptions. When the rat poked its head into the tube at least 1 cm, a 28-v, 0.24 M.S.C.P., lamp housed outside the opposite end of the tube was activated for the duration of the poke. In this study the dependent measures were recorded at 10-min intervals across the 60-min test session.

RESULTS

The mean number of pokes during the 1-hr session as a function of maternal diet and handling condition is presented in Fig. 3. Animals in the 32% conditions poked more often than animals whose mothers were fed an isocaloric, non-alcoholic diet. Furthermore, handling appeared to have only a marginal effect. An analysis of variance with maternal diet and handling condition as between-subject factors, and blocks as a within-subject factor, indicated a significant effect of diet, $F(1,28)=10.35$, $p<0.01$, confirming that the 32% groups poked more. Additionally, there was a significant linear decline in responding across blocks, $F(1,28)=96.90$, $p<0.001$, and blocks did not interact with either between-subject factor, indicating similar rates of decline for all groups. Although it appears that handled subjects responded more, this effect was not significant.

Mean poke duration was calculated for each 10-min block and an analysis of these data revealed only nonsignificant effects. This finding would indicate that animals decreased the number of discrete pokes made within a session, but the duration of each response remained relatively constant.

The mean daily alcohol intake of the mothers in the 32% group was 14.19 (SE ± 0.58) g/kg, with blood alcohol levels averaging 0.12 (SE ± 0.08)%. Percent maternal weight gain during pregnancy (54.6 and 51.4% for the 32 and 0% groups) and litter sizes were equivalent for both the 32 and 0% groups, as were the survival rates of the offspring from birth to weaning.

EXPERIMENT 3

The following study was conducted to determine whether prenatal alcohol exposure would result in increases in head dipping comparable to those obtained for nose poking. Furthermore, this response was measured under conditions of high and low stimulus complexity.

METHOD

Animals

The parental stock and mating procedures described in Experiment 1 were used. In this study, maternal diets administered from Day 6 through Day 20 of gestation provided 35 (n=10), 17.5 (n=10), or 0% (n=9) EDC. The compositions of these diets are presented in Table 1 and again a pair-feeding procedure was utilized. Also, a lab chow control group (n=9) was included. Blood alcohol concentrations were assessed on Day 15 as described previously.

Just prior to parturition, breeding cages were checked three times daily and litters were weighed and culled to 10 where possible. Pups were next weighed at 7, 14, and 21 days of age. Six male and six female animals were randomly selected for testing at 18 days of age, with the restriction that each litter was represented by no more than one animal of each sex.

Apparatus and Procedure

The apparatus consisted of a 30×30×30 cm clear Plexiglas chamber with an opaque black floor. Four holes were positioned in this floor, 7 cm apart and 8 cm from the adjacent walls. Hollow transparent Plexiglas cylinders, 4 cm long and 3.5 cm in diameter, were attached to the floor beneath each hole. A 12-v red light source centered on the underside of the floor, projected to a photocell located behind each cylinder.

Small objects could be placed at the bottom of each cylinder, at a depth which prevented the animal from reaching them, except with its vibrissa. A shiny nickel and a piece of Ivory soap were used as stimuli. These objects were always placed in diagonal holes, but the particular holes used were randomized across subjects. The remaining two holes were empty during the 15-min test session. This head-dipping apparatus was mounted on a stabilimeter platform (Lafayette model no. 86010) which provided a measure of overall activ-

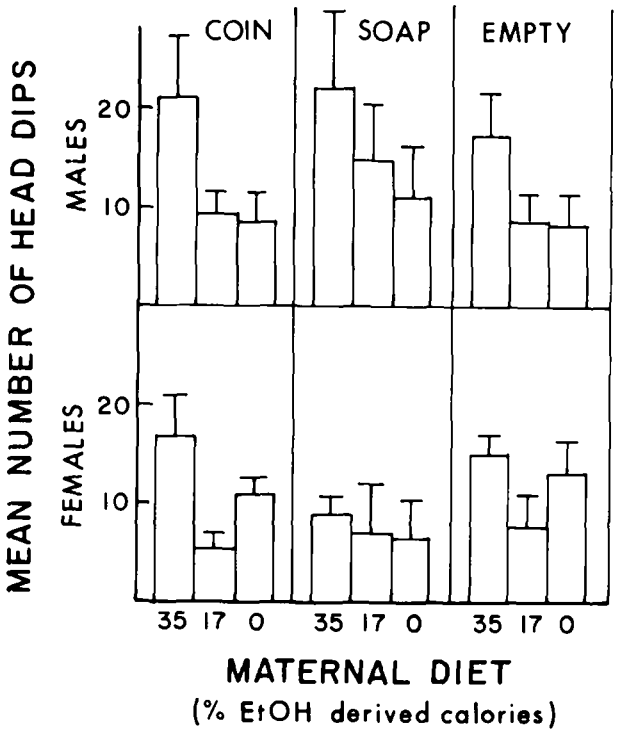

FIG. 4. Mean number of head dips (± SE) performed in each hole condition for male and female offspring in each maternal diet group.

ity during the test session. Each time the animal dipped its head at least 1.5 cm into the hole a count and the duration of the dip were recorded. The frequency of head dips in the coin, soap, and two empty holes were recorded separately, while duration was recorded for the two object holes collectively, and for the empty holes combined. Data were recorded in 2.5-min blocks.

The chamber was housed in a sound-attenuating box and was illuminated by a 12-v lamp located 15 cm above the top of the chamber. A ventilating fan located in the box provided masking noise.

RESULTS

The mean number of head dips as a function of maternal diet, sex, and hole is presented in Fig. 4. The number of dips made to the two empty holes was averaged in order to equate the three stimulus choices. As can be seen, in male offspring there is a definite tendency for 35% offspring to dip more often than the other two groups, regardless of the stimulus. This tendency is also true for females although the same monotonic relation is not evident since the 17% offspring responded less than the 0% animals in both the coin and empty holes. However, an analysis of variance with maternal diet and sex as between-subject factors and blocks and hole as within-subject factors, indicated only significant effects of maternal diet, $F(2,30)=3.37$, $p<0.05$, and blocks, $F(5,150)=7.04$, $p<0.001$. Neither the effect of sex, $F(1,30)=1.14$, $p>0.05$, hole, $F<1$, nor any interaction with sex or hole approached significance. An analysis comparing the 0% and lab chow controls indicated no effect of the liquid diet, $F(1,20)=3.72$, $p>0.05$, although the 0% animals had a tendency to head dip more frequently than the lab chow controls, 11.64 times as opposed to 7.17 times.

An analysis of the average duration per dip revealed no significant effects besides blocks, $F(5,150)=3.49$, $p<0.01$. However, the nutritional comparison indicated a significant effect of the liquid diet, $F(1,20)=10.30$, $p<0.01$. Animals consuming the 0% liquid diet had longer head-dip durations than did the lab chow controls.

An analysis of the stabilimeter activity showed no significant group differences, $F<1$, indicating that overall activity rates were equivalent, although there was a tendency in male animals for the alcohol-exposed groups to have higher activity rates. There was a significant effect of blocks, $F(5,150)=7.75$, $p<0.001$, although blocks did not interact with groups.

Given the significant effects of both liquid diet and prenatal alcohol treatment, pertinent data concerning maternal intakes and offspring development are provided. Mothers in the 35 and 17% EDC diet groups consumed an average (± SE) of 13.78 (± 1.27) and 6.78 (± 0.20) g of alcohol per kg of body weight per day, respectively. Blood alcohol concentrations averaged 0.13% (± 0.02) for the 35% diet group and 0.01% (± 0.004) for the 17% group. Percent weight gain during gestation was equivalent across the liquid diet groups, $F<1$, (36.9, 36.7, and 39.6%, for the 35, 17, and 0% groups, respectively), although the lab chow mothers gained significantly more weight (59.5%) than the 0% controls, $F(1,16)=36.69$, $p<0.001$. Litter size was equivalent across all four groups.

TABLE 2
MEAN LITTER WEIGHTS OF OFFSPRING AS A FUNCTION OF MATERNAL DIET

Diet Group		Age			
		Birth	7	14	21
35%	Males	4.88	10.60	24.67	38.84
	Females	4.67	10.55	24.96	40.00
17%	Males	5.91	13.68	28.31	44.69
	Females	5.55	12.87	26.35	43.69
0%	Males	5.77	13.76	27.65	41.79
	Females	5.30	12.85	25.83	37.21
LC	Males	6.20	13.95	28.07	43.51
	Females	5.89	13.47	27.73	41.69

The mean weights of the offspring at birth, 7, 14, and 21 days of age are presented in Table 2. These means were calculated from litter averages so that each litter is weighted equally regardless of litter size [1]. As can be seen in the table, offspring of the 35% diet group appear to be the lightest in most cases. An analysis of variance performed on litter averages at each age with sex and maternal diet as between-subject factors revealed significant effects of the maternal diet at birth, $F(2,53)=15.20$, $p<0.001$, and at 7 days of age, $F(2,47)=10.80$, $p<0.001$. A significant sex effect was found at birth only, $F(1,53)=5.45$, $p<0.05$ and at no age did an interaction between sex and maternal diet prove significant.

Separate comparisons were made between the 0% and lab chow offspring groups. Analyses of variance performed on weights at each age revealed that lab chow offspring were

significantly heavier at birth only, $F(1,34)=7.87$, $p<0.01$. In addition, there was a significant difference between males and females at birth, $F(1,32)=4.67$, $p<0.05$. No interactions were present at any age.

Marked differences were also evident in terms of offspring survival rates from birth to 21 days of age, with only 69% of the offspring in the 35% group surviving to 7 days of age, compared to 88 and 94% for the 17 and 0% groups, respectively. A 3×2 (maternal diet × survival rate) Chi-square analysis revealed a significant relation between the amount of alcohol in the maternal diet and survival rate to 7 days of age, $\chi^2(2)=22.55$, $p<0.001$. The percentages of offspring surviving to 14 days of age were 63, 87 and 92%, for the 35, 17, and 0% groups respectively, and these also were significantly different, $\chi^2(2)=27.13$, $p<0.001$. Similarly, survival rates of 59, 85, and 92%, $\chi^2(2)=30.78$, $p<0.01$, were found at 21 days of age. Offspring survival in the 0% and lab chow control groups was equivalent.

DISCUSSION

In three separate experiments, animals exposed to alcohol prenatally exhibited more exploratory responses than controls. This tendency was evident whether the response was nose poking or head dipping, regardless of the presence or absence of response-produced feedback, in both handled and non-handled offspring, and independently of stimulus complexity. This heightened exploratory behavior thus appears to be a rather pervasive and robust finding. These data help to support the contention that alcohol exposure *in utero* results in a deficit in response inhibition since other treatments, which presumably disinhibit behavior, also enhance response rates in paradigms similar to those used in the present study [21].

While previous studies have frequently reported that overactivity is a consequence of prenatal alcohol exposure [3, 4, 6, 17] most of these investigations were conducted in the open-field. The interpretation of activity scores in this apparatus has been subject to debate [2,19] since activity level, emotionality, and exploratory tendencies are confounded. Presumably, the hole-board provides measures of exploratory tendencies independent of general arousal, activity, and ambulation [20]. Thus, prenatal alcohol exposure might result in an increase in exploratory responses or perhaps a deficit in the ability to inhibit these exploratory behaviors. It may be that exploration rather than general activity is being affected by prenatal alcohol exposure since activity as measured in the stabilimeter in Experiment 3 failed to differentiate the various groups. However, there still was a nonsignificant tendency for the alcohol-exposed animals to have the higher stabilimeter activity rates and perhaps this measure is simply not as sensitive as the open-field.

The detrimental influence of prenatal alcohol exposure on intrauterine growth and subsequent survival rates was shown in Experiment 3 and similar data were also found in the first experiment but these are being presented elsewhere (Lochry *et al.*, manuscript in submission). These data are consistent with data reported by others. For example, Tze and Lee [18] studied the effects of maternal alcohol consumption prior to and during pregnancy on the physical condition of rat offspring at birth. They found a marked decrease in birth weights and litter sizes of alcohol-treated animals. Likewise, Henderson and Schenker [10] investigated the effects of prenatal alcohol exposure on physical development in the rat and found increased neonatal mortality and decreased body weights in their alcohol-treated groups.

Finally, it should be pointed out that cross-fostering procedures were not utilized in the present study. Therefore, it is possible that the behavioral effects observed are due to alcohol-induced changes in maternal behavior. While this possibility must be considered, previous investigations have consistently reported behavioral differences between alcohol-exposed animals and controls even when cross-fostering was utilized [5, 13, 17]. It would thus appear that alcohol insult *in utero* may have behavioral consequences independent of any obvious physical anomalies. As such, these data support the notion of a broad concept of FAS [17] including behavioral dysfunction at one end and gross physical abnormalities at the other.

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