

Prolonged Behavioral Effects of *in Utero* Exposure to Lead or Methyl Mercury: Reduced Sensitivity to Changes in Reinforcement Contingencies during Behavioral Transitions and in Steady State¹

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Postnatal exposure to lead or methyl mercury results in mental retardation, learning deficits, and other neurobehavioral effects in humans, and adverse consequences of prenatal exposure have been clearly documented with methyl mercury. To examine the developmental neurotoxicity of these metals, especially lead, concurrent schedules of food reinforcement were used to identify learning deficits in squirrel monkeys exposed during gestation to either methyl mercury or lead. Pregnant squirrel monkeys were administered methyl mercury (0.7 to 0.9 ppm in maternal blood) or lead (21 to 79 $\mu\text{g}/\text{dl}$ in maternal blood) during the last half to two-thirds of gestation. At about 5-6 years of age, offspring were trained to lever press under concurrent schedules of reinforcement in which separate random interval reinforcement schedules operated independently on two levers. Reinforcement densities were varied such that 20 to 90% of the reinforcers were programmed to derive from the left lever (i.e., one lever was "richer" than the other). At steady state, the behavior of the controls was sensitive to reinforcement density and showed little lever bias, but the behavior of monkeys exposed to more than 40 $\mu\text{g}/\text{dl}$ of lead and to methyl mercury was less sensitive to reinforcement rates and heavily biased. When relative reinforcement density on a lever changed, the unexposed animals' response rates gradually shifted to the newly rich lever. The behavior of monkeys exposed to methyl mercury or more than 40 $\mu\text{g}/\text{dl}$ of lead changed slowly, not at all, or in the wrong direction. Steady-state behavior of monkeys exposed to less than 40 $\mu\text{g}/\text{dl}$ resembled controls, but acquisition progressed more slowly and required 2-4 times as many reinforcers to complete. These effects suggest a behavioral mechanism—insensitivity to changing reinforcement contingencies—by which learning deficits and behavioral changes associated with these metals might be related to toxicant exposure. Since maternal blood lev-

els corresponded to those that could be experienced in occupational settings, the present data raise the possibility of fetal hazards associated with maternal lead exposures at levels tolerated in humans in occupational settings. © 1994 Academic Press, Inc.

Learning deficits, retardation, and other neurobehavioral effects have been associated with lead or methyl mercury exposure during development in human and nonhuman species (Amin-Zaki and Majeed, 1981; Bellinger *et al.*, 1987; Davis *et al.*, 1990; Laughlin, 1986; Rice, 1984, 1985, 1990b). Methyl mercury has been firmly established as a developmental neurotoxicant when administered during gestation (Amin-Zaki and Majeed, 1981; Burbacher *et al.*, 1990; Cox *et al.*, 1989; Inskip and Piotrowski, 1985) but the extent to which prenatal lead exposure produces long-lasting neurotoxicity is poorly understood (Laughlin, 1986; Silbergeld, 1984). The general sensitivity of the prenatal nervous system to chemical insult, the appearance of lead in the fetus during maternal exposure, and subtle effects seen in rodents exposed during gestation all raise concerns (Angell and Weiss, 1982; Lögdberg *et al.*, 1987, 1988; Needleman, 1986).

Recent years have witnessed increasing concern about childhood exposure to lead at levels as low as 10 $\mu\text{g}/\text{dl}$ (Davis *et al.*, 1993). Much higher levels are tolerated in adults, including pregnant women, in occupational settings and the resultant risk to a fetus is unknown (Rice, 1990b; Laughlin, 1986). A major influence over increased concern about ambient lead levels has been reports of lead's effects on operant behavior (Cory-Slechta, 1990; Davis *et al.*, 1990; Johnson and Mason, 1984; Rice, 1990b). Operant responses, by definition, are influenced by their consequences and thereby permit behavioral adaptation to rapidly changing environments (Palmer and Donahoe, 1992; Skinner, 1981). Accordingly, operant behavior provides the mechanism by which much learning takes place (Kupfermann, 1985). While many reports of chemical-induced alterations in operant behavior have used steady-state behav-

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ior, some have examined behavior in transition—the act of learning.

Operant behavior in transition is especially sensitive to chemical effects (Branch, 1991; Gentry and Middaugh, 1988; Newland *et al.*, 1986; Thompson *et al.*, 1979), but quantification of transition states has proven difficult. Concurrent schedules of reinforcement, which maintain behavior on one of two or more response alternatives, permit precise characterization of the manner by which different consequences acquire control over operant behavior (Boelens *et al.*, 1988; Boelens and Kop, 1983; Mazur, 1992). Usually most behavior occurs on a manipulandum associated with the higher reinforcer density (the “rich” schedule), but the relative responding on either schedule depends upon relative reinforcement density, the response cost imposed for changing levers, and discriminative stimuli associated with the different levers (Boelens and Kop, 1983; Davison and McCarthy, 1988; de Villier, 1977; Findley, 1958; Hanna *et al.*, 1992; Todorov, 1971).

The present report presents new data on the consequences of *in utero* exposure to lead and represents an novel application of concurrent schedules toward a quantification of behavioral toxicity. These data also form the basis for an hypothesis about learning deficits associated with metal exposure: behavioral deficits are associated with insensitivity to changes in the consequences of behavior. The hypothesis is developed from the monkeys exposed to lead. Data from monkeys exposed to methyl mercury provide an extension of the developmental neurotoxicity of this metal, but, more important, they test the generality of the proposed behavioral mechanism of neurotoxicity. These two metals both produce retardation but have different neural mechanisms of toxicity. If similar behavior effects of these two metals have a common source, then the argument that insensitivity to changes reinforcement forms a common behavioral mechanism of toxicity is strengthened.

METHODS

Animals. The subjects were 5 to 6-year-old squirrel monkeys (*Saimiri sciureus*, Roman Arch type), born at the Institute for Hygiene, Lund University, Sweden, and housed according to Swedish standards for the care of primates. Two cohorts were examined separately. Cohort 1 contained three control, three methyl mercury, and three lead-exposed monkeys. Cohort 2 contained five control and five lead-exposed monkeys.

The squirrel monkeys were group-housed in 5 × 2 × 2.3-m stainless steel cages (four to six per cage) with perches in the cage. Room temperature was kept at 23°C, and relative humidity at 60 ± 5%. Lights were on from 0700 to 1900. Their diet consisted of pellets *ad libitum*, amounting to about 80 to 100 g per monkey daily, supplemented with folic acid in the drinking water and half an apple/day during the winter half-year.

The monkeys used here were the offspring of timed-pregnant squirrel monkeys which had been used for breeding. Three lead-exposed monkeys (310, 325, and 351) had the same mother and different fathers. Two control monkeys (315 and 331) had the same mother (but different from 310, 325, and 351) and different fathers. The reason that three monkeys exposed to relatively high levels of lead were born of the same mother is that

some other monkeys exposed to high levels miscarried or had to have the pregnancy terminated before term (Lögberg *et al.*, 1987).

Twenty milligrams of iron was injected *im* between gestational ages of 9 to 18 weeks to prevent iron deficiencies. No other pharmaceuticals were given prior to the end of gestation. Pregnancies were timed to ±3.5 days by limiting matings to 1 week every month, with diagnostic abdominal palpitations after a few weeks. The offspring had been nursed by the natural mother, so some exposure through maternal milk was possible.

Exposure. Exposures began Gestational Week 8.5 for monkeys 310 and 325 (59 and 79 µg/dl maternal blood lead) and at Week 5 for all other lead-exposed monkeys. Exposure began between Weeks 11 and 14.5 for the methyl mercury-exposed monkeys. These are periods during which mitosis and migration of cells to the outer cerebral cortex takes place (Sidman and Rakic, 1973). Gestation is about 22 weeks. Other monkeys born at about the same time as those used in the present study, and exposed similarly, were euthanized close to birth so brain levels of mercury or lead could be established and pathological consequences of exposure could be determined. Monkeys of the same sex and born in the same year served as controls. When tested, neonatal blood levels closely matched maternal levels (details about exposure details, pathology, and tissue levels of cohorts are in Lögberg *et al.* (1987, 1988)). Blood lead levels in the unexposed monkeys averaged 6.5 µg/dl (range, 4 to 9 µg/dl).

Doses were adjusted on an individual basis to provide consistent maternal blood concentration, which was monitored weekly. All doses represented a geometric mean across all weeks of exposure. Lead was administered in pieces of apple and in water. Methyl mercury, containing ²⁰³Hg-isotope, was administered by gavage. Lead concentrations were analyzed using flame AA and were corrected for variations in hemoglobin by multiplying them by the mean hemoglobin value/simultaneous hemoglobin value. Methyl mercury concentrations were analyzed with γ counting.

Behavioral testing. Training on the concurrent schedules began when the monkeys were 5–6 years of age. The monkeys' body weight was monitored daily and kept at about 90% of the free-feeding body weight (which was redetermined semiannually by permitting free access to food).

During testing, a monkey sat in a chair and faced a panel containing two levers. An independent Random Interval (RI) schedule of reinforcement by sucrose pellets operated on each lever. For example, under a schedule described as a concurrent RI 15° RI 60° schedule, responses on the left lever produced a sucrose pellet at unpredictable times but with an average interreinforcer interval of 15 sec. The schedule operating on the right lever ran similarly but with a 60-sec average interreinforcer interval. If a reinforcer became available on the left lever while the monkey was responding on the right lever, then that reinforcer was held until the monkey made a response on the left lever; in other words, the schedules operated independently. A “changeover delay” of 2 sec had to lapse before a response could produce a reinforcer after changing levers. This provides a response cost on changing levers that increases sensitivity to schedule differences (Davison and McCarthy, 1988).

The monkeys were trained to press each lever and then exposed to a RI 30° schedule of reinforcement operating separately on each lever alone, then a concurrent RI 30° RI 30° schedule and a series of concurrent schedules were imposed. All sessions were 30 min in length and were conducted 5 days/week.

After training, a concurrent RI 30° RI 30° schedule was followed by a concurrent RI 60° RI 15°. That is, the relative programmed reinforcers on the left lever changed from 50 to 20%. The second transition was to concurrent RI 15° RI 60° (the rich lever, formerly right, became the left one). Subsequent transitions were to concurrent RI 60° RI 15°, concurrent RI 15° RI 60°, concurrent RI 60° RI 60°, and concurrent RI 60° RI 30° (except for therapeutic interventions described below), and are shown in Table 1. Each schedule remained in place until performance showed no systematic changes in overall response rate, proportion of left-lever responses, or rate of changing levers, across five sessions.

Prior to training under the concurrent schedule of reinforcement, the monkeys had performed under fixed-interval and fixed-ratio schedules of

TABLE 1
Sequence of Conditions for Examining Behavior under
Concurrent Schedules in Steady State and Transition

Condition	Reinforcement rate (reinforcers/min)			Proportion of reinforcers on left	Reinforcer ratio (left/right)
	Left lever	Right lever	Overall		
1	2	2	4	0.5	1.0
2	1	4	5	0.2	0.25
3	4	1	5	0.8	4.0
4	1	4	5	0.2	0.25
5	1	0.12	1.12	0.89	8.3
6	1	2	3	0.33	0.5
Left therapy ^a	6	0.06	6.06	0.99	100.
Right therapy ^a	0.06	6	6.06	0.01	0.01

^a If no change in behavior occurred about 15 sessions after a change in the schedule, "therapy" was applied to facilitate the transition.

reinforcement for operating a Lindsley Manipulandum—a device that the animals had to pull against a spring (Newland *et al.*, 1992).

Data analysis. The proportion of left-lever responses was the primary behavioral measure used to describe behavior in transition. This was the proportion of responses on the left lever divided by the total responses on the left and right levers. The proportion of time spent responding on the left lever was also examined but provided no additional information so is not reported. Overall response rates were not systematically unaffected.

The ratio of left lever:right lever responses was used to describe steady-state behavior because this measure is a preferred and frequently reported behavioral measure used when describing concurrent schedule performance in steady state. Regressing this measure against the ratio of left-lever to right-lever reinforcers provides a measure of sensitivity to differences between the two levers in the reinforcement rates that they provide (Davison and McCarthy, 1988).

Both linear and nonlinear regressions were conducted by least-squares techniques. Linear regression of log-transformed data was used to describe steady-state performance. Nonlinear regression techniques were used to fit logistic functions. Several forms of the logistic equation were attempted before settling on the form used (Eq. (2), below; see also Ratkowski (1989)), which had the best performance as judged by convergence upon a solution, the size of the standard errors of the obtained coefficients, and visual inspection of the quality of the fit and of residuals.

The parameters obtained from the regression analysis were treated as dependent measures and compared using *t* tests or one-way ANOVAs (see Cox *et al.* (1989) for a treatment of the general approach). Because of the small number of points, and occasional outliers, the probabilities associated with obtained values of *t* and *F* were calculated using randomization techniques. This provides a nonparametric estimate of the probability of obtaining a value at least as extreme as the one obtained by randomly redistributing the numbers obtained at least 10,000 times (Edgington, 1980).

RESULTS

Representative Transitions of Monkeys Exposed to Methyl Mercury and High Doses of Lead

When reinforcement rates were changed, the resultant behavioral changes for all three control monkeys was simi-

lar to the one shown in the top two panels of Fig. 1. Behavior (filled circles) tracked the schedule change, and the transition was complete within three to six sessions (90 to 180 min of contact with the new contingencies). The methyl mercury-exposed monkey showed practically no change in behavior during the first transition. The behavior of the lead-exposed monkey changed after the first transition, but in the wrong direction, so most responses appeared on the lever producing the lower reinforcer density.

Two more transitions appear in the right column of Fig. 1. Other transitions for control monkeys were smooth and

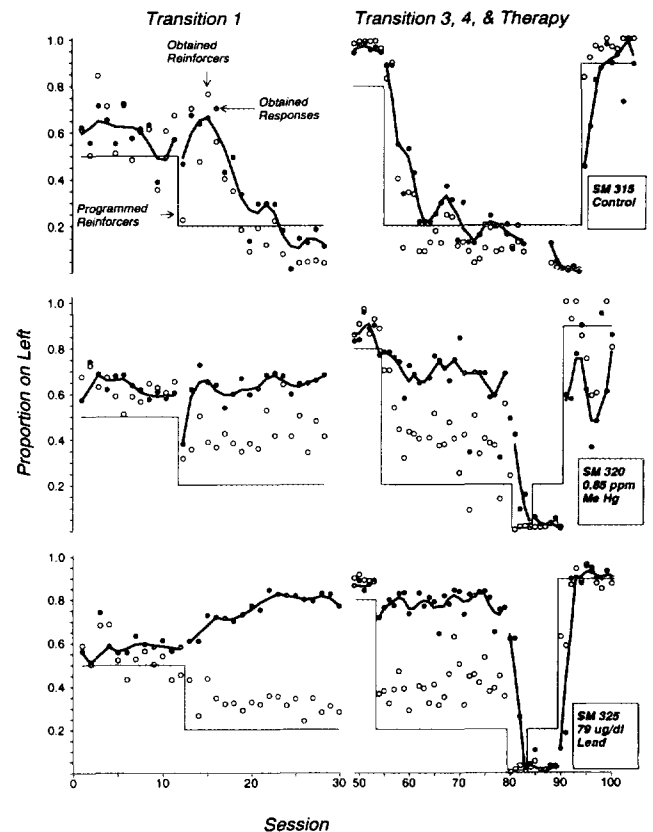


FIG. 1. Representative transitions showing behavior change subsequent to a change in the reinforcement densities on the two levers. The ordinate is relative response rates on the left lever. The thin line shows programmed relative reinforcement rates. Open circles show obtained relative reinforcement rates on the left lever (left-lever reinforcers divided by all reinforcers). Filled circles show obtained relative response rates on the left lever and the thick line is a smoothed (using lowess smoothing) version of these data. Transition behavior was smooth for the unexposed monkey but either pathological or of relatively small magnitude for the exposed monkeys. The first transition (beginning on session 13) is in the left column. The third and fourth transitions (beginning on session 54 and 90, respectively) appear in the right column. This column also shows the therapeutic intervention for the two exposed monkeys: increasing the ratio in reinforcement rates on the two levers to 1:100 (sessions 80 to 83). This intervention was required to force a change in the exposed monkeys' behavior. No sessions were conducted for the unexposed monkey during this time.

ended when relative responses matched or exceeded the relative reinforcement rates on the two levers. Exposed monkeys' transitions were slower, often ended before response ratios approximated programmed reinforcement ratios, and tended to show more volatility. For both exposed monkeys, most responses occurred on the right lever although most reinforcers were programmed to derive from the left lever.

The insensitivity to the source of reinforcement evident in exposed monkeys was overcome by changing dramatically the programmed reinforcement ratio. Performance of monkeys F320 and F325 appeared stable 26 sessions after the first transition, so a therapeutic intervention was attempted. The programmed ratio of left-lever to right-lever reinforcers was changed from 4:1 to 100:1 (a concurrent RI 10" RI 1000" was imposed) and after a few sessions behavior changed. When programmed reinforcement ratios were restored to 4:1 the preference for the right lever did not reappear. This could reflect better control by the concurrent RI 15" RI 60" schedule or it could reflect insensitivity to the transition from the concurrent RI 10" RI 1000" schedule.

Transition 4 (session 91), to the left lever, was smooth for the control monkey, and smooth and rapid for the lead-exposed monkey, a rapidity that probably reflected a left-lever bias. All transitions to the left lever occurred more quickly than to the right lever for that monkey. The transition for monkey F320 began quickly but was generally more ragged and variable. That monkey exhibited a similar pattern in subsequent transitions (data not shown).

Steady-State Performance of Monkeys Exposed to Methyl Mercury or High Levels of Lead

During steady state, a monotonic relationship typically appears between relative responses maintained by a schedule and relative reinforcement provided by that schedule (de Villiers, 1977; Davison and McCarthy, 1988). This relationship is analyzed by regressing the ratio of left-lever:right-lever responses onto the ratio of left-lever:right-lever reinforcers. The power function in Eq. (1) describes steady-state performance:

$$\log\left(\frac{B_l}{B_r}\right) = a + b \log\left(\frac{R_l}{R_r}\right) \quad (1)$$

B_l and B_r are response rates on the left and right levers and R_l and R_r are programmed reinforcement rates on those levers. The intercept a is lever bias (positive for left). The slope b is interpreted as sensitivity to reinforcement. Complete insensitivity produces a b of 0 and positive values indicate greater sensitivity.

Figure 2 reveals the degree to which reinforcer ratios influence responding for each monkey. The best-fit lines for the unexposed monkeys show a slope of 1 or greater and the

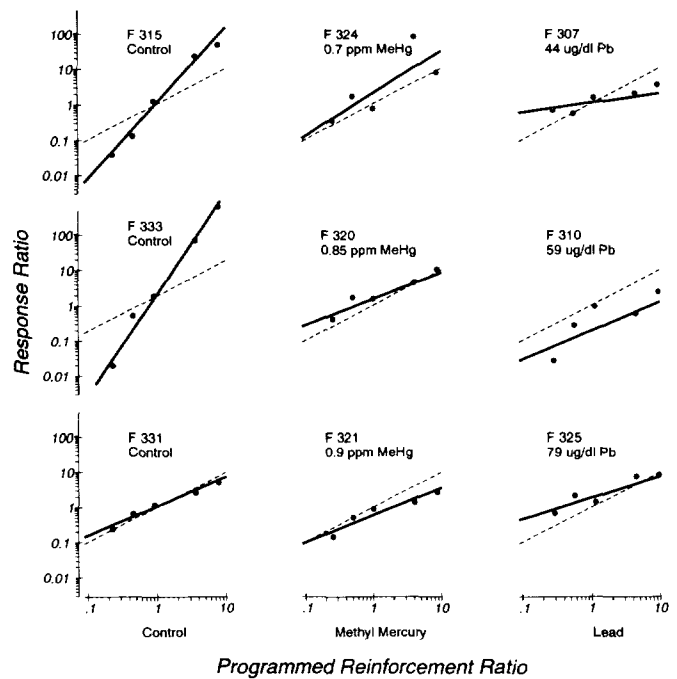


FIG. 2. Steady-state performance for control, lead-exposed, and methyl mercury-exposed monkeys. The ratio of left-lever to right-lever response rates is expressed as a function of the ratio of reinforcement rates programmed for responding on those levers (note the log scales). Filled circles are the average of the four sessions just before a transition (or therapeutic intervention) for an individual monkey at single schedule parameters. The solid lines indicate best-fit linear regressions fitted to Eq. (1). The dashed line shows a line of identity between response and reinforcer ratios to provide a visual reference. Exposed monkeys tended toward indifference between the two levers, as indicated by lines that tend toward the horizontal.

points fall close to the regression line fitted to the data. Relatively weak control by the programmed reinforcement rates over exposed monkeys' behavior is visible in shallower slopes and generally greater dispersion of points about the regression line.

The slopes and intercepts of a best-fit line describing log (response ratios) vs log (reinforcer ratios) for each monkey are summarized in Fig. 3. Exposed monkeys had heavily biased performance that was relatively insensitive to the discrepancies in reinforcement rates between the two levers. Control monkeys had little or no bias and a slope of 1 or greater. A nonparametric one-way ANOVA using randomization techniques (Edgington, 1980) revealed a main effect of group on the intercept ($p = 0.012$) and slope ($p = 0.03$). Some overlap occurred in the ranges among the groups, but even with this sample size, the effects were unlikely to have occurred by chance.

Table 2 contains overall response rates for the monkeys obtained immediately prior to the first transition, at the end of the concurrent RI 30" RI 30" schedule. The males responded at a higher rate than the females ($p < 0.0001$ for a

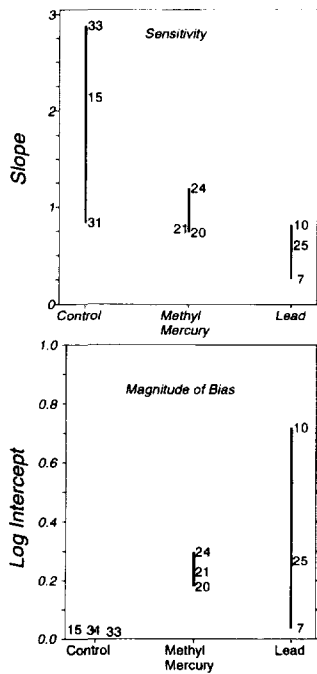


FIG. 3. Bias and sensitivity to reinforcement ratios. These numbers were obtained by regressing log (response ratios) against log (reinforcement ratios) for each monkey and producing the lines shown in Fig. 2. The intercept indicates bias and the slope indicates sensitivity (see Eq. (1)). Only the absolute value of the intercept was used, as the direction of bias was unimportant. Exposed monkeys showed biased responding that was relatively insensitive to the different reinforcement rates programmed. Numbers show the last two digits of the monkey's identification number.

test of the medians) but there was no effect of exposure in this sample. Overall, response rates showed no systematic relationship to exposure through the course of these experiments.

Transitions in Monkeys Exposed to Lower Lead Levels

Quantitative analyses of transitions were conducted on a cohort of monkeys exposed to lower levels of lead, since acquisition was erratic and relatively small for the monkeys described in Fig. 2. Figure 4 illustrates the analytic approach. A logistic function (Eq. (2)) was fitted using least-squares techniques to data relating relative responding on the right (newly rich) lever to the cumulative reinforcers derived from that lever:

$$Y = P_0 + \frac{P_\infty}{1 + e^{(k(R_{\text{half}} - X))}} \quad (2)$$

This equation contains four parameters: P_0 and P_∞ are the lower and upper asymptotes, respectively, R_{half} is the inflection point of the S-shaped curve representing cumulative reinforcers when the transition is half complete, and k is the rate of the transition once it begins. Increases in R_{half} would

slide the S to the right, and increases in k steepen the function (Ratkowski, 1989). Cumulative reinforcers were used as the independent variable since it is the reinforcer that makes contact with behavior and is an important determinant of concurrent schedule performance (Davison and McCarthy, 1988).

Figure 5 shows the parameters obtained for the best-fit logistic function to the second transition for control and lead-exposed monkeys. The magnitude of the transition is shown for all monkeys. The rate (k) and half-maximal reinforcers (R_{half}) are only shown for cohort 2, those exposed to lower levels of lead, since there was very little transition to analyze for the high-dose monkeys. For the low-dose monkeys, the transition was completed, but more slowly, and required 2–4 times as many reinforcers.

DISCUSSION

Analyses of steady-state and transitional behavior indicated, in nonhuman primates, a lasting learning impairment due to methyl mercury or lead exposure during gestation. The allocation of behavior between two alternatives during steady state and the acquisition of new behavior patterns were affected more than 6 years after exposure terminated. This observation extends knowledge of the behavioral toxicity of lead to exposures that are only *in utero*.

TABLE 2
Overall Response Rates for Individual Animals

Subject	Gender	Exposure	Maternal exposure ^a	Response rate (responses/min)
315 ^b	M	Control		11.5
331 ^b	M	Control		27.2
333	M	Control		24.8
345	F	Control		24.7
350	F	Control		135.8
363	F	Control		7.5
371	F	Control		3.6
375	F	Control		4.8
372	F	Lead	21	8.2
365	F	Lead	23	5.0
367	F	Lead	23	9.3
348	F	Lead	37	8.0
351 ^c	F	Lead	37	25.4
307	M	Lead	44	24.5
310 ^c	M	Lead	59	23.5
325 ^c	M	Lead	79	24.2
324	M	Methyl mercury	700	40.0
320	M	Methyl mercury	850	14.2
321	M	Methyl mercury	900	27.6

^a Blood levels are expressed as $\mu\text{g}/\text{dl}$. Methyl mercury levels are expressed as ppb of mercury. All values pertain to maternal blood.

^b Half-siblings.

^c Half-siblings.

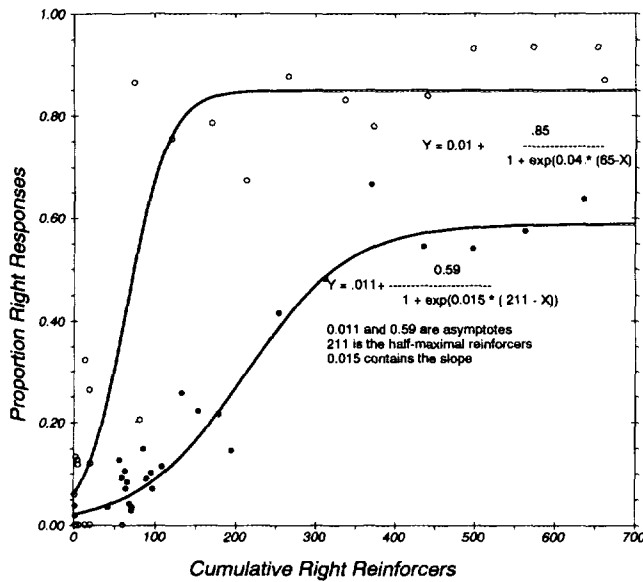


FIG. 4. Transition 2 for monkeys F371 (unexposed, open circles) and F351 (exposed to 37 $\mu\text{g}/\text{dl}$ maternal blood lead) showing the shift in response allocation from the left (formerly rich) lever to the right (currently rich) lever. Data are shown as a function of cumulative reinforcers derived from the rich lever. For example, the first nonzero point for F351 is over 41 and indicates that 41 reinforcers were derived from right-lever responding during the first session after a transition. The next point, over 56, shows that 5 more right-lever reinforcers occurred in the second transition session. Points over zero show the last three sessions before the transition. A logit function was fit to the data and the resulting equation is shown in the figure.

These data also extend knowledge of methyl mercury toxicity to a new behavioral preparation that permits quantification of behavior change. Together, the data from both metals form the basis for suggesting that the behavioral deficits associated with *in utero* exposure to these metals can be reduced to a common mechanism, namely, insensitivity to changes in the consequences of behavior.

Steady-State Behavior

Concurrent schedules of reinforcement permit an investigator to examine behavior in a setting that provides a choice to the subject. The presence of a choice might enhance the sensitivity of the preparation to drug or chemical effects. This is because the rate of responding on a lever is evaluated as a function not just of the schedule of reinforcement operating on that lever, but also as a function of alternate sources of reinforcement, which can be manipulated experimentally. The allocation of responses seen in human and nonhuman species performing under concurrent schedules is determined, in part, by the relative rate of reinforcement obtained for responding on that lever (for review see de Villiers, 1977; Davison and McCarthy, 1988).

Quantification of the sensitivity of behavior to the source of reinforcement has been achieved by calculating the ratio of responses on, say, the left lever to the responses on the right lever over a range of reinforcement ratios, computed similarly. The response ratios are regressed against the reinforcement ratios, usually after a log transformation as in Eq. (1). The slope of the resulting line provides an index of sensitivity of behavior to the source of reinforcement. This value is influenced by a variety of contextual variables, including the cost of changing levers, the reinforcement schedules operating on the levers, the effort required to respond on a lever, and the similarity of reinforcers, so it is important to hold these parameters constant.

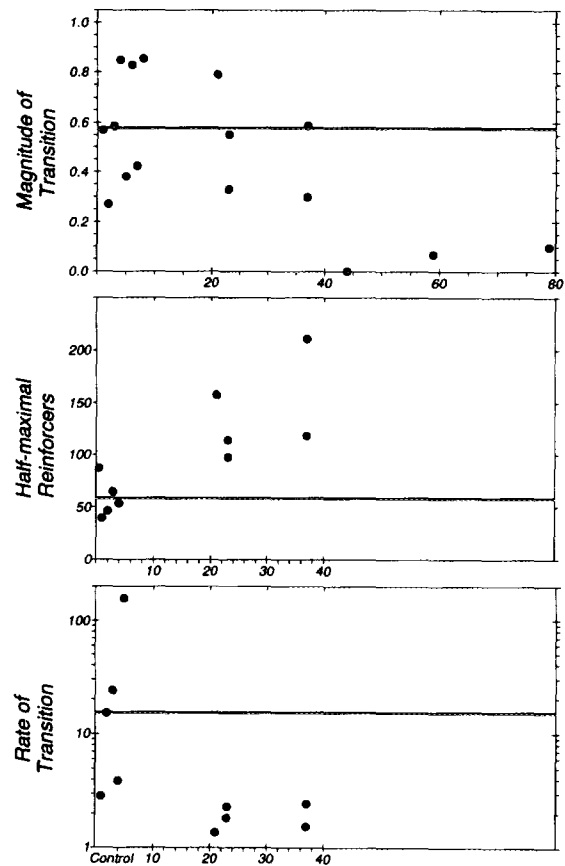


FIG. 5. The result of a least-squares regression applying Eq. (2) to the second transition. Data from unexposed monkeys are staggered laterally to enhance visibility. The solid line represents the median from the control conditions. The magnitude of the transition ($P_{\infty} - P_0$) for the low-dose monkeys was indistinguishable from controls as seen in the top graph, but that value was nearly zero for the high-dose monkeys. The dynamics of the transition were analyzed further for the five monkeys whose behavior changed, along with their five age-matched controls. Low-dose monkeys completed the transition but more slowly ($p = 0.008$), as seen in the bottom graph showing k . They also required about 2 to 4 times as many reinforcers as controls ($p = 0.007$ for the difference) as seen in the middle middle showing R_{half} .

When performance under concurrent schedules of reinforcement is examined in unimpaired organisms, the response ratios are usually expressed as a function of obtained, not programmed, reinforcement ratios (Davison and McCarthy, 1988). The justification for using programmed reinforcement ratios in the present experiment is twofold. In our experiments (see especially the exposed monkeys in Fig. 1) the obtained reinforcement ratio was not an independent variable but a joint function of programmed reinforcement ratios and behavior. Examination of a dependent measure of behavior as a function of an independent measure, like programmed reinforcement ratios, was more revealing. The second justification bears on the generality of the conclusions drawn. The goal of the analysis of steady-state behavior was not the determination of the mechanisms by which obtained reinforcers influence or select behavior. Instead, the goal was to characterize the extent to which structure in behavior reflected the structure in the environment, as represented in reinforcement contingencies. To examine that question, the actual reinforcement contingencies must be used as the independent variable.

Behavior in Transition

A simple shift in the source of most reinforcers from one lever to another was enough to uncover profound disturbances in the behavior of exposed monkeys. During the transitions examined, the monkeys exposed prenatally to methyl mercury or high doses of lead showed little change in behavior as compared with controls, even after a new steady state was established. This observation is in accordance with the suggestion that the behavioral toxicity is mediated by insensitivity of behavior to changes in the source of reinforcement. Further evidence for this mechanism derives from the "therapeutic" interventions. Dramatically increasing the discrepancy in the rate of reinforcement from the two levers, while simultaneously increasing the density of reinforcement from the rich lever, was enough to provoke a transition where one had not been provoked previously.

Quantification of behavior change during transition states was accomplished by fitting a logistic equation to the changes in proportion of rich-lever responses as a function of cumulative rich-lever reinforcers during the transition, as described in Eq. (2). Behavior change typically is examined as a function of time, trials, sessions, or some similar correlate. The characterization of behavior as a function of cumulative reinforcers in the present report was motivated by considerations of the importance of consequences in the emergence of structure in behavior.

The parameter describing half-maximal reinforcers, R_{half} , in Eq. 2 determines the horizontal location of the S-shaped curve in Fig. 4. A smaller parameter would dis-

place the same curve laterally to the left. The magnitude of R_{half} influences when the transition begins to "snowball," that is, when the rate of change becomes so large that it is visible as a positively accelerating curve. The parameter k describes the rate at which the transition takes place, once it begins, and contains the maximal slope, obtained at the inflection point. A smaller value for k , with the same R_{half} , would have an inflection over the same location on the x axis, but a shallower slope.

Detailed examination of behavior during a transition state uncovered an impairment that had been undetected in the steady-state behavior of those animals exposed to lower levels of lead *in utero*. The magnitude of the transition was indistinguishable between the unexposed animals and those exposed to lower levels of lead *in utero*, but the course of the transition was quite different. These differences were quantifiable in two ways: half-maximal reinforcers and the rate of transition. The number of reinforcers required to advance half-way through the transition was 2 to 4 times greater for the lead-exposed monkeys. Once again, this points to a mechanism of insensitivity to changes in the rate or source of reinforcement: the transition occurred, but only after 2–4 times as many reinforcers as required by the unexposed monkeys.

Comparison with Lead Effects

The present report is of note because of the presence of clear behavioral effects associated with *in utero* exposure to lead. The blood levels experienced by the mothers, which were close to those seen in neonates shortly after birth (Lögberg *et al.*, 1987), are generally in the moderate to upper range of those used in other studies of animals (Cory-Slechta, 1990; Rice 1990b). A consistent conclusion from animal studies of the postnatal lead exposure is that subtle but reproducible effects at blood lead concentrations greater than about 20 $\mu\text{g}/\text{dl}$ (Cory-Slechta, 1986; Davis *et al.*, 1990; Laughlin, 1986). These include elevations in fixed-interval response rate (acquisition and maintenance), deficits in discrimination, perseverative responding, and disruptions in social behavior. Often, behavioral baselines that entail behavior change or that especially challenge the organism are most sensitive to lead, or other metal, exposure (Bushnell and Bowman, 1979; Gilbert and Rice, 1987; Levin and Bowman, 1989; Mele *et al.*, 1984; Newland *et al.*, 1986; Rice, 1990a,b; Rice and Karpinski, 1988; Winneke *et al.*, 1982).

A common observation seen with lead-exposed primates is perseveration: persistent responding even in the face of an absence of reinforcement (Bushnell and Bowman, 1979; Levin and Bowman, 1989; Rice, 1990a, 1992; Rice and Karpinski, 1988). Rice and Karpinski (1988) argued that this perseveration appears unrelated to memory mechanisms since it is not associated with delay in a delayed spa-

tial alteration task. Moreover, it may not be related in a straightforward way to attention to irrelevant stimuli, since the addition of irrelevant, distracting stimuli to a spatial discrimination procedure did not further disrupt performance. Rice succinctly described this phenomenon as follows: "It has been observed many times in our laboratory that lead-exposed monkeys are impaired when first introduced to a novel set of contingencies but not after these contingencies become familiar" (Rice, 1990a, p. 588). Insensitivity to consequences is a plausible, common mechanism of the different results seen in these studies producing perseveration or other forms of persistence: when the reinforcement contingencies change, behavior remained unchanged, as in the experiments reported here. If this commonality holds, then it suggests that with *in utero* exposure, the behavioral consequences of lead resemble those seen with other forms of developmental exposure.

Direct comparisons with studies of children exposed *in utero* are difficult because most epidemiological studies entail pre- and postnatal exposure, and in the present studies, exposure was only prenatal. Maternal blood levels examined in the present study were within the range of what might be experienced occupationally, so the present studies suggest a risk to the offspring of pregnant women employed in some settings. It has been estimated that occupational exposure to a time-weighted average of 25 $\mu\text{g}/\text{m}^3$ would result in blood lead levels of greater than about 20 $\mu\text{g}/\text{dl}$ in 33% of workers and greater than 60 $\mu\text{g}/\text{dl}$ in about 0.5% of workers inhaling these atmospheric concentrations of lead (Fronies *et al.*, 1986; Skerfving, 1988). The blood levels achieved in the present study could result from ambient lead in occupational settings. Some investigators have noted a close correspondence between blood lead levels that produce adverse effects in humans and animals (Cory-Slechta, 1990; Davis *et al.*, 1990). If this correspondence can be extended to *in utero* exposure, then the present results suggests a risk to the offspring of mothers exposed occupationally to lead at levels currently tolerated.

Comparisons with Methyl Mercury

The three animals exposed to methyl mercury provide a positive control and an opportunity to advance knowledge of the developmental neurotoxicity of this metal at blood levels selected such that behavioral effects would be likely. In rodents, deficits in differential reinforcement of high-rate behavior (DRH) and disruptions on discrimination tasks have been associated with developmental exposure to methyl mercury (Bornhausen *et al.*, 1980; Elsner, 1986), with peculiar behavioral patterns in spatial alternation procedures described as unstable responding, distractibility, and short attention spans (Elsner, 1986). In nonhuman primates, deficits in visual acuity, fine motor control, and hearing have been reported at these levels (Bornhausen *et*

al., 1980; Berlin, 1986; Gunderson *et al.*, 1988; Rice and Gilbert, 1990; Rice, 1985, 1992). This report, then, extends the range of effects of methyl mercury toxicity to behavior in transition, and therefore to behavior that qualifies as learning, and could provide a model for investigating learning deficits associated with developmental exposure to methyl mercury.

Insensitivity to Changes in Consequences as a Mechanism

Differences in both steady state and acquisition can be reduced to a generalized insensitivity to changes in reinforcing stimuli. The insensitivity to discrepancies in relative densities of reinforcement rate could be overcome by producing extreme differences in reinforcement rates derived from the different schedules. The data are consistent with a conclusion that a generalized insensitivity to changes in reinforcement contingencies results from prenatal lead or methyl mercury exposure. At high levels of lead or methyl mercury exposure, the intervention required to overcome the insensitivity is a sizeable increase in reinforcement density on one lever, or in the disparity in rates of reinforcer delivery between different sources. This suggestion does not mean that the animals were insensitive to reinforcement altogether. That the monkeys responded, often at high rates, indicates otherwise. It only suggests that when a change in reinforcement rates provided by different sources occurs, that change produces small changes in the behavior of exposed animals, relative to what is seen in unexposed animals.

The suggestion that there is a commonality in the behavioral mechanisms common to the effects associated with *in utero* exposure to lead and methyl mercury is not intended to imply that the behavioral deficits are mediated by similar neural mechanisms. More likely, they are not. Instead, this reduction to a common behavioral mechanism is an example of homogeneous reduction, in which a wide variety of observations is described using an economy of terms (Marr, 1990). Homogeneous reduction is distinct from the tactic of identifying mechanisms of action at different levels (called heterogeneous reduction), but it is similar in spirit to attempts at identifying behavioral mechanisms of action in other arenas. For example, many abused drugs maintain drug taking by virtue of their reinforcing actions, a behavioral mechanism that parsimoniously accounts for a wide variety of determinants over drug taking, even among abused drugs acting through very different receptor systems (Schuster, 1986).

The parsimonious account attempted here permits similarities to be drawn across populations, disorders, and may even point to therapeutic interventions. Insensitivity to consequences could underlie academic impairment and behavior disorders reported among children exposed to lead. Multiple, competing contingencies present in a classroom

compete for a child's behavior. If a lead-exposed student is insensitive to consequences of his or her behavior or, especially, to consequences provided by a teacher, then that student could display the distractable, disorganized, or hyperactive behavior similar to those reported in lead-exposed children (Needleman *et al.*, 1974; Needleman, 1986), e.g., distractable, disorganized, hyperactive, or impulsive behavior. Specific behavior therapy might be indicated as treatment.

The validity of extending conclusions drawn from animal studies to classroom activities is supported by investigations showing that explicitly applying reinforcement contingencies similar to those described above systematically increases targeted, and decreases untargeted, behavior in human adults and children. This has been reported under laboratory conditions and in natural settings such as classrooms, in normal children, and even in children referred for behavior problems (Mace, 1990; McDowell, 1981, 1982; Martens *et al.*, 1992; Neef *et al.*, 1992; Perone *et al.*, 1988). Indeed, in controlled studies, developmentally disabled students of unknown chemical histories sometimes show less sensitivity to direct manipulation of relative reinforcement rates and even persistent responding in the face of lowered reinforcement rates (Neef *et al.*, 1992). While direct extensions to lead-exposed students have not been made, the hypothesis is readily amenable to the formation of such extensions.

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