Comparative Toxicity and Tissue Distribution of Lead Acetate in Weanling and Adult Rats

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The relative toxicity of low doses of lead acetate provided steadily in drinking water or by mouth once per week was studied in weanling and adult rats. Free erythrocyte protoporphyrin and urinary δ-aminolevulinic acid levels were measured, as well as lead levels in blood and kidney. The accumulation of lead in brain tissue and in bone (femur) was measured to determine the effect of age and schedule of administration on tissue distribution and retention of lead. Total intakes of lead during the 60-week experimental period were: weanling and adult rats exposed to drinking water supplemented with 200 μg of lead acetate/ml: 127 ± 10 mg and 160 ± 16 mg, respectively; weanling and adult rats dosed with lead acetate orally once per week: 132 mg and 161 mg, respectively. Increased toxic effects of lead in the weanling animals were apparent in most of the parameters measured (urinary δ-aminolevulinic acid and blood, brain, femur and kidney lead levels). This pattern was observed in weanling rats exposed to lead steadily through drinking water or dosed orally with an equivalent quantity of lead once per week. Lead levels in blood were highly correlated with the accumulation of lead in brain, femur, and kidney tissue in both groups of weanling rats. In adult rats, significant correlations between blood lead and kidney lead and between blood lead and femur lead were found only in the rats receiving lead steadily in drinking water.

Introduction

The higher incidence of acute lead intoxication among children than among adults has been recognized for a number of years (1, 2). Children are exposed to higher levels of lead than are adults because of behavioral patterns (for example, characteristic mouthing of objects, pica). In addition, exposures to lead from sources such as air, food, and water are higher on a per kilogram of body weight basis for children than for adults. Although a portion of the elevated incidence of lead toxicity is due to excessive lead exposure, recent studies indicate that there are also significant age-related differences in the physiological handling of lead. These include age-specific variations in absorption, retention, and tissue distribution of lead. There is also a higher prevalence among children than adults of specific nutritional deficiencies (for example, those of calcium and iron) known to increase susceptibility to lead toxicity (3-7).

Defining the metabolic, physiological and behavioral characteristics that contribute to the increased susceptibility of the young to lead toxicity (1, 8) may be valuable in the prevention of lead poisoning. One emphasis of such research is to define factors that influence the sensitivity to lead of the rapidly developing nervous system of the young. The identification of conditions of lead exposure which may damage the central nervous system while indicators used for screening (for example, blood lead) remain at levels thought to be safe is of particular importance. Although the effects of lead on the central nervous system have been reviewed (9-12), the level of lead exposure at which detrimental effects begin has not yet been determined (13).
In spite of the widespread use of animal model systems (14-18), few data are available that relate equivalent quantities and schedules of lead exposure to differences in tissue lead levels in young and adult animals. One purpose of the present study was to determine the degree to which blood lead levels are predictive of tissue lead levels in young and adult rats exposed to lead on different dosage schedules. Another purpose was to determine the effects of age on tissue retention and distribution of lead as shown by accumulation of lead in brain and bone.

Materials and Methods

Animals

Weanling and adult male albino Sprague-Dawley rats (Blue Spruce Farms, Altamont, N.Y.) were divided into groups and fed a nutritionally adequate, purified diet (AIN-76, 19) (prepared by Zeigler Brothers, Gardners, Pa.) for 6 weeks.

Exposure to Lead

One group each of weanling and adult rats served as the controls (group I). One group of weanling and one group of adult rats received a drinking solution containing 200 µg of lead/ml (as lead acetate) (group II). Water consumption in these groups was measured throughout the experimental period, and lead intakes were calculated on the basis of milligrams of lead/kilogram of body weight/week. A single oral dose of lead acetate in water equivalent to that consumed by rats receiving lead acetate-supplemented drinking water was administered to each animal in the third groups of weanling and adult rats on a weekly basis (group III). All rats were housed individually in suspended stainless steel cages; food and water were supplied ad libitum.

Twenty-four hour urine collections for the determination of δ-aminolevulinic acid (δ-ALA) were made during the fifth week of the study. Urine was collected in foil-covered 50-ml Erlenmeyer flasks containing 0.25 ml of glacial acetic acid. Samples were stored in the dark at 5°C for one week before assay. At sacrifice, rats were anesthetized with Nembutal (50 mg/kg of body weight) and blood was collected by cardiac puncture. Vacutainers from lots previously established as being contaminated with not more than 0.10 µg of lead (Environmental Sciences Associates, Bedford, Mass.) were used for collection of blood samples for lead analysis. Kidneys, femurs, and brains were obtained by dissection, freed of adhering tissues, and fresh weights were recorded.

Analytical Methods

Urinary δ-ALA was determined by the method of Davis and Andelman (20). Free erythrocye protoporphyrins (FEP) were measured by using the method of Piomelli (21). Complete blood counts and differential white cell determinations were performed by Metpath Laboratories, Cincinnati, Ohio. Lead was determined in blood, brain, femur, and kidney samples using anodic stripping voltammetry (Environmental Sciences Associates, Bedford, Mass.).

Results

Adult rats consumed 25% more of the lead-supplemented water during the 6-week experimental period than did the weanling rats (799 ± 78 ml for group II adults versus 636 ± 50 ml for group II weanlings; p < 0.005). Total intake of lead by group II adult rats was 159.8 ± 15.5 mg compared to 127.1 ± 9.9 mg for group II weanling rats (p < 0.005). Exposure to lead acetate, calculated on the basis of milligrams of lead/kg/week, was considerably greater in the weanling rats (Tables 1 and 2). Growth was not affected by the level of lead exposure which occurred during the study.

Summaries of weight gain, hematological values and tissue lead concentrations for weanling and adult rats exposed to lead acetate are shown in Tables 1 and 2, respectively. Percent coefficients of variation are also listed. Levels of lead in blood and brain of both weanling and adult control groups were substantially less than among lead-dosed animals. The ranges of blood lead levels for both weanling and adult control rats were < 3-13 µg/dl. Blood lead values of < 3 µg/dl were obtained for 12 of 17 (71%) weanling control rats and 10 of 16 (63%) adult control rats. Ranges of brain lead levels for weanling and adult control rats were < 0.007-0.052 µg/g and < 0.005-0.047 µg/g, respectively. Five of 18 (28%) weanling control brain lead concentrations were < 0.007 µg/g, and 13% (2 of 16) of adult control brain lead concentrations were < 0.006 µg/g. A mean value could not be computed for three of these four measurements.

Coefficients of variation, representing variation among individual rats within each group, were large for some of the parameters measured: 37-102% for brain lead values, 30-97% for kidney lead, 21-45% for femur lead, and 29-55% for δ-ALA. Percent coefficients of variation were 6-28 and 5-15 for
Table 1. Lead intake, weight gain, hematological values and tissue lead concentrations in weanling rats exposed to lead acetate.*

| Parameter                          | Group I, Control (% CV) | Group II, Pb in water (% CV) | Group III, Pb once/week (% CV) |
|------------------------------------|-------------------------|-------------------------------|---------------------------------|
| Lead intake, mg/kg/week            |                         |                               |                                 |
| Lead intake, mg/kg/week            | –                       | 134 ± 22                      | 144 ± 16                        |
|                                    | 2                       | 115 ± 9                       | 117 ± 13                        |
|                                    | 3                       | 104 ± 10                      | 104 ± 15                        |
|                                    | 4                       | 100 ± 0                       | 102 ± 14                        |
|                                    | 5                       | 98 ± 11                       | 101 ± 12                        |
|                                    | 6                       | 83 ± 22                       | 85 ± 11                         |
| Initial body weight, g             | 78 ± 10 (10)            | 79 ± 8 (10)                   | 79 ± 9 (12)                     |
| Final body weight, g               | 342 ± 28 (28)           | 337 ± 21 (6)                  | 325 ± 39 (12)                   |
| Brain weight, g                    | 1.99 ± 0.20 (10)        | 1.92 ± 0.09 (5)               | 1.87 ± 0.12 (6)                 |
| Femur weight, g                    | 0.86 ± 0.06 (7)         | 0.80 ± 0.09 (11)              | 0.80 ± 0.08 (10)                |
| Kidney weight, g                   | 1.43 ± 0.15 (11)        | 1.56 ± 0.18 (12)              | 1.52 ± 0.18 (12)                |
| Hemoglobin, g/dl                   | 15.2 ± 1.6 (10)         | 14.1 ± 2.1 (15)               | 14.7 ± 1.1 (8)                  |
| Hematocrit, %                      | 43.0 ± 4.7 (11)         | 41.7 ± 6.1 (15)               | 42.3 ± 3.4 (8)                  |
| FEP, µg/dl                         | 26 ± 9 (34)             | 39 ± 10 (26)                  | 35 ± 11 (32)                    |
| δ-ALA, µg/24 hr                    | 109 ± 32 (29)           | 261 ± 143 (55)                | 245 ± 132 (54)                  |
| Blood lead, µg/dl                  | b                       | 33 ± 12 (36)                  | 21 ± 7 (32)                     |
| Brain lead, µg/g                   | c                       | 0.946 ± 0.964 (102)           | 0.358 ± 0.138 (39)              |
| Kidney lead, µg/g                  | 0.145 ± 0.138 (97)      | 10.78 ± 7.32 (68)             | 4.67 ± 1.52 (33)                |
| Femur lead, µg/g                   | 7 ± 2 (21)              | 171 ± 78 (45)                 | 95 ± 28 (30)                    |

*Values represent means ± SD. n = 17 animals (group I), 15 animals (groups II, III). % CV: Percent coefficient of variation.

Table 2. Lead intake, weight gain, hematological values and tissue lead concentrations in adult rats exposed to lead acetate.*

| Parameter                          | Group I, Control (% CV) | Group II, Pb in water (% CV) | Group III, Pb once/week (% CV) |
|------------------------------------|-------------------------|-------------------------------|---------------------------------|
| Lead intake, mg/kg/week            |                         |                               |                                 |
| Lead intake, mg/kg/week            | –                       | 63 ± 8                        | 62 ± 3                          |
|                                    | 2                       | 72 ± 14                       | 67 ± 4                          |
|                                    | 3                       | 68 ± 16                       | 68 ± 4                          |
|                                    | 4                       | 64 ± 13                       | 64 ± 4                          |
|                                    | 5                       | 63 ± 7                        | 63 ± 4                          |
|                                    | 6                       | 59 ± 9                        | 59 ± 4                          |
| Initial body weight, g             | 328 ± 25 (8)            | 329 ± 21 (6)                  | 338 ± 19 (6)                    |
| Final body weight, g               | 458 ± 33 (7)            | 468 ± 31 (7)                  | 475 ± 35 (7)                    |
| Brain weight, g                    | 2.16 ± 0.10 (5)         | 2.03 ± 0.14 (7)               | 2.12 ± 0.15 (7)                 |
| Femur weight, g                    | 1.11 ± 0.09 (8)         | 1.12 ± 0.09 (8)               | 1.17 ± 0.07 (6)                 |
| Kidney weight, g                   | 1.66 ± 0.17 (10)        | 1.96 ± 0.17 (9)               | 1.83 ± 0.20 (11)                |
| Hemoglobin, g/dl                   | 15.5 ± 1.4 (9)          | 14.7 ± 0.8 (5)                | 14.9 ± 0.9 (6)                  |
| Hematocrit, %                      | 45.0 ± 4.6 (10)         | 41.5 ± 3.0 (7)                | 42.6 ± 3.2 (8)                  |
| FEP, µg/dl                         | 37 ± 11 (31)            | 43 ± 8 (20)                   | 38 ± 12 (31)                    |
| δ-ALA, µg/24 hr                    | 80 ± 4 (30)             | 159 ± 71 (45)                 | 117 ± 37 (32)                   |
| Blood lead, µg/dl                  | b                       | 24 ± 4 (18)                   | 15 ± 5 (33)                     |
| Brain lead, µg/g                   | 0.020 ± 0.014c (70)     | 0.340 ± 0.127 (37)            | 0.258 ± 0.139 (55)              |
| Kidney lead, µg/g                  | 0.075 ± 0.048 (71)      | 6.56 ± 1.92 (30)              | 2.75 ± 0.81 (30)                |
| Femur lead, µg/g                   | 8 ± 2 (21)              | 59 ± 14 (23)                  | 96 ± 15 (42)                    |

*Values represent means ± SD. n = 16 animals (group I), 15 animals (groups II, III). % CV: Percent coefficient of variation.

Despite the magnitude of some of the coefficients of variation, the results from an analysis of variance (22) showed a significant different (α = 0.05) among treatments for both weanling and adult lead measurements. A summary of the results of the univariate analysis of variance is shown in Table 3.
Table 3. Summary of Duncan’s test from the univariate analysis of variance.

| Parameter                  | Weanling rats | Adult rats |
|----------------------------|---------------|------------|
|                            | Control       | Lead once/week | Lead daily in water | Control       | Lead once/week | Lead daily in water |
| Initial body wt, g         | 78            | 79          | 79          | 328           | 338          | 329          |
| Final body wt, g           | 342           | 325         | 337         | 458           | 475          | 468          |
| Brain wt, g                | 1.99          | 1.87<sup>a</sup> | 1.92      | 2.16          | 2.12         | 2.03<sup>a</sup> |
| Femur wt, g                | 0.86          | 0.80        | 0.80        | 1.11          | 1.17         | 1.12         |
| Kidney wt, g               | 1.43          | 1.52        | 1.56        | 1.66          | 1.83<sup>a</sup> | 1.96<sup>a</sup> |
| Hemoglobin, g/dl           | 15.2          | 14.7        | 14.1        | 15.5          | 14.9         | 14.7         |
| Hematocrit, %              | 43.0          | 42.3        | 41.7        | 45.0          | 42.6         | 41.5<sup>a</sup> |
| FEP, µg/dl                 | 26            | 35<sup>a</sup> | 39<sup>a</sup> | 37            | 38          | 43          |
| δ-ALA, µg/24 hr            | 109           | 245<sup>a</sup> | 261<sup>a</sup> | 80            | 117<sup>a</sup> | 159<sup>a,b</sup> |
| Blood lead, µg/dl          | c             | 21<sup>a</sup> | 33<sup>a,b</sup> | c             | 15<sup>a</sup> | 24<sup>a,b</sup> |
| Brain lead, µg/g           | c             | 0.358<sup>a</sup> | 0.946<sup>a,b</sup> | 0.020         | 0.253<sup>a</sup> | 0.349<sup>a,b</sup> |
| Kidney lead, µg/g          | 0.143         | 4.67<sup>a</sup> | 10.79<sup>a,b</sup> | 0.07          | 2.75<sup>a</sup> | 6.50<sup>a,b</sup> |
| Femur lead, µg/g           | 7             | 95<sup>a</sup> | 171<sup>a,b</sup> | 8             | 36<sup>a</sup> | 59<sup>a,b</sup> |

<sup>a</sup>Significantly different from control at α = 0.05 level.

<sup>b</sup>Significantly different from value for other treatment group (within same age group) at α = 0.05 level.

<sup>c</sup>Means could not be calculated for these values; more than 20% of values < x.

Differences among mean values were determined by Duncan’s test (23). In general, daily exposure to lead via drinking water resulted in the highest lead content in blood, brain, kidney, and femur for both weanling and adult rats. Values resulting from both lead treatments were significantly different from corresponding values in the untreated control groups. This was true despite the variations noted above and the slight differences in brain weights (weanlings, adults) and kidney weights (adults) (Table 3). A significant reduction in hematocrit was observed only in adult rats exposed to lead daily via drinking water. FEP levels were significantly elevated only in lead-exposed weanling rats; δ-ALA levels were elevated in all four groups of lead-exposed rats.

The hypothesis that the two schedules of lead exposure were equivalent was also tested using a multivariate analysis of variance (MANOVA) (24). Five variables (blood, brain, kidney and femur lead and urinary δ-ALA) were included in the analysis. The means were significant (α = 0.05), confirming the univariate analysis.

The relationships between blood lead values and concentrations of lead in brain, femur, and kidney are shown in Figures 1-3, respectively. Correlations among the lead variables were examined by computing linear regressions (22) of blood lead versus brain, femur and kidney lead levels for the two schedules of lead exposure and for the two age groups. The correlation coefficients, slopes, standard deviations of slopes, and an F-ratio resulting from the regression analyses are presented in Table 4. Significant F ratios, indicative of a linear relationship, were found in both weanling groups for all parameters examined. In adult rats, significant correlations were found between blood lead-femur lead and blood lead-kidney lead in rats receiving lead daily via drinking water, and between blood

![Figure 3. Relationship between blood lead and kidney lead levels in weanling (---) and adult (●) rats exposed to lead acetate in drinking water (left panel) or by a single weekly oral administration (right panel). Linear correlation coefficients and results of regression analyses are presented in Table 4.](image)
Figure 2. Relationship between blood lead and femur lead levels in weanling (—○) and adult (—●) rats exposed to lead acetate in drinking water (left panel) or by a single weekly oral administration (right panel). Linear correlation coefficients and results of regression analyses are presented in Table 4.

Figure 3. Relationship between blood lead and kidney lead levels in weanling (—○) and adult (—●) rats exposed to lead acetate in drinking water (left panel) or by a single weekly oral administration (right panel). Linear correlation coefficients and results of regression analyses are presented in Table 4.

Table 4. Summary of regression analyses for the dependence of tissue lead concentration on blood lead concentration in weanling and adult rats exposed to lead acetate in water.

| Relationship                  | Group/age                | Correlation coefficient r | Slope     | Standard deviation of slope | F-ratio<sup>a</sup> | t-value<sup>b</sup> |
|-------------------------------|--------------------------|---------------------------|-----------|----------------------------|----------------------|---------------------|
| Brain lead-blood lead (Fig. 1)| Lead in water            |                           |           |                           |                      |                     |
|                               | Weanlings                | 0.699                     | 0.0566    | 0.0161                     | 12.42<sup>c</sup>    | 3.96<sup>c</sup>    |
|                               | Adults                   | 0.229                     | 0.0066    | 0.0078                     | 0.72                 |                     |
|                               | Lead once per week       |                           |           |                           |                      |                     |
|                               | Weanlings                | 0.796                     | 0.0161    | 0.0034                     | 22.46<sup>c</sup>    |                     |
|                               | Adults                   | -0.037                    | -0.0010   | 0.0079                     | 0.02                 |                     |
| Femur lead-blood lead (Fig. 2)| Lead in water            |                           |           |                           |                      |                     |
|                               | Weanlings                | 0.910                     | 5.923     | 0.7490                     | 62.53<sup>c</sup>    | 5.67<sup>c</sup>    |
|                               | Adults                   | 0.627                     | 1.919     | 0.6609                     | 8.43<sup>c</sup>     |                     |
|                               | Lead once per week       |                           |           |                           |                      |                     |
|                               | Weanlings                | 0.867                     | 3.558     | 0.5679                     | 39.26<sup>c</sup>    | 4.94<sup>c</sup>    |
|                               | Adults                   | -0.016                    | -0.050    | 0.8618                     | 0.003                |                     |
| Kidney lead-blood lead (Fig. 3)| Lead in water            |                           |           |                           |                      |                     |
|                               | Weanlings                | 0.585                     | 0.332     | 0.1279                     | 6.75<sup>c</sup>     | 1.29                |
|                               | Adults                   | 0.432                     | 0.181     | 0.1051                     | 2.98<sup>c</sup>     |                     |
|                               | Lead once per week       |                           |           |                           |                      |                     |
|                               | Weanlings                | 0.509                     | 0.109     | 0.0512                     | 4.54<sup>c</sup>     |                     |
|                               | Adults                   | 0.024                     | 0.004     | 0.0462                     | 0.01<sup>c</sup>     |                     |

<sup>a</sup>A significant F-ratio indicates that the null hypothesis (H<sub>0</sub>: slope = 0) is rejected.

<sup>b</sup>t-Tests were performed to examine the hypothesis that estimates of slopes of weanling and adult values are equal.

<sup>c</sup>Significant at α = 0.05 level.
lead-kidney lead in rats receiving lead once per week. Blood lead values of weanling animals were much more likely to be indicative of high lead levels in brain, femur, and kidney than were adult blood lead levels. The t-test values (Table 4) confirm this observation, indicating that the slopes for the weanling groups were significantly higher than those for the adult estimates in five of the six parameters examined. t-Test values were also calculated for comparisons of slopes of regression lines obtained in weanling rats exposed to lead on a daily basis or by weekly oral administration. The slopes were significantly different, indicating that blood lead levels are more likely to be indicative of high body burdens of lead when exposure is constant than when exposure is intermittent. t-Values for comparisons of slopes between the two weanling groups were: blood lead versus brain lead, \( t = 3.49 \); blood lead versus femur lead, \( t = 5.35 \); blood lead versus kidney lead, \( t = 2.29 \). All values were significant at the \( \alpha = 0.05 \) level.

Discussion

Young animals are more sensitive to the toxic effects of lead than juvenile or adult animals (3, 25-27). The increased susceptibility of young animals is due in part to their increased capacity to absorb lead from the gastrointestinal tract (3, 4, 27-29). Such observations have been extended to include young children (1, 5, 10, 30, 31). In addition to increased lead retention, age-related differences in tissue distribution also contribute to the enhanced sensitivity of the young to lead poisoning. In the present study, comparison of total tissue lead levels with the amount of lead ingested indicated that the femurs of weanling rats exposed to lead acetate in drinking water contained 0.11% (mean value) of the ingested dose. Femurs of the comparable group of adult rats retained 0.04% (mean value) of the ingested lead. The more rapid formation of bone in young animals and the incorporation of lead into the newly formed bone contribute to this increased retention. The same pattern was observed for accumulation of lead in brain, although absolute brain lead levels were considerably lower than femur or kidney lead levels. Mean brain lead retention as percent of ingested dose was approximately 3-fold higher in weanling rats receiving lead in drinking water (0.0014%) than in the corresponding group of adult rats (0.0004%).

The results of the present study indicate that when immature and adult rats consume drinking water containing the same concentration of lead, younger animals are exposed to considerably greater quantities of lead relative to body weight than are the older animals. Although the weanling rats in the present study ingested less lead (127-132 mg) than did the adult animals (160-161 mg), the increased toxic effects of lead in the younger animals are apparent from the data presented in Tables 3 and 4. Accumulation of lead in the brain and femur of the immature animals is especially pronounced. When an equivalent dose of lead was administered to young or adult animals on a weekly basis, a similar pattern was observed, with the manifestations of lead toxicity being more pronounced in the younger animals.

In young animals exposed to lead, the hematopoietic and nervous systems appear to be the critical target organs (i.e., those organs in which the toxic metal first accumulates to an extent which leads to adverse effects on the health of the whole animal). In the weanling rats in the present study, both FEP and urinary δ-ALA excretion increased in response to lead exposure. The magnitude of the increase in urinary δ-ALA excretion was greater than that for FEP. However, in adult animals, FEP levels did not change significantly, but urinary excretion of δ-ALA increased in response to lead exposure.

Inhibition by lead of δ-aminolevulinate dehydratase (ALA dehydratase) activity in various tissues results in increased urinary excretion of the substrate δ-ALA. Among the parameters examined in the present study, urinary ALA excretion was the most sensitive indicator of lead effect in both weanling and adult rats. Mean blood lead values of 15 μg/dl in adult rats and 21 μg/dl in weanling rats were associated with significant increases in ALA excretion. We observed in the present study that urinary ALA excretion was higher in both groups of lead-exposed weanling rats than in the corresponding groups of adult rats (Table 3). Our results do not reveal if ALA dehydratase activity is differentially inhibited in various tissues of weanling and adult rats. In vitro comparison of ALA dehydratase activity in tissues of normal and lead-exposed rabbits reported by Gibson and Goldberg (32) indicated that the activity of the enzyme was reduced in brain, liver, kidney and bone marrow of the lead-treated animals. In the lead-treated rabbits, the enzymes in brain and liver were more sensitive to inhibition by lead than were those in kidney and bone marrow. The ALA dehydratase activity of brain appears to be especially sensitive to lead. A 42% inhibition of ALA dehydratase activity occurred when the mean brain lead level was 2.3 μg/g, while a 50% reduction in the activity of the kidney enzyme occurred with a mean tissue lead level of 29.9 μg/g (32).

In the present study, we observed that free
erythrocyte protoporphyrins were significantly elevated only in the lead-exposed weaning rats (Table 3). As noted in Tables 1 and 2, the weanling rats were exposed to higher levels of lead on a milligram/kilogram/week basis than were the adult rats. The lowest mean brain lead value at which elevations in FEP were measured was 21 μg/dl in the group of weanling animals exposed to lead acetate once per week. FEP levels in adult rats receiving lead acetate daily in drinking water (mean blood lead concentration 24 μg/dl) were not significantly elevated. These observations suggest that the blood lead concentration associated with a significant elevation in FEP is lower for weanling rats than for adult animals. A corresponding age-related (children versus adults) difference in the blood lead level at which elevations in FEP are observed has also been reported in human studies (6).

Considerable information has been obtained in experimental animals on the effects on the nervous system of exposure to lead (10, 12, 33).

Statistical analysis of the correlation between blood lead and brain lead values in the present study (Table 4 and Fig. 1) shows that these parameters are highly correlated in weanling rats but not in the adult animals. The data in the literature relating dose of lead to accumulation of lead in brain tissue are based on acute studies. Goldstein et al. (17) observed that 24 hr after a single administration of 210Pb to 4-week-old rat pups, the concentration of lead in blood and brain was directly proportional to the dose. In a recent study of the relationship between brain lead and blood lead in adult rats exposed to lead-supplemented drinking water, Savolainen and Kilpio (34) found that these lead values were proportional during 11 days of treatment. Differences between these authors' observations and the lack of such a proportionality in the adult animals in the present study may be due to the considerably higher lead doses used by Savolainen and Kilpio (34) (50-fold higher than those used in the present study) or by the shorter duration of their study (11 days versus 42 days in the present study).

In a study of the effects of lead on the energy metabolism of the brain, Bull et al. (35) found that brain lead levels averaging 0.41 μg/g (range 0.34-0.52 μg/g) and higher resulted in significant inhibition of potassium-stimulated respiration in rat cerebral cortex slices. Brain lead concentrations in this range were found in three of the four lead-treated groups in the present study and would be expected to cause impairments in brain function similar to those described by Bull et al. (35).

Figure 1 illustrates lead accumulation in the brain as related to blood lead levels. Retention of lead by brain persists after blood lead levels fall (14, 17, 36). When intake of lead is episodic (as in the group III rats), the concentration of lead in blood may not be an accurate measure of the amount of lead actually accumulated in brain tissue; progressive accumulation may occur without pronounced elevations in blood lead levels. Although considerable information has been obtained on the effects of large doses of lead, more knowledge is needed to determine the consequences of long-term (chronic) deposition of lead in the brain. Adult animals and/or humans are beyond the critical developmental periods which make young animals particularly vulnerable to the neurotoxic effects of lead; however, the adult nervous system is still susceptible to lead toxicity (33).

Statistical analyses of correlations between blood lead and femur lead (Table 4 and Fig. 2) show that these parameters are highly correlated in weanling rats receiving lead acetate-supplemented water or an equivalent quantity of lead once per week. A weaker correlation was observed in adult rats receiving lead-supplemented water, but no correlation was found in the adult rats receiving lead intermittently.

Lead accumulation in the skeleton accounts for the largest fraction of the total body burden of lead (94-95% in adults and approximately 70% in young children) (37). Whereas pools of lead in blood and soft tissues turn over rapidly, turnover of lead in the skeleton is considerably slower; the residence time of lead in bone may be as long as 30 years (37, 38). At the present time, neither the role of skeletal lead per se nor its function in re-equilibration processes between blood and soft tissues is fully understood.

A number of factors may cause a redistribution of lead within the body. For example, conditions such as dietary deficiencies, hormonal imbalances, physiological stresses, or metabolic bone diseases may result in some skeletal demineralization. Under such circumstances, skeletal lead may be released to the blood and soft tissues. Lead accumulated in the skeleton of the young animal would become a potential hazard if mobilized to blood and soft tissues during adult life. Direct toxic effects on bone metabolism may result from long-term accumulation of lead. Betts et al. (39) observed changes in bone density in 93% of children whose blood lead was treater than 60 μg/dl and in 24% of children with blood lead between 37 and 60 μg/dl. Bone formation was disturbed when beagle dogs were fed low doses of lead over a 6-month period. [Average blood lead values at the end of the study were 55 μg/dl (40).]

Few data are available on dose-response relation-
ships for renal function impairment caused by lead (41). Intranuclear inclusion bodies have been observed in kidneys at renal lead concentrations of 10 μg/g (42). In a previous study (43), we observed rare intranuclear inclusion body formation, inflammatory cell changes, and cloudy swelling in renal tubular cells in 35% of young rats with mean renal lead levels of 13 μg/g.

In the present study, the accumulation of lead in the kidneys was highly correlated with blood lead levels in weanling rats exposed to lead in their drinking water (Fig. 3 and Table 4). Lower correlations were observed in adult rats receiving lead in drinking water and in weanling rats dosed with lead once per week. The relationship between blood lead levels and renal effects of lead is poorly documented. Inclusion body formation in renal tubular cells will occur when blood lead levels are in the range of 40-80 μg/dl (44). In our previous study (43), mean blood lead values for rats with histological evidence of kidney damage were 68-72 μg/dl.

Dose-response relationships derived from animal studies cannot be translated directly into implications for human exposures to the same compound. However, some qualitative inferences may be drawn from the present study: When exposed to identical sources of lead contamination, younger rats show more pronounced manifestations of lead intoxication than older rats; when exposures to low levels of lead are intermittent, the toxic effects of the metal are decreased, but are still more apparent in the young animals than in the older animals.

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