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Tissue Mineral Levels in Victims of Sudden Infant Death Syndrome I. Toxic Metals—Lead and Cadmium [29]

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Summary

Lung, liver, kidney, and rib specimens were obtained at autopsy from 66 sudden infant death syndrome (SIDS) infants and 23 infants who died suddenly from other causes between the ages of 4–26 wk. Tissue levels of lead and cadmium were measured by atomic absorption spectroscopy and are expressed as μg/g dry weight. Because these metals are cumulative with age in storage tissues, the levels were corrected for age (adjusted to age 13 wk). The SIDS liver and rib specimens contained significantly more lead than non-SIDS tissues (liver, 1.095 μg/g *versus* 0.761 μg/g, $P < 0.05$; rib, 1.754 μg/g *versus* 1.041 μg/g, $P < 0.01$, respectively). There were no significant differences in cadmium concentration between the SIDS and non-SIDS tissues. All four tissues showed significant increases with age in both lead and cadmium concentrations in SIDS. The increase in lung lead concentration with age was significantly greater in SIDS than in non-SIDS cases, $P < 0.05$. In non-SIDS only kidney cadmium showed an increase with age ($P < 0.0001$). These data collectively suggest an increased exposure of the SIDS infant to lead either prenatally and/or postnatally. Any physiologic effects of the increased tissue lead levels are unknown. They may be only a marker of the known epidemiology of SIDS.

Abbreviations

AAS, atomic absorption spectrophotometry
SIDS, sudden infant death syndrome

Among the many studies on SIDS little attention has been given to the possible effects of toxic metals. A recent examination of the relationship of seasonal variations of atmospheric pollutants and SIDS revealed that peaks in airborne pollutants preceded the seasonal increase in SIDS by 7 wk (13). Several investigators have found that sudden infant deaths were strongly associated with the frequency of maternal smoking during pregnancy (5, 15, 19, 25) and with the frequency of smoking of both parents postnatally (5). The incidence of prematurity and low birthweight is greater among infants of mothers who smoked (12). This parallels an increased incidence of SIDS among premature and low birthweight infants (18). Peterson *et al.* (20) found a pattern of postnatal growth retardation among SIDS infants. In a reassessment of the data, the pattern was found to be similar to those of babies born to mothers who smoke during pregnancy (19).

Cadmium and lead are among the many components of cigarette smoke and air pollution. There are many sources of lead in the environment and lead and cadmium frequently occur together but, except for industrial pollution, cigarette smoke is the greatest source of cadmium (10). Animal (2, 24) and human (9) studies have shown that *in utero* exposure to lead or cadmium can produce premature births and/or infants that are small for gestational age. Postnatally, lead and cadmium are absorbed from both the lungs and the gastrointestinal tract. Studies have shown that gastrointestinal absorption and retention of both toxic and essential elements are considerably greater in infants than in adults (21, 28) and that the toxicity of lead is increased in the young of many species.

To evaluate any existing relationship between toxic metal exposure and SIDS, levels of lead and cadmium were measured in tissues of SIDS victims and of infants who died of other causes.

MATERIALS AND METHODS

The right kidney, the entire right 5th rib, and a portion of lung and liver were obtained fresh (not fixed) from infants autopsied at the St. Louis City and County Medical Examiners Offices. The age ranged from 4–26 wk. There were 66 SIDS cases and 23 non-SIDS cases. The causes of death in the non-SIDS group were pneumonia, asphyxia, meningitis, and congenital heart defects. Because all cases were in the jurisdiction of the medical examiner, informed consent of the parents was not required to obtain specimens.

Each specimen was packaged separately in plastic bags and stored in a −20°C freezer until the analyses were performed. Care was taken to avoid metal contamination during handling. Only the cortex of the kidney was used for analysis. All soft tissue was removed from the ribs, which then were split and washed with a stream of deionized water to remove the marrow. All tissues were dried and pulverized. National Bureau of Standards SRM 1577 bovine liver was used as a reference tissue. Portions of the dried tissues were digested with nitric acid. Tissue digests were analyzed for cadmium and lead using electrothermal AAS, a Perkin-Elmer Model 403 spectrophotometer equipped with an HGA 2200 graphite furnace. Backround correction was used.

Maternal smoking history was obtained for 44 SIDS cases and five non-SIDS cases. Statistical analyses were performed using SAS programs (Statistical Analysis System, SAS Institute, Raleigh, NC). Pearson's coefficients of correlation were calculated using the logarithms of the mineral concentrations. The log transformations produced more nearly normal distributions, permitting the use of a parametric test. Because cadmium and lead are cumulative with age in their major storage sites, kidney and bone, respectively, the tissue levels were adjusted for age [adjusted to 13 wk, $M_{13} = M + B\ (13 - T)$ or $M_{13} = M - B\ (T - 13)$, where M, initial metal value; B, slope; and T, age in wk].

RESULTS

The mean age was 11.9 wk for the SIDS group and 13.4 wk for the non-SIDS group. The age distributions are shown in Table 1

and are not significantly different by chi square analysis. The SIDS group was composed of 35 males and 31 females; 27 white and 39 black infants. The non-SIDS group had 13 males and 10 females; 5 white and 18 black infants.

In SIDS maternal smoking history showed no significant effect on tissue lead and cadmium concentrations. There was insufficient information from the non-SIDS group to be able to compare the effects of maternal smoking between the two groups.

The unadjusted tissue cadmium and lead concentrations are shown in Table 2. Age correction did not make any significant changes in results. The liver and rib lead levels are significantly higher in the SIDS group. Table 3 shows the seasonal distribution of infant deaths and the respective rib and liver lead values. As expected non-SIDS show a uniform distribution of cases throughout the year whereas SIDS show a late fall peak which is typical for St. Louis. A seasonal variation in rib or liver lead was not seen in either SIDS or non-SIDS, however. These total distributions are not significantly different by chi square analysis.

Significant intertissue lead correlations were found in SIDS. Rib lead correlated with lung lead, $P < 0.002$; liver lead, $P < 0.0001$; and with kidney lead, $P < 0.0004$. Also in SIDS, kidney cadmium correlated with lung and liver cadmium, $P < 0.0001$; with lung and liver lead, $P < 0.02$; and with rib lead, $P < 0.005$. No significant relationships were found among the non-SIDS tissues.

Plots of tissue metal concentration *versus* age indicated that changes in metal levels appeared to be uniform with no marked curvature or tendency to plateau. Pearson correlation coefficients were identical or nearly identical to linear regression correlation coefficients. Increases in cadmim and lead concentrations with age are shown in Figures 1 and 2. These increases were significant ($P < 0.05$) in the SIDS group except for rib cadmium. The only significant increases in the non-SIDS group are the kidney cadmum ($P < 0.0001$) and kidney lead ($P < 0.01$). The slopes of the SIDS and non-SIDS lines are significantly different only for lung lead ($P < 0.05$) and these regression lines plus the actual data scatter can be seen in Figure 3. The intercepts are not significantly different for the two groups. Although the liver lead intercept value for SIDS is more than twice that for non-SIDS, the standard deviation ranges overlap putting the difference beyond the significance level.

There were no significant differences in lead or cadmium levels between black and white infants or between males and females. The urban St. Louis City cases had slightly higher tissue lead concentrations than the suburban St. Louis County cases but the differences between the SIDS and non-SIDS groups still existed. No differences were seen between prematurely born infants and infants born at term.

Table 1. *Age Distribution*

Age (wk)	4–7	8–11	12–15	16–19	20–23	24–26
SIDS (*n*)	24	10	14	8	5	5
Non-SIDS (*n*)	7	5	2	3	3	3

Table 2. *Tissue cadmium and lead concentrations*[1]

	SIDS[2]		non-SIDS[2]	
Mineral/tissue	*n*	Mean ± S.D.	*n*	Mean ± S.D.
Cadmium				
Lung	66	0.0181 ± 0.0133	23	0.0189 ± 0.0105
Liver	66	0.0258 ± 0.0150	23	0.0227 ± 0.0139
Kidney (cortex)	66	0.0738 ± 0.0807	23	0.0781 ± 0.0678
Rib	57	0.0068 ± 0.0043	21	0.0087 ± 0.0047
Lead				
Lung	66	0.188 ± 0.079	23	0.151 ± 0.050
Liver	66	1.062[3] ± 0.793	23	0.766 ± 0.651
Kidney (cortex)	66	0.471 ± 0.278	23	0.484 ± 0.224
Rib	57	1.672[3] ± 1.204	21	1.047 ± 0.580

[1] Mineral concentrations are expressed in μg/g dry weight.
[2] Mean SIDS age = 11.9 wk, mean non-SIDS age = 13.4 wk.
[3] Significant difference, Liver Pb $P < 0.05$, Rib Pb $P < 0.01$.

DISCUSSION

Although the methodology used in this study is superior to previous colorimetric studies or earlier AAS studies, the tissue levels are within expected ranges. When converted to approximate wet weight values, the tissue lead levels are in the range found by Barry (4). In SIDS, clear increases are seen in both liver and rib lead possibly representing both acute and chronic exposure. The suggestive but not significantly higher lung lead would be consistent with the lung as a major route of entry. The increase in lung lead with age was significantly greater for the SIDS ($r = 0.569$, $P < 0.001$) than for the non-SIDS infants. That these differences are real is supported by the correlation of intertissue lead concentrations and by the significant increases of concentration with age seen in SIDS but not non-SIDS cases.

In adults virtually all the lead deposited in the lungs is absorbed. The finding of lead accumulation in the lungs of SIDS infants may be due to several factors. Infants inhale far more air in proportion to body weight than adults because of their proportionately greater oxygen demand. It follows that pulmonary deposition of inhaled lead particles would be correspondingly greater. The increased retention of lead characteristic of infants and young children may be the result of immature mechanisms of elimination; thus, pulmonary lead accumulation in SIDS may be the result of greater exposure to airborne lead, immature or impaired mechanisms of absorption, and/or elimination, or some combination of these factors.

The average absorption of ingested lead is about 10% in adults but can range up to about 50% in children (26). Major routes of lead excretion are in feces and urine.

Kinetic studies with a stable lead isotope [^{204}Pb] in five healthy men led Rabinowitz, *et al.* (22) to suggest a three compartmental model for lead metabolism: blood and some rapidly exchanging soft tissues with $t_{1/2}$ about 19 days; soft tissues and a rapidly exchangeable bone fraction with a $t_{1/2}$ about 21 days; and the

Table 3. *Seasonal distribution*

	Rib						Liver					
	SIDS			Non-SIDS			SIDS			Non-SIDS		
	n	Age[1]	Pb[2]	*n*	Age[1]	Pb[2]	*n*	Age[1]	Pb[2]	*n*	Age[1]	Pb[2]
Jan–Mar	8	13.4 ± 6.2	1.930 ± 0.788	7	13.7 ± 8.1	0.515 ± 0.126	10	12.5 ± 4.2	1.549 ± 0.705	7	13.7 ± 8.1	0.620 ± 0.736
Apr–Jun	11	15.8 ± 11.3	1.342 ± 0.815	4	14.3 ± 8.8	1.434 ± 0.663	13	12.5 ± 6.5	0.933 ± 0.628	5	16.2 ± 8.8	0.996 ± 0.752
Jul–Sep	14	11.9 ± 7.9	1.877 ± 1.113	4	12.2 ± 7.5	0.905 ± 0.319	17	12.2 ± 7.5	1.004 ± 0.611	5	10.8 ± 7.2	0.855 ± 0.822
Oct–Dec	23	11.0 ± 5.7	1.426 ± 0.701	6	13.2 ± 7.1	1.505 ± 0.463	25	10.8 ± 5.7	0.857 ± 0.746	6	13.2 ± 7.1	0.669 ± 0.344

[1] Mean age in wk ± S.D.
[2] μg/g, mean ± S.D.

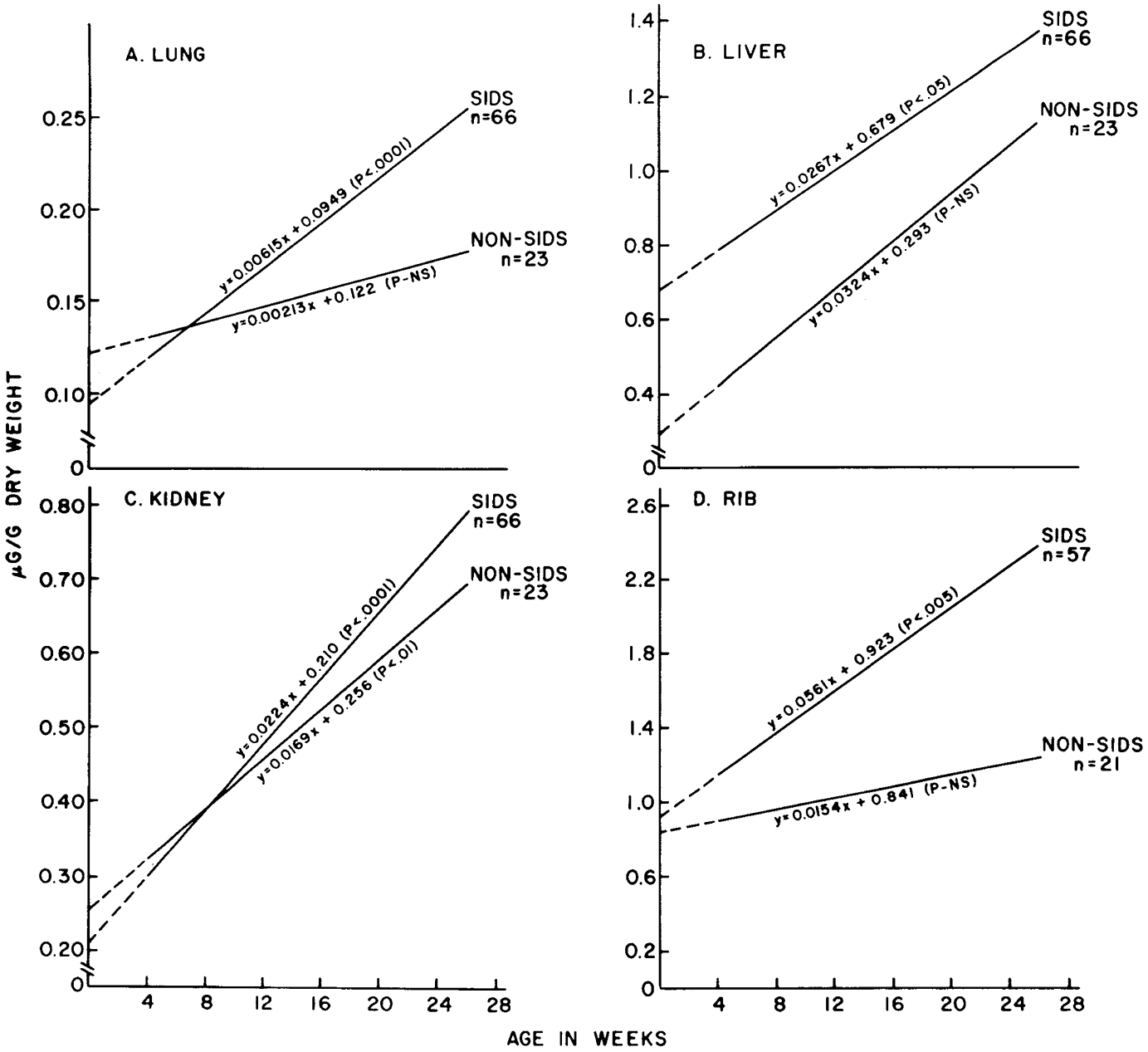

Fig. 1. Changes with age in tissue lead concentration. There is a significant increase with age in the lead concentration of all four SIDS tissues and only the kidney of the non-SIDS tissues. Pearson correlation coefficients: lung, $r = 0.569$ and 0.316; liver, $r = 0.261$ and 0.361; kidney, $r = 0.513$ and 0.563; rib, $r = 0.396$ and 0.192 for SIDS and non-SIDS, respectively. The two slopes for lung lead are significantly different, $P < 0.05$. There are no significant differences between SIDS and non-SIDS for other slopes and intercepts.

skeleton with a $t_{1/2}$ about 20 years. Ninety percent of the total body lead is stored in the skeleton.

Lead is known to be transferred relatively freely across the placenta to the fetal circulation (3, 6, 8, 14, 23, 27). Several investigators have suggested that increased maternal bone turnover during pregnancy could release stored lead which would then be free to traverse the placenta to the fetus (3, 6, 27). This effect might be greatest for the young multigravida, the woman at greatest risk of having a SIDS infant. Fahim, et al. (9) in their study of effects of subtoxic lead levels on pregnant women, found that women who delivered full term infants had a mean blood lead concentration of 14.3 µg/dl whereas women who delivered prematurely had a mean blood lead of 29 µg/dl. Cord blood level levels were 32% (term) and 60% (preterm) of maternal levels. We were not able to appreciate any difference between term and premature infants at the time of death.

The indications are that a woman's exposure to lead both before and during pregnancy determines the amount of lead to which the fetus is exposed. One possible interpretation of our data is that the suggestively higher intercept at time zero of liver lead represents a higher *in utero* lead exposure and that the increase in rib lead with age in part represents a redistribution of the lead from a short term to a long term storage site.

Postnatal lead exposure can come from many sources. The very young infants usually do not have access to lead-based paint chips but airborn lead from dry, flaking lead-based paints, emission from motor vehicles using leaded gasoline, industrial emissions, and smoke from fires burning coal or newspapers can be major contributors to the daily lead intake. House dust can also contribute significant amounts of lead particularly when it is transmitted from hand to mouth by finger or thumb-sucking infants. In a study by the National Science Foundation in which 239 samples

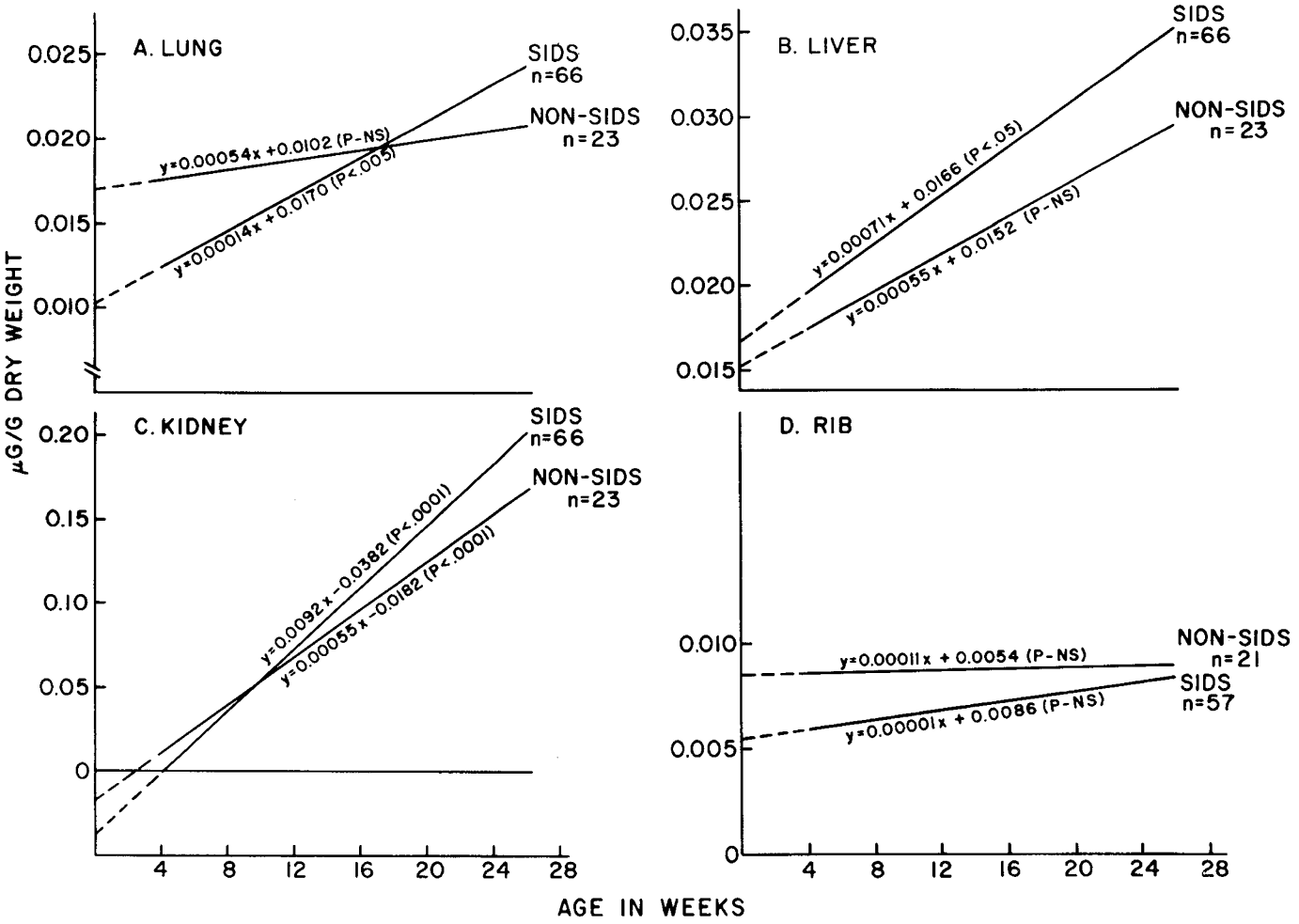

Fig. 2. Changes with age in tissue cadmium concentration. SIDS lung, liver, and kidney and non-SIDS kidney show significant increases in cadmium concentration with age. Pearson correlation coefficients: lung, $r = 0.366$ and 0.098; liver, $r = 0.311$ and 0.297; kidney, $r = 0.731$ and 0.789; rib, $r = 0.163$ and 0.018 for SIDS and non-SIDS, respectively. Slopes and intercepts are not significantly different between the SIDS and non-SIDS tissues.

of floor dust were taken from 12 homes, the lead concentrations in the dust ranged from 100–2580 µg/g (11). Other potential sources of significant amounts of lead are water from lead pipes and foods from lead-soldered cans.

In balance studies in infants of under 2 years, Ziegler, *et al.* (28) found a wide variation in lead intakes from normal infant foods (0.83–22.61 µg/kg per day; mean 9.43 µg/kg per day). Net absorption averaged 42% of intake and net retention averaged 32% of intake.

Momcilovic and Kostial (16) studied the fate of labled lead [^{203}Pb] in suckling and adult rats after a single intraperitoneal injection. Whole body measurements of radioactivity showed the label had decreased in adult rats to 50% of the injected dose by 72 h and to 34% by 192 h whereas, in suckling rats 85% of the dose remained after 192 h. After 192 h the % of [^{203}Pb] retained in suckling rat tissue as compared with adults was about 8 times higher in the brain (0.25 *versus* 0.03%), and higher in whole blood (1.18 *versus* 0.48%), teeth (1.43 *versus* 0.88%), and femur (1.87 *versus* 1.21%), but lower in liver (0.86 *versus* 1.12%), and kidneys (0.79 *versus* 1.70%). If human infants have a similar lead distribution and retention pattern one can see the potential for damage to the developing brain, especially with chronic exposure. The limitations of diet variety and general mobility of the infant within the peak SIDS age, 2–4 months, make the oral route less likely and the finding of a significantly greater increase in lung lead with age in the SIDS infants suggests that the respiratory route of exposure could be a major source of the increased body lead burden. This would be consistent with the data on a relationship between air pollution and postnatal smoking and SIDs.

Absorption of cadmium from the gastrointestinal tract is about 6% in human adults on calcium-sufficient diets and up to 10% on calcium- or protein-deficient diets (21, 25). Gastrointestinal absortion by infants and young animals is considerably greater. Twenty-five to 50% of inhaled cadmium is absorbed (10).

After either acute or chronic exposure, cadmium accumulates in almost every tissue in the body. The highest concentrations are found in the kidneys, liver, spleen, pancreas, and testes. Eventually cadmium is redistributed and the renal cortex and liver become the major storage sites. The estimated half-life of cadmium in the human body is from 9 to 30 years (21). A study of cadmium uptake by rat embryos demonstrated that very little cadmium is transferred to the fetus after a functional placenta is formed and that the amount was dose dependent. The placenta itself accumulates increasing amounts of cadmium with increasing gestational age (1).

The present study shows no significant differences in tissue cadmium levels between the SIDS and non-SIDS groups; however, rib lead was highly correlated with lung, liver, and kidney lead and with kidney cadmium in the SIDS group but not in the non-SIDS group. Likewise, kidney cadmium was highly correlated with lung and liver cadmium and with lung and kidney lead in SIDS but not in non-SIDS. These data suggest that SIDS infants may have had the expected concomitant increased exposures to lead and cadmium from either environmental pollution or cigarette smoke, but that overall retention of lead was more pronounced than for cadmium. Another possible explanation is that this represents concomitant and similar postnatal exposure to lead and cadmium and that because cadmium is not transferred across

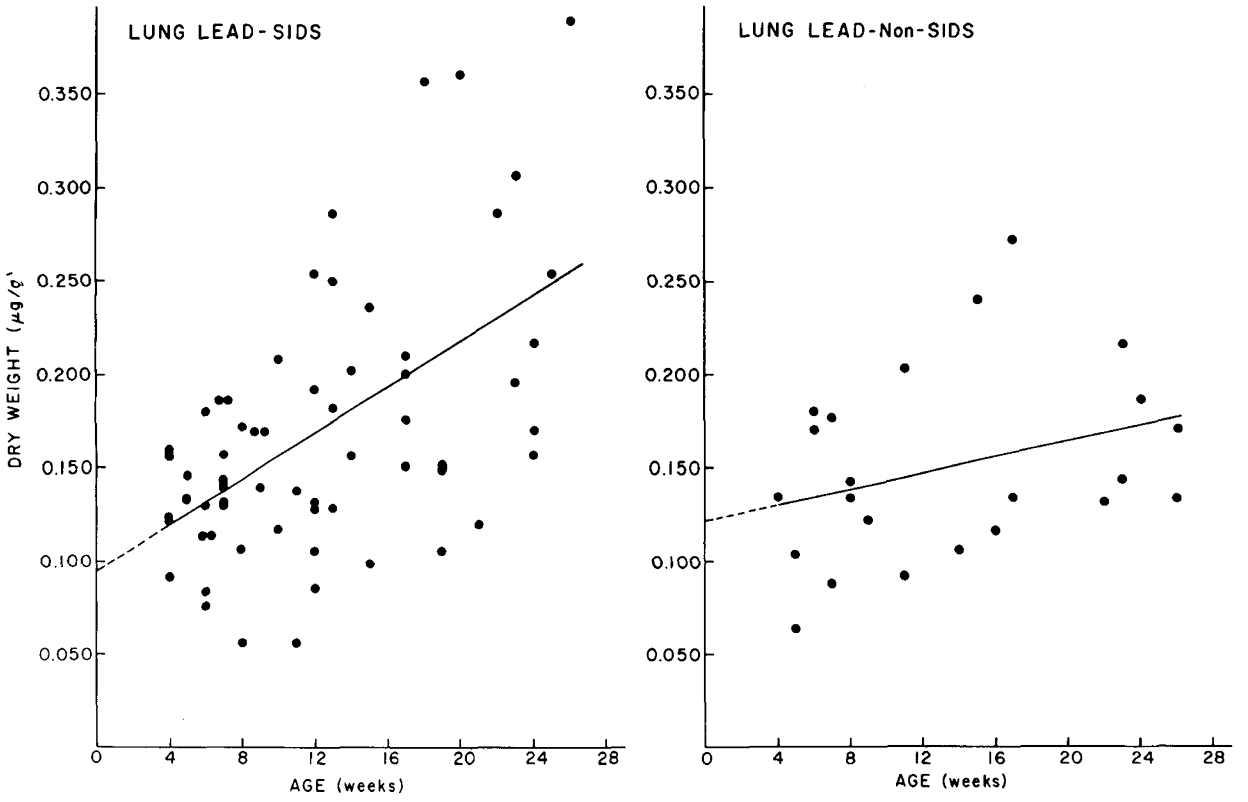

Fig. 3. Distribution of lung lead *versus* age data points around regression lines for SIDS and non-SIDS.

the placenta as freely as is lead; a minimal *in utero* component is seen. Such an interpretation would suggest that *in utero* lead accumulation was more specific for SIDS than postnatal lead accumulation.

The higher lead levels found in the 4–26-wk-old SIDS infants do not provide sufficient evidence to say that lead toxicity contributes to sudden infant death syndrome. Two excellent review articles describe the problems associated with the recognition of the effects of low level exposure to lead (7, 17). Little is known on the possible subtle detrimental effects in humans of subclinical lead exposure or of low-level exposure in infants during gestation or during the first year of life. It seems possible that the prenatal and/or postnatal exposure to lead of a rapidly developing human infant could impair neurologic development in such a fashion as to put the infant at increased risk for SIDS. On the other hand, the increased tissue lead levels could be just a marker for the known epidemiology of SIDS. Further study is needed to elucidate the relevance of these findings.

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Tissue Mineral Levels in Victims of Sudden Infant Death Syndrome II. Essential Minerals: Copper, Zinc, Calcium, and Magnesium[45]

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Summary

Deficiencies of various vitamin and minerals *per se* have been suggested as possible causes of sudden infant death syndrome (SIDS). Further, a deficiency of essential minerals may lead to enhanced toxicity of toxic elements, in particular, lead and cadmium. To explore the possibility of mineral deficiencies or interactions with the toxic metals, lead and cadmium, lung, liver, kidney, and rib specimens were obtained at autopsy from 66 SIDS infants and 23 infants who died suddenly from other causes. Tissue copper, zinc, calcium, and magnesium were measured by atomic absorption spectroscopy. No differences were found between SIDS and non-SIDS for any element in any tissue except for more magnesium in the liver ($P < 0.0001$) and less copper in the lungs ($P < 0.02$) in the SIDS group. Only sporadic interactions between toxic and essential elements could be found. We found no evidence of any essential mineral deficiencies *per se* or significant interactions of essential and toxic minerals that might potentiate the effects of toxic metals. The physiologic significance, if any, of the higher liver magnesium and lower lung copper found in SIDS is unclear.

Abbreviations

AAS, atomic absorption spectrophotometry
CaBP, calcium-binding protein
SIDS, sudden infant death syndrome

Because of their wide ranging effects, deficiencies of various vitamins and minerals have been suggested as a possible cause of SIDS including biotin (22), thiamine (11, 37), vitamin D (21) vitamin E and/or selenium (29, 38), and magnesium (5). Lapin, *et al.* (25) measured selenium, magnesium, copper, and zinc concentrations in liver samples from 13 SIDS cases ranging from 1–10 months of age and 14 non-SIDS cases, age 5 days to 13 years. They found no significant differences between the two groups; however, because different deficiencies are manifest in different tissues and because some tissue concentrations vary with age, mineral deficiencies were not totally excluded.

Mineral interactions are known to occur both among the essential elements and between toxic and essential elements (20, 35, 42). Copper and zinc are antagonistic to each other (10), while normal calcium metabolism, in some instances, depends on the presence of normal amounts of magnesium (1). A deficiency of copper or zinc will lead to enhanced toxicity of lead or cadmium whereas an excessive dietary intake of the essential minerals will be protective (9, 23, 35). Tissue lead concentrations are greatly elevated when dietary calcium is low (27, 28, 36). Magnesium supplementation has been shown to effect increased excretion of lead in rats (41).

The determination of copper, zinc, calcium, and magnesium concentrations in tissues of SIDS victims was undertaken to see if any relationships existed between these elements and the cadmium and lead levels previously reported (14) and at the same time with a larger number of cases and with appropriately age-matched controls to further examine the possibility of the presence of deficiencies or excesses of these elements in multiple tissues.

MATERIALS AND METHODS

Fresh lung, liver, right kidney, and right 5th rib specimens were obtained from infants autopsied at the St. Louis City and County Medical Examiners' Offices. The ages at death ranged from 4–26 wk. There were 66 SIDS and 23 non-SIDS infants. Each tissue was packaged separately in plastic bags and stored at −20°C until the analyses were run. The tissues were processed as previously described. (14). The tissue acid digests were analyzed for copper using electrothermal AAS and for zinc, calcium, and magnesium using air-acetylene flame AAS. A Varian Model 1200 AAS was used for rib zinc measurements and a Perkin-Elmer Model 403 equipped with an HGA 2200 graphite furnace was used for all other mineral measurements. Deuterium background correction was used for copper and zinc. Lanthanum was used to suppress