Behavioral Effects of Lead: Commonalities between Experimental and Epidemiologic Data

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Enormous effort has been focused over the last decade and a half on characterizing the behavioral effects of lead in the developing organism. While age-appropriate standardized measures of intelligence (IQ) have been the dependent variable most often used to assess lead-induced cognitive impairment in epidemiologic studies, researchers have also used a variety of other methods designed to assess specific behavioral processes sensitive to lead. Increased reaction time and poorer performance on vigilance tasks associated with increased lead body burden suggest increased distractibility and short attention span. Assessment of behavior on teachers’ rating scales identified increased distractibility, impulsivity, nonpersistence, inability to follow sequences of directions, and inappropriate approach to problems as hallmarks of lead exposure. Robust deficits in learned skills such as reading, spelling, math, and word recognition have also been found. Spatial organizational perception and abilities seem particularly sensitive to lead-induced impairment. Assessment of complex tasks of learning and memory in both rats and monkeys has revealed overall deficits in function over a variety of behavioral tasks. Exploration of behavioral mechanisms responsible for these deficits identified increased distractibility, perseveration, inability to inhibit inappropriate responding, and inability to change response strategy as underlying deficits. Thus, there is remarkable congruence between the epidemiologic and experimental literatures with regard to the behavioral processes identified as underlying the deficits inflicted by developmental lead exposure. However, careful behavioral analysis was required from researchers in both fields for such understanding to emerge. — Environ Health Perspect 104(Suppl 2):337–351 (1996)

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Introduction

Lead has long been recognized as a poison, from ancient times to the present (1,2). In the second century BC, Dioscorides observed that “lead makes the mind give way” (3). Benjamin Franklin documented colic and neurologic signs (wrist drop) in typesetters and painters (4). Lead poisoning in children was recognized before the turn of this century by physicians in Australia (5,6), who recognized the source of this frank poisoning as lead-based paint (7). American physicians also began reporting cases of lead poisoning in children early in the 20th century; by the mid-1920s lead-based paint was recognized as a serious and not uncommon source of illness in children (8–10). Lead-based paint was banned in Australia in 1920; lead remained in paint in the United States for another half century.

The inclusion of tetraethyl lead as a gasoline additive in the 1920s was a landmark event, as this decision resulted in a steep increase in lead emitted into the environment (11). The addition of lead as a gasoline additive engendered grave warnings by health professionals concerning the potential threat to the general health as a result of lead exposure (12). This concern was based on occurrences of mortality and severe neurologic and psychiatric signs in workers exposed in the process of the manufacture of this additive. A committee convened by the Surgeon General warned in 1926,

It remains possible that if the use of leaded gasoline becomes widespread conditions may arise very different from those studied by us... Longer experience may show that even such slight storage of lead as was observed in these studies may lead eventually in susceptible individuals to recognizable or to chronic degenerative diseases of a less obvious character (12).

Despite the recommendation by the committee that the matter be studied further, the interests of the automotive and oil industries won out, lead remained in gasoline, and no further data were collected.

In the 1940s it was recognized by astute physicians that children who had been treated for lead poisoning suffered permanent neurologic damage (13). They reported poor school performance, impulsive behavior, short attention span, restlessness, and occasional neurological signs in these children. These observations were later replicated by other investigators (14–16).

Early in the 1970s, deficits in IQ, fine motor performance, and behavioral disorders such as distractibility and constant need for attention were observed in children who had never exhibited overt signs of lead intoxication (9,17). Concern arose in the United States and elsewhere that the many tons of lead being introduced into the environment every year by the use of leaded gasoline, as well as other industrial processes, were producing significant health effects, particularly in children. A new understanding of the insidious effects of lead on the intellectual capacity of a large number of children arose in 1979 with the landmark study of Needleman et al. (18). These investigators reported decreased IQ and increased incidence of distractibility and inattention in middle-class children with no exposure to lead from paint. The
conclusion drawn from this research was that environmental sources were responsible for the increased lead burden in these children and that this environmental contamination at levels that had come to be regarded as normal could be insidiously robbing children in industrialized countries of their intellectual birthright.

Largely as a result of that study, the last decade and a half has witnessed intense research into the health effects of lead and on the sources of exposure to the general population. The issue has generated a great deal of political as well as scientific controversy. Physicians, epidemiologists, chemists, geologists, animal researchers, representatives of the lead industry, and members of a host of government agencies in a number of countries have been involved. The result of this intense scrutiny is that probably more is known about the health effects of lead than of any other noncarcinogenic environmental contaminant. The result in the United States has been a rapid decrease over the last two decades by the Centers for Disease Control and Prevention (CDC) in the blood level considered safe for children to the present level of 10 µg/dl (19).

The purpose of this paper is to compare findings from the animal and epidemiologic literature concerning the behavioral toxicity produced by low-level lead exposure. While there have been a number of reviews of both literatures, many of them review one or the other literature but not both. Even those reviews that discuss both the human and animal data typically do not discuss the congruence of the two literatures with respect to the types of behavioral deficits observed or the behavioral processes underlying these deficits. In particular, reviewers of the epidemiologic literature often ignore the large body of positive data from experimental research when they draw conclusions about the evidence regarding the developmental neurotoxicity of lead. This paper summarizes selected epidemiologic findings, concentrating on non-IQ end points and the contribution of the experimental literature in interpreting the types of impairments identified and characterized in the epidemiologic literature.

**Human Studies**

The modern studies on the effects of developmental exposure to lead have been extensively reviewed (20–24). Most reviews have focused on the effects of lead exposure on measures of IQ, presumably, at least in part because this is the outcome measure most consistently assessed, which allows comparison across studies. IQ was the outcome variable used in metaanalyses of modern lead studies (25,26), although this method of analysis has been criticized as invalid in part because nonidentical end points are combined (27).

The current discussion on the behavioral effects of lead in children will briefly address some of the issues related to interpretation and comparison of results of tests of IQ across studies. This will not constitute a complete review of the recent literature but will focus on illustrative examples. (See Table 1 for summary of studies discussed.) The remainder of the section on human studies will focus on the efforts by investigators to measure behavior other than or in addition to IQ. Such measures may provide information on behavioral processes underlying the deficits in function assessed by IQ measures. Results from a number of such assessments are at least indicative of specific behavioral deficits produced by an increased body burden of lead, while other strategies demonstrate a global failure of functioning.

The body of data on measures of intelligence tests has been referred to as inconsistent (24,64) on the basis of the fact that different subscales of IQ tests have been found to be affected in different studies or in the same (prospective) study at different ages, or associated with lead body burden measured at different ages. Assessment of intelligence in younger children has been performed using a number of scales including the various Bayley Scales of Infant Development, particularly in very young children, and the McCarthy Scales of Children’s Abilities (MSCA). Most tests in older children used the Weschler Intelligence Scales for Children–Revised (WISC-R). In the Cincinnati prospective study (55), blood lead levels were correlated with the Bayley Mental Development Index (MDI) but not the Psychomotor Development Index (PDI) at 3 and 6 months of age; these effects had disappeared by 2 years of age (56). At 4 years of age, children from the poorest families had a lead-related deficit on all scales of the Kaufman Assessment Battery for Children (K-ABC) (57); there was a weak association for all children on the visual-spatial and visual-motor subscales. In the Boston prospective study (43–45), there was a significant relationship between prenatal blood lead levels and the Bayley MDI at 3, 6, 12, and 24 months of age; there was no effect on the PDI at 6 months of age (43), and it is unclear whether the PDI was assessed at later ages. In the Port Pirie study (50), on the other hand, postnatal rather than prenatal blood lead levels were associated with deficits on the Bayley MDI during infancy. At 4 years of age, lead-induced impairment was observed on the General Cognitive Index (GCI: verbal, perceptual performance, and quantitative scales) and memory scale but not on the motor scale of the MSCA (51). In apparent contrast in the Boston prospective study, assessment of performance on the MSCA at 57 months of age revealed the most effect on perceptual performance and then on the quantitative component, with the verbal, memory, and motor components being insensitive (46). When the Boston children were tested at 10 years of age (47), the verbal subscale of the WISC-R was more sensitive than the performance scale. In the Port Pirie study (52), all scales of the WISC-R were affected when the children were 7 years old, although the information and block design were the most sensitive.

### Table 1. Summary of lead levels in studies included for discussion.

| Studies          | Mean lead levels                                      | References |
|------------------|-------------------------------------------------------|------------|
| Cross-sectional  |                                                       |            |
| Boston           | Dentine = 6 µg/g vs 24 µg/g                            | (18,28)    |
| Germany          | Blood = 7–8 µg/g                                      | (29)       |
|                  | Blood = 14 µg/g, dentine = 6 µg/g                     | (30,31)    |
|                  | Dentine = 2 µg/g vs 5 µg/g                            | (32)       |
| London           | Blood = 13 µg/dl                                      | (33–35)    |
| Mexico           | Blood = 19 µg/dl                                      | (36)       |
| Scotland         | Blood = 14 µg/dl                                      | (37,38)    |
| Denmark          | Dentine = 5 µg/g vs 16 µg/g                            | (39,40)    |
| Greece           | Blood = 24 µg/g                                       | (41)       |
| Dunedin          | Blood = 11 µg/dl                                      | (42)       |
| Boston           | Blood <8 µg/dl at all ages                            | (43–49)    |
| Port Pirie       | Blood, antenatal = 9 µg/dl                            | (50–54)    |
|                  | Postnatal = 14–20 µg/dl, highest at 2 years           |            |
| Cincinnati       | Blood = 8–18 µg/dl, highest at 2 years                | (55–59)    |
| Christchurch     | Dentine = 6 µg/g                                      | (60–63)    |
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(Performance on the block design is, in part, dependent on motor function, as well as on spatial visualization and perceptual organization and synthesis.) In the Cincinnati study (58), performance but not verbal IQ was inversely associated with postnatal blood lead levels at 6.5 years of age. In the longitudinal study in New Zealand (60,61), tooth lead was correlated with verbal, performance, and full IQ in children at 9 years, while the performance IQ was less sensitive than the other two measures at 8 years.

The fact that the subscales of apparently greater sensitivity change between ages, or are different between studies, may reflect a global impairment produced by lead, as suggested by one group of researchers (47). On the other hand, there are several other potential explanations. It is generally recognized that early tests of intelligence such as the Bayley scales do not measure the same functions as tests used at school age such as the WISC-R and have little predictive validity for individual children (65). [It may be the case, however, that the Bayley scales have better predictive power for low-functioning children (66).] It would not be surprising, then, if there were little correlation between results of tests performed during infancy and of tests performed on older children, either within or across studies. Despite this, prospective studies have been consistent in revealing lead-related deficits in IQ from infancy through at least early school age. These studies have, in general, not assessed the rank of particular children at various ages since that was not the variable of interest. However, Baghurst et al. (52) reported a high correlation \( r = 0.65; p < 0.01 \) between performance on the GCI of the McCarthy Scales at 4 years of age and full-scale IQ on the WISC-R at 7 years of age.

In addition to the issue of comparability of the different instruments used for assessing intelligence, differences in concurrent or historic blood lead levels at the time of testing, as well as differences in pattern of blood lead levels over the lifetime, may contribute to differences in results. Different behavioral functions may have different sensitive periods. The prospective studies have revealed that performance may be related to blood lead values at one age or ages and not at others and that this may change as the study progresses. For example, measures from 6 to 24 months in the Boston study were linked to cord but not postnatal blood (45), while performance at 10 years of age was most associated with lead levels at 2 years (47). Similarly, early measures in the Port Pirie study were associated with early blood lead levels (51), while performance on the MSCA at age 4 was associated with blood lead at 2 and 3 years of age but not earlier (53). Results of the WISC-R at 7 years of age best correlated with lifetime blood lead levels averaged from birth to ages between 15 months and 4 years, while early blood lead levels alone were uncorrelated. Such results underscore the power of prospective studies relative to other study designs; if the blood lead histories of each child had not been known, the conclusion from these studies and others at particular time points might well have been negative. These results also demonstrate a shifting pattern of association between blood lead levels and performance measures, with correlation at later ages shifted toward later but not necessarily concurrent blood lead values. Studies that have collected both tooth and blood lead levels as markers of lead exposure are also revealing. Bellinger et al. (46) found performance of children on the MSCA in the Boston prospective study to be associated with measures of blood lead but not tooth lead at 57 months of age. In contrast to the result of IQ measures, performance on the Wisconsin Card Sort Test was associated with blood levels at 57 months and 10 years but not earlier (48). In the Danish study, Hansen et al. (39) reported that tooth lead was a better predictor of intellectual function, while concurrent blood lead levels were a better predictor of psychomotor speed in first-grade children. Since tooth lead levels reveal average past exposure but not the detailed pattern, more precise statements cannot be made regarding the pattern of lead body burden and its relation to performance on various tests. These results suggest that different functions may be sensitive to impairment at different periods of development. Such results further suggest that different patterns of blood lead levels between studies would result in different patterns of impairment between studies, even without differences in such variables as average blood lead levels, population demographics, and testing instruments. In addition, there are indications from the animal literature that spatial and nonspatial behavioral tasks may be differentially susceptible to lead exposure at different periods of development. It therefore may be naive to expect absolute congruence between or within studies; certainly, the lack of consistency of effect on a particular subscale does not constitute evidence that lead does not consistently produce behavioral impairment in children.

One advantage of using IQ tests is that they are standardized for the population. The various subscales also assess a number of intellectual functions, albeit in a rather global manner. This is an advantage if the behavioral domains affected are in fact unknown. While the use of IQ as the main dependent variable in most studies has proven a sensitive indicator of lead exposure even at low body burdens, the use of more specific tests may provide even greater sensitivity. Moreover, assessment of specific behavioral processes rather than global functioning might provide insight into avenues for the development of teaching techniques that may allow children to at least partially overcome behavioral deficits induced by undue lead exposure.

Perhaps the ancillary assessment most often included in both retrospective and prospective designs is some version of the teacher’s rating scale. In the cross-sectional study in Boston (18), a dose-dependent impairment in functioning was associated with increased dentine lead on such measures as “distractable, not persistent, dependent, impulsive, easily frustrated, does not follow simple and complex directions” (Figure 1). These effects were observed in first-grade children who also showed a decrease in IQ as measured by the WISC-R. These findings were replicated using the same rating scale on a population of children in London (33). Yule et al. (32) reported a significant increase in hyperactivity, conduct problems, and inattentive/passive behavior on the Conners scale in these same children who were also impaired on the WISC-R (34). In the prospective study in children in New Zealand, Ferguson et al. (62) reported increased inattention and restlessness, short attention span, and increased distractibility as functions of dentine lead in children at 8 and 9 years of age (Table 2). In the Mexican cross-sectional study using blood as the measure of lead exposure, increased lead body burden was associated with decreased knowledgability and socialization skills on a teacher’s rating scale, as well as impaired performance on the WISC-R (36). In the Scottish cross-sectional study with blood lead as the independent variable (37), a dose-related increase on the aggressive/antisocial and hyperactive measures of the Rutter scale was observed in a group of 6- to 9-year-old children with low blood lead levels, who also exhibited a dose-related decrease in IQ (38). In a
A cross-sectional study in Dunedin, New Zealand, significant associations were found between blood lead levels and increased behavioral problems, as assessed by both teachers and parents on the Rutter Behavioral Scale, and increased scores on inattention and hyperactivity scales in the absence of changes in IQ (42). In the Boston prospective study (49), behavior was assessed by a teacher's rating scale when the children were 8 years old. Umbilical cord lead levels in girls were associated with an increased probability of being dependent and nonpersistent, while both umbilical and dentine lead were related to an inflexible and inappropriate approach to tasks. In boys, umbilical cord blood was associated with difficulty in following simple directions and sequences of directions.

Several investigators have included measures of school performance in their assessments. In the cross-sectional study in Scotland (38), deficits in number skills and reading were found in addition to deficits in IQ. In the New Zealand prospective study (60–62), robust deficits in school performance including reading, math, spelling, and handwriting, as assessed by the teachers,

![Graph A](image1.png)

**Figure 1.** Teachers' ratings of students on a forced-choice questionnaire. Proportion of negative comments within each group, as measured by dentine lead levels (A) or blood lead levels (B). Data from Needleman et al. (18) and Yule et al. (33).
were present in the absence of deficits in IQ, as measured by the WISC-R when the children were 9 years old. At 8 to 12 years of age, these children exhibited significant impairment in word recognition correlated to dentine lead levels at 6 to 7 years of age (63). Yule et al. (34) also found deficits in school performance such as spelling and reading, in conjunction with decreased WISC-R scores, in 6- to 12-year-old children. Girls but not boys in the Boston prospective study showed reading and spelling difficulties related to levels of dentine lead at 8 years of age (49).

A measure of global failure that has been linked to increased lead burden is academic failure and the need for special education. In the Danish study, Lyngbye et al. (40) found an increased need for special education, especially verbal, in first-graders as a function of increased lead body burden. In a follow-up of the 1979 Boston cross-sectional study, Bellinger et al. (28) assessed school performance in sixth-graders as a function of their first-grade tooth lead levels. They found a tendency toward an increased need for remedial education and grade retention as a function of increased lead level (Table 3). As assessed by a teacher's questionnaire, there was also a marginally significant decrease in IQ and increase in dysfunction in these children based on tooth lead determined 5 years previously. In the prospective Boston study (47), there was a significant negative correlation between blood lead levels at 2 years of age and performance on both the WISC-R and the Kaufman Test of Educational Achievement at 10 years of age.

An interesting end point assessed in the 1979 Boston cross-sectional study (18) was simple reaction time. Children with higher dentine lead levels had longer reaction times than children with lower dentine levels. This same paradigm was used in the London cohort (35), in which blood lead levels were the marker of lead exposure. Since the blood lead levels of some of the Boston children were known, the two studies may be combined to reveal an orderly dose-effect function, with the London children having lower lead body burdens than the Boston cohort (67) (Figure 2). These results have also been replicated in the cohort of Greek children (41). This observation was pursued by Winneke's group in Germany (29-32) by assessing this function on a vigilance task using an automated device. Both visual and auditory stimuli were used with two different signal presentation rates (approximately 1-2 sec). Both false hits and failure to respond correctly were analyzed. In the first study (30,31), there was an indication of an effect on this device in the absence of an effect on the German WISC-R as a function of tooth lead in 9-year-old children. In a subsequent study from two cities in Germany in 6- to 9-year-old children, a robust effect was observed in both groups of children (29) (Figure 3). Effects were greater at the higher signal rate. As in the previous study, there was a greater effect on false responses than on the number of failures to respond. The authors point out that this measure was not influenced by the typical confounders affecting IQ and that, at the blood lead values and sample size of the study, effects would not be expected to be detected on the WISC. These results have been replicated using the same device in a population of Greek children with higher blood lead levels (41). In a study in first-graders in Denmark (39), attention was assessed using a continuous performance task. One of 12 letters appeared on a screen with interstimulus intervals of 1.5 sec. The child was instructed to respond to an H when it was preceded by an S. Performance was marginally associated with dentine lead levels; false responses showed a greater correlation than failure to respond. While the child was performing the task, a trained psychologist assessed the child for on-task behavior. There was a significant correlation between lead body burden and off-task behavior. There was also a dose-related deficit on the WISC-R in this group of children.

**Table 2.** Mothers' and teachers' ratings on behavior scales as a function of dentine lead values (log µg C\(^{-1}\)).

| Ratings                      | 8 years | 9 years |
|------------------------------|---------|---------|
| Maternal ratings             |         |         |
| Activity                     |         |         |
| Restless, overactive         | 0.07    | <0.05   | 0.05    | <0.10  |
| Excitable, impulsive         | 0.07    | <0.05   | 0.05    | <0.10  |
| Constantly fidgeting         | 0.03    | NS      | 0.04    | NS     |
| Always climbing              | 0.07    | <0.05   | 0.04    | NS     |
| Squirm, fidgety              | 0.09    | <0.05   | 0.06    | <0.05  |
| Attention                    |         |         |
| Short attention span        | 0.08    | <0.01   | 0.08    | <0.05  |
| Inattentive, easily distracted|0.08    | <0.01   | 0.05    | <0.10  |
| Cannot settle to tasks      | 0.06    | <0.05   | 0.04    | NS     |
| Total score                  | 0.11    | <0.01   | 0.08    | <0.05  |
| Teacher ratings              |         |         |
| Activity                     |         |         |
| Restless, overactive         | 0.09    | <0.01   | 0.11    | <0.001 |
| Excitable, impulsive         | 0.03    | NS      | 0.10    | <0.001 |
| Squirm, fidgety              | 0.11    | <0.001  | 0.13    | <0.001 |
| Very restless                | 0.10    | <0.001  | 0.13    | <0.001 |
| Attention                    |         |         |
| Inattentive, easily distracted|0.16    | <0.001  | 0.14    | <0.001 |
| Short attention span        | 0.11    | <0.001  | 0.12    | <0.001 |
| Poor concentration           | 0.13    | <0.001  | 0.12    | <0.001 |
| Total score                  | 0.13    | <0.001  | 0.14    | <0.001 |

NS, not significant. *One-tailed test. Data from Fergusson et al. (62).

**Table 3.** Indices of academic failure in sixth-grade children as a function of dentine lead levels at 6 years of age.

| Dentine lead level | Academic aid\(a\) | Grade retention\(b\) |
|--------------------|--------------------|----------------------|
| Low                | 17.0% (8/47)       | 4.3% (2/47)          |
| Midrange           | 18.6% (13/70)      | 11.6% (8/69)         |
| Elevated           | 36.4% (6/22)       | 22.7% (5/22)         |
| Total              | 20.9% (29/139)     | 10.5% (15/138)       |

\(\chi^2(2) = 3.84, p < 0.20, \chi^2(2) = 5.61, p < 0.10.\) Data from Bellinger et al. (28).

**Figure 2.** Simple reaction times at two different delay intervals (3 and 12 sec) over a series of four blocks of trials for children at different average blood lead levels. Data from Needleman (67).
Another variable that has proved sensitive to lead exposure is auditory processing. In the Boston cross-sectional study, performance on the Seashore Rhythm Test and Sentence Repetition Test was adversely affected by increased tooth lead levels (18). The Seashore Rhythm Test requires the subject to discriminate whether pairs of tone sequences of various complexity are alike or different. The Sentence Repetition Test requires the repetition of sentences of increasing length and complexity. This effect on the Seashore Rhythm Test was not replicated in the large Danish cohort with lower blood lead levels (39). Dietrich et al. (59) assessed auditory processing in children from the Cincinnati prospective study at 5 years of age. The child was required to identify words delivered monaurally through an earphone. There was a lead-related deficit in processing ability in the presence of masking noise or when identification of the word was made more difficult by eliminating certain frequencies. These associations were weak after complete covariate adjustment, but the overall pattern was consistently in the direction of poorer performance as a function of increased lead levels. These results were adjusted for individual impairment in hearing thresholds, which may be affected by lead exposure (68).

Some investigators have also assessed motor or visuomotor processes. The most direct assessment was performed on the Cincinnati cohort in which postural sway was assessed at 5.7 years of age (54). Performance with eyes closed was correlated with blood lead levels during the second year of life. The authors interpreted the results as potentially due to proprioceptive or vestibular deficits. Winneke et al. (30) observed an effect on a test of perceptual motor integration in the absence of effects on finger-tapping speed per se. Muñoz et al. (36) reported a lead-related decrease in agility as reported on a teacher’s rating scale in the Mexican cross-sectional study. In the Boston cross-sectional study (18), no effect was found on specific tests of motor function or visual–motor interaction, despite effects on reaction time. In the Boston prospective study, finger-tapping speed at 10 years of age was associated with blood lead history at various ages, although the pegboard test and a standard test of visual–motor integration were largely unaffected (48). On the other hand, performance on the Bender Visual Motor Gestalt test was highly sensitive to lead body burden in first-graders in the Danish study (39); effects were also observed on this test in a cohort of German children (31). This test assesses spatial visualization, hand–eye coordination, fine motor control, and planning and regulation of activity. It therefore measures more than motor performance; for example, deficits in attentional processes could result in poorer performance on this task.

The ability to extract general rules and change response strategy was assessed in children from the prospective Boston cohort at 10 years of age (48) by performance on the Wisconsin Card Sort Test. In this task, correct responses depend on generalizing whether the relevant domain is color, number, or suit. The investigator may change the relevant stimulus class at any time; the subject must infer the rule by whether a series of responses is correct or incorrect. An increase in perseveration for a nonadaptive strategy was significantly related to recently measured but not historic blood lead levels. This was in contrast to scores on the WISC-R, which were most strongly correlated to blood lead levels at 24 months of age.

Summary of Effects in Humans

It is clear that increased body burden of lead results in decreased scores on measures of intelligence from early infancy through school age. This may be reflected in an increased need for special education and even an increase in grade retention (Table 4). Results of teachers’ rating scales on young school-age children are consistent in reporting increased distractibility, short attention span, impulsivity, and inability to follow simple and complex sequences of directions as a function of increased lead body burden. Increased distractibility may also be responsible for increased simple reaction time, as well as failure to respond to correct stimuli in vigilance tasks. Inability to inhibit inappropriate responding is reflected on teachers’ rating scales, as well as by an increased number of incorrect responses on vigilance tasks. Perseveration on the Wisconsin Card Sort Test may also be considered a failure to inhibit inappropriate responding and an inability to change response strategy. Auditory processing appears to be affected, as measured by direct tests of auditory processing ability, as well as by some subtests of general intelligence scales. The effects of lead on motor and visuomotor processes are less clear. Such tests as finger tapping and pegboard seem relatively insensitive, while a test such as the Bender Gestalt may be quite sensitive. It seems likely that at low body burdens of lead, motor ability per se is unaffected, whereas tests that
make high demands on spatial processing and attentional mechanisms are affected. A number of behavioral processes underlying lead-induced deficits in various tasks are proposed above, and more than one mechanism may be responsible for observed effects. Deficits in attention may not be distinguishable from increased distractibility or perseveration, for example, or indeed may be responsible for these deficits. Discriminating the primary mechanisms underlying lead-induced dysfunction would require devising specific experiments to address these issues.

### Animal Studies

The recognition of the vulnerability of children to lead toxicity, resulting in encephalopathy and permanent sequelae, prompted early investigators to focus on development of an animal model of childhood lead encephalopathy. Penschew and Garro (69) produced overt neurotoxicity in sucking pups of rats exposed to a diet containing 4% lead carbonate. In the early 1970s, discussions of lead neurotoxicity in children in the clinical literature used the term hyperactivity. This was apparently translated by experimental investigators as meaning locomotor activity in animals. Early research in both the mouse (70) and the rat (71) revealed increased locomotor activity as a result of high-dose developmental lead exposure. There followed a number of reports through the 1970s and into the 1980s focusing on high-dose developmental exposure in rodents, with locomotion or similar activity measures as the main dependent variable. Results were often contradictory, which is a reflection of the fact that locomotion is not a sensitive or specific indicator of behavioral toxicity produced by lead.

The experimental lead literature has also reflected issues that are inherent in all toxicity testing using animal models. For example, studies using ip injection as the route of lead exposure yielded largely negative results (72), presumably because lead did not reach target organs (73). Lead in high doses produces weight loss; this is particularly true in developmental studies. Early studies frequently failed to control for this effect; however, later studies using lower doses have not been confounded by the behavioral effects of undernutrition per se. Animal studies are typically performed on subjects in which vitamin and mineral intake is optimum, which does not accurately reflect the situation in humans. Lead absorption and tissue retention is affected by such nutrients as calcium, copper, iron, zinc, phosphorus, and vitamins C, D, and E. Dietary constituents may have a profound effect on lead body burden (74), which may make the relationship between dose and measures of body burden between studies extremely variable, even within the same species.

Most of the research on behavioral toxicity of lead in animal models has focused on characterization of the nature of the behavioral effects produced by lead. Initial studies used simple learning tasks or performance on intermittent schedules of reinforcement. Much of the later research focused on complex learning and memory, sometimes taking cues from the results of epidemiologic studies in children. Effects have been observed at blood lead levels similar to those in children; a no observable effect level has not been identified in either children or animals. Research in the last decade has often included analyses to identify the behavioral processes underlying the observed lead-induced behavioral deficits (75).

Much of the earlier work in animal models assessed the effects of high doses of lead on simple learning problems. Studies in which rats were exposed prenatally plus postnatally usually produced positive results on simple discrimination problems (76–78), while rats exposed postnatally or during adulthood generally showed no impairment on simple learning problems even at high doses (79–83). However, even on these simple problems there was some indication that spatial problems might be more sensitive to disruption by lead exposure than simple discrimination tasks (81, 84, 85).

In a study in rats exposed to lead prenatally, Winneke et al. (86) found no effect on a visual discrimination problem that was easy for control rats (vertical vs horizontal stripes), whereas lead-exposed rats were severely impaired on a difficult discrimination (bigger vs smaller circle) (Figure 4). In a study in lambs exposed prenatally and postnatally (87), six visual discrimination problems were presented sequentially. The first five were shape discriminations, while the sixth was a size discrimination problem. Lead-exposed sheep were only impaired on the last problem. This problem was the most difficult problem for control lambs as measured by the number of days required to reach criterion; it also represented a change in relevant stimulus dimension from form to size. These two studies provided a preview of two findings that would be consistently observed in later studies: difficult tasks are more sensitive to lead-induced impairment than easier ones, as are studies in which there is a change in the relevant stimulus–response class.

Lead research using animal models over the past decade and a half has revealed lead-induced impairment at increasingly lower doses and on a wide range of behavioral
tasks. The remainder of this section will largely discuss research in monkeys performed at the University of Wisconsin or at the Health Protection Branch in Canada and in rats at the University of Rochester. Most of this research has focused on postnatal or lifetime exposure, although there have been a few studies on the effects of in utero exposure. Research in these laboratories has used tasks that presumably made demands on behavioral processes other than, or in addition to, those necessary for simple discrimination learning and that have proven more sensitive to behavioral impairment produced by lead.

A strategy adopted early in this research was the introduction of two additional requirements to the visual discrimination task: the requirement for reversal performance on an already-learned discrimination task and the addition of irrelevant cues. In a discrimination reversal task, the formerly correct stimulus becomes the incorrect one, and vice versa. In the nonspatial version of the task, the relevant stimulus dimension is form or color, for example, rather than the position of stimuli. Typically, the subject is required to perform a series of such reversals. This allows the degree of improvement in performance across reversals to be assessed, which is indicative of how quickly the subject learns that the rules of the game change in a predictable pattern. Nonspatial discrimination reversal performance has been found to be affected as a result of postnatal exposure in rhesus monkeys tested during infancy (88) and in cynomolgus monkeys tested as juveniles (89). Monkeys with blood lead levels of 15 or 25 µg/dl during infancy and steady-state levels of 11 or 13 µg/dl were impaired on a series of nonspatial discrimination reversal tasks with irrelevant cues (90). Lead-treated monkeys in this latter study were not impaired on the acquisition of any of the three tasks; they were impaired over the set of reversals on the form discrimination, which was their introduction to a discrimination reversal task, and on the color discrimination with irrelevant cues, their introduction to irrelevant cues. Analysis of the kinds of errors made by treated monkeys revealed that they were attending to irrelevant cues in systematic ways, either responding on or avoiding a particular position or stimulus. This suggests that lead-treated monkeys were being distracted by these irrelevant cues to a greater degree than controls, which may have been responsible at least in part for their poorer performance.

A subsequent study on possible sensitive periods for deleterious effects produced by lead, monkeys were exposed to lead either continuously from birth, during infancy only, or beginning after infancy. Lead levels were about 30 to 35 µg/dl when monkeys were exposed to lead and given access to infant formula, and 19 to 22 µg/dl when monkeys were dosed with lead after withdrawal of infant formula (91). These monkeys were tested as juveniles on the same nonspatial discrimination reversal tasks described above (91). Both the group dosed continuously from birth and the group dosed beginning after infancy were impaired over the course of the reversals in a way similar to that observed in the study discussed above, including increased distractibility by irrelevant cues. The higher exposure levels in this study were reflected in impairment on all three tasks, whereas in the previous study lead-treated monkeys were impaired on only the first two tasks. The group exposed only during infancy was unimpaired on these tasks. In addition, the group dosed continuously from birth was impaired in the acquisition of the task in which irrelevant cues were introduced; there were no other impairments in acquisition.

Deficits on visual discrimination problems have also been observed in the absence of the requirement for reversal performance under some circumstances, such as high blood lead levels or increased task difficulty. Lilienthal et al. (92) studied the effects of developmental lead exposure on learning-set formation for visual discrimination problems in which a series of visual discrimination problems was learned sequentially. Rhesus monkeys were exposed to lead in utero and continuing during infancy at doses sufficient to produce blood lead values up to 50 µg/dl in the lower dose group and 110 µg/dl in the high dose group. When tested as juveniles, both groups of lead-exposed monkeys displayed impaired improvement in performance across trials on any given problem, as well as impaired ability to learn successive problems more quickly as the experiment progressed. Such a deficit represents impairment in the ability to take advantage of previous exposure to a particular set of rules. This deficit is reminiscent of the failure of lead-treated monkeys to improve as quickly as controls over a series of discrimination reversals.

Concurrent discrimination performance was assessed in the group of monkeys described above in which the contribution of the developmental period of exposure to the behavioral toxicity of lead was explored by exposing them to lead continuously from birth, during infancy only, or beginning after infancy (93). Monkeys were required to learn a set of six problems concurrently; after criterion was reached on all six pairs, a second set of six was introduced. All three treated groups learned more slowly than controls, although monkeys dosed during infancy only were less impaired than the other two groups. Treated monkeys were most impaired on the first task, upon introduction of a new

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**Figure 4.** Effect of prenatal exposure to lead in rats on two visual discrimination problems. Lead exposure produced impairment on the difficult but not the easy problem. Data from Winneke et al. (86).
set of contingencies. In addition, all three treated groups exhibited perseverative behavior, responding incorrectly more often than controls at the same position that had been responded on in the previous trial.

Performance on a simple reaction time task, which assesses attentional processes, was assessed in a group of monkeys exposed to lead from birth, with preweaning blood lead values of 50 µg/dl and steady-state blood lead levels of 30 µg/dl, when they were adults (94). Reaction times of lead-treated monkeys did not differ from those of controls over a number of delay values, although treated monkeys exhibited an increased incidence of holding the bar longer than the maximum 15 sec allowed. However, they were able to react as quickly as controls when required to respond as quickly as possible.

Early experiments in rats suggested that performance on spatial tasks may be particularly sensitive to lead-induced impairment. Performance on spatial discrimination reversal tasks, analogous to the nonspatial discrimination reversal tasks already described, has also proved sensitive to disruption by developmental lead exposure. A subset of the monkeys in the Bushnell and Bowman study (95), in which effects on both spatial and nonspatial discrimination reversal had been found during infancy, exhibited impairment on a series of spatial discrimination reversal tasks with irrelevant color cues at 4 years of age, despite the fact that lead exposure had ceased at 1 year and blood lead levels at the time of testing were at control levels. In the group of monkeys with stable blood lead levels of 11 or 13 µg/dl discussed above (90), deficits were also observed on a series of three spatial discrimination reversal tasks, the first one with no irrelevant cues and the last two with irrelevant cues of various types (96). Treated monkeys were impaired relative to controls over the series of reversals in the presence, but not in the absence, of irrelevant stimuli. Moreover, the lower dose group was impaired only during the first task after the introduction of irrelevant cues but not on the second task with irrelevant cues, when irrelevant stimuli were familiar. The higher dose group, on the other hand, was impaired over the series of reversals on both tasks with irrelevant cues, as well as on the acquisition of the tasks with irrelevant stimuli but not on the task without irrelevant cues. As in the nonspatial discrimination reversal task, there was evidence that lead-exposed monkeys were attending to the irrelevant stimuli in systematic ways, suggesting that this behavior was responsible for, or at least contributing to, the impairment in performance. This is also suggested by the fact that lead-treated monkeys were impaired in the presence of but not in the absence of irrelevant stimuli. In the group of monkeys in which the relevance of the developmental period of exposure was being assessed, described above (91), spatial discrimination reversal performance was also assessed (97). Treated monkeys were the most impaired over the series of reversals on the first task after the introduction of irrelevant cues, although performance was impaired on all three tasks. Contrary to the result of the nonspatial discrimination reversal task in which the group dosed only during infancy was unimpaired, all three dose groups were impaired to an equal degree. These data suggest that spatial and nonspatial tasks may be affected differentially depending on the development period of lead exposure.

Another task that has proved sensitive to lead-induced impairment in a number of studies is the delayed spatial alternation task. In this task, the subject is required to alternate responses between two positions; there are no cues to signal which position is correct on any trial. Delays may be introduced between opportunities to respond in order to assess spatial memory. Rhesus monkeys exposed to lead from birth to 1 year of age, with peak blood levels as high as 300 µg/dl and levels of 90 µg/dl for the remainder of the first year of life, were markedly impaired on this task as adults (98). Delays between 0 and 40 sec were assessed within each session; a greater deficit was observed at shorter rather than longer delay values. In our laboratory, increasingly longer delays were introduced over successive sessions in adult monkeys from two studies, those with steady-state blood lead levels of 11 or 13 µg/dl (99) and the groups in which potential sensitive periods were assessed [dosed during infancy only, beginning after infancy, or continuously from birth (100)]. All treated groups in both studies were impaired on the acquisition of the task because of indiscriminate responding on both buttons. Treated monkeys were unimpaired at short delay values and increasingly more impaired as the delay period was lengthened (Figure 5). In the study assessing sensitive periods, all three lead-exposed groups were impaired to an approximately equal degree, as was the case on the spatial version of the discrimination reversal task, which provided further evidence of a lack of sensitive period for lead-induced impairment on spatial tasks. In addition, treated monkeys in the latter study responded more during the delay periods than did controls, indicating failure to inhibit inappropriate responding. Treated monkeys in both studies also displayed marked perseverative behavior, responding on the same position repeatedly (Figure 6).

In a study in rats, improved performance on delayed alternation was observed in young and old animals but not in rats exposed as adults (101). The training procedure consisted of many sessions of a cued alternation procedure, i.e., the rat had only to respond on the lever associated with a cue light as it alternated between positions from trial to trial. The authors interpreted the improved performance of the lead-treated groups as perseveration of alternation behavior as a result of the extensive training procedure. This explanation is consistent with the interpretation of the results of the monkey studies.

Another spatial task that has been used to study attention and spatial memory is the Hamilton Search Task. In this task, a row of boxes is baited with food and then
closed. The monkey lifts the lids to obtain the food. The most efficient performance requires that each box be opened only once, necessitating that the monkey remember which boxes have already been opened. Monkeys exposed postnatally to doses of lead sufficient to produce blood lead levels of approximately 45 or 90 μg/dl or in utero at blood lead levels of 50 μg/dl were impaired in their ability to perform this task at 4 to 5 years of age (98). These results were replicated in another group of monkeys exposed postnatally to higher lead levels and tested at 5 to 6 years of age (102). The effects of lead on the Hamilton Search Task were in general less robust than effects on delayed spatial alternation tested in the same monkeys, despite the fact that both tests presumably assess attention and spatial memory. The greater deficit observed on the delayed alternation task may have been due to the requirement for alternation or adaptation of response pattern, an ability that seems to be globally impaired in lead-exposed monkeys.

A recent assessment of spatial learning and memory in the rat revealed an interesting pattern of errors responsible for the overall poorer performance of lead-treated subjects (103). Rats were exposed to lead in drinking water beginning at weaning and tested beginning at 55 days of age on a task with two components. The repeated acquisition component of the schedule required the rat to learn a new sequence of lever presses every day. In the performance component, the rat was required to perform the same sequence of lever presses every session. Significant impairment of performance was observed on the repeated acquisition component but not on the performance component in lead-exposed rats compared to controls. Analyses of error patterns revealed that the decrease in the percent of correctly completed sequences in lead-treated rats on the repeated acquisition component was the result of specific types of perseverative behavior (Figure 7), providing evidence that perseveration is a consistently observed effect of developmental lead exposure across species.

A delayed matching-to-sample paradigm was used to assess both spatial and nonspatial memory in a group of monkeys with preweaning blood lead values of 50 μg/dl and postweaning values of 30 μg/dl (104). In this task, the monkey was presented with a stimulus of a particular color or position to be remembered. In the nonspatial version of the task, three colors were used as the discriminative stimuli, which were balanced for position and correct choice across trials. For the spatial version three buttons lit with green constituted the response choices. Delays from zero seconds to several minutes were interspersed within each session. Lead-exposed monkeys were impaired on both the spatial and nonspatial versions of this task. They were not impaired in their ability to learn the matching task per se, but were increasingly impaired as the delay between exposure to the sample stimulus and the set of stimuli to be matched was increased (Figure 8). Investigation of the error pattern revealed that for the nonspatial matching task, lead-exposed monkeys responded incorrectly on the position that had been responded on correctly on the previous trial. This type of behavior may be considered to represent perseverative behavior and is reminiscent of the perseverative errors in other groups on delayed alternation. On the other hand, it may be considered to be the result of increased distractibility by irrelevant cues by lead-treated monkeys, similar to the increased attention to irrelevant cues displayed in the discrimination reversal tasks. (These interpretations are not mutually exclusive.) This behavior is at least partly responsible for the apparent deficit in short-term memory observed in lead-treated monkeys on the nonspatial matching-to-sample task, although other mechanisms may also play a part. The lack of interference from previous trials on the spatial version of the task, however, may indicate a pure deficit in spatial short-term memory on that task.

Intermittent schedules of reinforcement have been used rather extensively in the study of the developmental effects of lead exposure. Unlike the earlier studies using
locomotor activity as the end point and in which results varied considerably between studies, the congruence between studies assessing performance on intermittent schedules has been remarkably good. A schedule that has proven sensitive to the effects of developmental lead exposure is the fixed interval (FI) schedule. Although this schedule requires the subject to make only one response at the end of a specified (uncued) interval, FI performance is typically characterized by a gradually accelerating rate of response terminating in reinforcement. On this schedule, blood lead levels between about 10 and 30 μg/dl resulted in a dose-dependent increase in rate of response in both the rat and monkey (105-112). In general, other measures of FI performance were not affected. However, monkeys with blood lead levels during infancy above 100 μg/dl exhibited differences in the temporal distribution of responses across the interval compared to controls when tested as adults (113). In addition, the study in monkeys in which sensitive periods were assessed revealed that exposure to lead only during infancy was sufficient to produce an increase in response rate during adulthood and that exposure beginning after infancy also produced an increased response rate (107).

The fixed ratio (FR) schedule requires the subject to emit a number of responses in order to be reinforced and typically generates a high response rate. This schedule appears to be less sensitive to lead-induced changes than is the FI. Low doses of lead sometimes resulted in increased rates of response, often transiently, while higher doses decreased response rates. This was true for both rats (106,110,114) and monkeys (107,108). When a time-out (TO) period was included in the assessment of performance on intermittent schedules (during which responses had no scheduled consequences), lead exposure resulted in increased TO rates of response (107,111).

Effects of lead have also been examined on schedules assessing temporal discrimination. Cory-Slechta et al. (115) assessed response duration performance on a task in which rats exposed to lead beginning at weaning were required to depress a lever for at least 3 sec to be reinforced. Lead-treated rats depressed the lever for a shorter time than controls. In addition, introduction of a tone signaling the 3-sec interval was effective in improving performance of control but not treated rats. Differential reinforcement of low rate (DRL) performance was assessed in the groups of monkeys in which increased rates of response on the FI had been observed. The DRL schedule required the monkey to space consecutive responses at least 30 sec apart to be reinforced. Monkeys with peak blood lead levels of 100 μg/dl and steady-state levels of 40 μg/dl exhibited a higher number of nonreinforced responses, a lower number of reinforced responses, and a shorter average time between responses over the course of the experiment than control monkeys (113). Performance on this schedule was also examined in the groups of monkeys having steady-state lead levels of 11 or 13 μg/dl (116). Lead-treated monkeys were able to perform the DRL task in a way that was indistinguishable from controls. However, they learned the task at a slower rate, as measured by the increment in reinforced responses and decrement in nonreinforced responses over the course of the daily sessions. Increased rates of response (117) and increased frequencies of responses emitted close together (short interresponse times) (118) have also been reported in rats performing on a DRL schedule.

The increased rate of response on the FI may be considered in some sense to represent failure to inhibit inappropriate responding, since treated animals made more responses than controls without increasing reinforcement density, i.e., their behavior was less efficient. The increase in the rate of responding may also be considered to represent perseveration. The higher rate of response on the DRL schedule, which actually resulted in fewer reinforcements, clearly represents a failure to inhibit inappropriate responding and may reflect the fact that lead-treated animals are less able to use internal cues for timing. This latter interpretation is also suggested by the poorer performance of lead-treated rats on the response duration task.

**Summary of Effects in Animals**

There are a number of generalizations that may be extracted from this overview of the more recent experimental literature with regard to the effects of developmental lead exposure. Lead-exposed animals exhibit impairment on a wide variety of tasks designed to assess learning and memory. Exploration of the behavioral processes responsible for these global effects have revealed a number of commonalities that may explain the observed lead-induced behavioral deficits; these suggested explanations are not necessarily mutually exclusive (Table 5).

- It is clear that performance on more difficult tasks is more sensitive to disruption by lead than performance on easy ones. Effects were observed on difficult visual discrimination problems but not on easy ones in rats and lambs, as well as on concurrent discrimination performance in monkeys unimpaired on visual discrimination problems per se. Both spatial and nonspatial discrimination reversal performance and performance in the presence of irrelevant stimuli were more affected than simple acquisition.

- Lead-treated animals are also more distractible by irrelevant stimuli, as evidenced by their increased attention to form, color, and position cues on the discrimination reversal task. Lead-treated animals also responded on positions that were previously correct on nonspatial tasks, which may be considered indicative of increased distractibility. Treated monkeys also failed to release the bar within the specified time period on a simple reaction-time task.

- Lead exposure results in marked perseveration on a number of tasks. Lead-treated animals show perseveration for position on spatial tasks such as delayed alternation and repeated acquisition, as well as perseveration on an incorrect (irrelevant) position on the concurrent discrimination and nonspatial delayed matching-to-sample tasks.

- Lead exposure results in an inability to inhibit inappropriate responding. Increased response rate on the FI may be considered indicative of this, since a higher rate does not result in increased reinforcement density. Increased rate on the DRL, which actually results in fewer reinforcements, certainly reflects an inability to inhibit responses. Inappropriate responding was also manifested by increased TO rates of response on intermittent schedules and increased delay responding on delayed alternation at higher doses of lead.

- Lead-treated animals have difficulty changing response strategy. The types of perseverative behavior observed on both the delayed alternation and repeated acquisition tasks may be interpreted in this way. The deficits in acquisition on the discrimination reversal tasks when the relevant stimulus class was changed (e.g., from form to color) also reflect this phenomenon. Treated animals also were more impaired at the beginning of new tasks than when the task was familiar; this was the case on the spatial and
Table 5. Summary of types of behavioral deficits in animals.

| Deficits                        | Tasks                                       | References          |
|---------------------------------|---------------------------------------------|---------------------|
| Easy less sensitive than difficult | Easy vs hard visual discrimination          | (85)                |
|                                 | Rat                                         |                     |
|                                 | Lambs                                       | (96)                |
|                                 | Concurrent discrimination, monkey           | (92)                |
|                                 | Acquisition vs reversal, visual discrimination, monkey | (88-91,95)         |
|                                 | No irrelevant stimuli vs irrelevant stimuli, visual discrimination, monkey | (90,91,95,96)     |
|                                 | Longer vs shorter delays                    |                     |
|                                 | Delayed alternation                         | (99,100)           |
|                                 | Matching-to-sample                          | (104)               |
| Increased distractibility, short attention span | Increased attention to irrelevant cues | (80,91)            |
|                                 | Nonspatial discrimination reversal, monkey  | (96,97)            |
|                                 | Spatial discrimination reversal, monkey      | (104)               |
|                                 | Attention to irrelevant position, monkey    |                     |
|                                 | Nonspatial matching-to-sample               |                     |
|                                 | Nonspatial discrimination reversal          | (90,97)            |
|                                 | Hold bar too long, reaction time, monkey    | (94)                |
| Perseveration for position      | Delayed alternation, monkey                 | (99,100)           |
|                                 | Delayed alternation, rat                    | (101)               |
|                                 | Repeated acquisition, rat                   | (103)               |
|                                 | Concurrent discrimination, monkey           | (93)                |
|                                 | Nonspatial matching-to-sample, monkey       | (104)               |
| Inability to inhibit inappropriate responses | Increased rate, Fl, monkey | (107-109,111)      |
|                                 | Increased rate, Fl, rat                     | (105,106,110,112)  |
|                                 | Increased rate, TO, monkey                  | (107,111)          |
|                                 | Increased rate, decreased reinforcements    | (113,116)          |
|                                 | DRL, monkey                                 | (117,118)          |
|                                 | DRL, rat                                    |                     |
|                                 | Increased delay responses, delayed alternation | (100)            |
| Deficits in changing response strategy | Repeated acquisition, rat                  | (103)               |
|                                 | Delayed alternation, monkey                 | (99,100,102)       |
|                                 | Delayed alternation, rat                    | (101)               |
|                                 | Concurrent discrimination, monkey           | (93)                |
|                                 | Change in stimulus class, lamb              | (87)                |
|                                 | Change in relevant stimulus class,          |                     |
|                                 | discrimination reversal, monkey             | (90,91,96,100)     |
| Deficits in acquisition of repeated learning | Learning-set, monkey                      | (92)                |
|                                 | Discrimination reversal, monkey             | (88,90,91,95,96,100) |
|                                 | Concurrent discrimination, monkey           | (93)                |

nonspatial discrimination reversal tasks, the concurrent discrimination task, and the delayed alternation task.

- Lead-treated animals may be impaired in the acquisition of general rules as opposed to the acquisition of a single task. Lead-treated animals do not improve over the course of a series of similar tasks as quickly as controls do, as reflected in performance on learning-set, discrimination reversal, and concurrent discrimination tasks.

Comparison of Human and Animal Data

While the methods used to identify the types of behavioral impairment produced by lead have in many cases differed between the animal and the human literature, both literatures nonetheless have identified common deficits in global functioning produced by developmental lead exposure. While there is no direct parallel to IQ tests for monkeys or rats, the fact that deficits have been observed as a result of lead exposure in a number of species on a wide variety of tests that assess attention/learning/memory suggests that the end result of lead exposure in animals is a global deficit in functioning, just as it is in children. Data on both children and animals suggest that spatial processing is particularly susceptible to impairment produced by lead. In addition, there is evidence of commonality in the behavioral processes that may underlie lead-induced behavioral impairment. Increased distractibility, inability to inhibit inappropriate responding, perseveration, and inability to change response strategy are common themes that may be extracted from both literatures. While deficits in auditory processing have been detected in a number of studies in humans, experimental researchers in general have not explored this domain [although physiological data suggest impaired auditory processing in monkeys (119)].

Data from studies in monkeys suggest that the pattern of lead exposure during development may affect the pattern of behavioral impairment; in particular, monkeys exposed only during infancy exhibited impaired spatial but not nonspatial abilities, while ongoing exposure beginning at birth or after infancy resulted in more global impairment. It is also apparent from the animal literature that the types of impairment observed are dose dependent, with impairment in certain behavioral domains not being manifested at lower blood lead levels or present only under certain circumstances. Results from the human prospective studies in which impairment in different functions was related to blood lead levels at different ages are also suggestive. It therefore may be naive to assume that the pattern of effects would or should be identical between epidemiologic studies.

In summary, the effects of developmental lead exposure have been extensively characterized by both epidemiologic and experimental research. Moreover, both approaches have identified underlying behavioral processes that contribute to these deficits. These bodies of data are remarkably consistent both internally and across disciplines. The challenge for the future is to identify strategies for attenuating these effects, such as devising alternative learning programs that compensate for the underlying behavioral deficits resulting from lead exposure.

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