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Lead in Bone: Implications for Toxicology during Pregnancy and Lactation

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Advances in understanding the distribution and retention of lead in mineralized tissues are important for two reasons: first, bone lead may be a more accurate dosimeter of integrated absorption associated with chronic exposures, and second, bone lead may be a source of internal exposure to the host organism. Little attention has been paid to this second aspect, the remobilization of lead from bone. Mobilization of lead from bone is likely to occur during periods of altered mineral metabolism; since calciotropic factors determine the uptake and storage of lead in this compartment, changes in calcium-related regulatory factors are likely to affect lead compartmentation. Calcium metabolism changes drastically in humans during pregnancy and lactation; although relatively little is known of lead kinetics during these critical periods, it is likely that bone lead is mobilized and transferred to the more bioavailable compartment of the maternal circulation, with potential toxic effects on the fetus and the mother.

Introduction

The title of this conference, "Lead in Bone, Implications for Dosimetry and Toxicology," examines two opportunities presented by the ability to measure lead in bone. The first opportunity is the improvement in evaluating lead dose, particularly chronic, integrated dose, or the influx of lead into bone. The second opportunity is the ability to study lead in bone as a source of internal lead exposure, or the efflux of lead from bone. Understanding the effects of lead on reproduction will be advanced by using bone lead measurements for both influx and efflux of lead into this compartment.

The effects of lead on fetal growth, intrauterine development, and postnatal status have long been of concern in occupational and environmental medicine. More recently, several large epidemiological studies have reported deficits in early infant development observed in children born to mothers whose blood lead levels during pregnancy were only slightly elevated as compared to a control group (*1–3*). Because these exposures, as measured by blood lead, fall within the range found in much of the population of the United States, the findings have implications for defining perinatal lead toxicity as an epidemic (*4*). Further definition of dose response and understanding of critical time periods during pre- and postnatal development for the neurotoxic effects of lead are critical for designing appropriate screening and intervention. The data currently available do not clearly separate the effects of prenatal exposure from those of postnatal exposure, particularly in terms of relative persistence.

The two large-scale prospective studies on lead exposure in the U.S. (*1,2*) and the prospective study underway in Yugoslavia (*5*), may provide data that will help to define these issues. At present, the results from the Cincinnati study (*2*) have been interpreted to support a hypothesis that prenatal lead exposure results in more persistent deficits in behavior than does early postnatal exposure, while the Boston study (*1*) results appear to support the opposite hypothesis.

A complication in interpreting these studies lies in major uncertainties concerning lead toxicokinetics during pregnancy. The most commonly used marker for lead exposure is the measurement of lead in blood, which is a useful indicator of relatively recent or steady-state lead exposure given that the half-life of lead in this compartment is only 35 days (*6*). The interpretation of these studies is based on the assumption that blood lead levels usually measured once, at delivery, accurately reflect exposure of the mother and the fetus over pregnancy. However, blood levels change over pregnancy, and lead is rapidly transferred across the placenta to the fetus (*7*).

To evaluate fully the significance of fetal lead exposure, it is critical to know the determinants of fetal lead dose. Total fetal dose reflects not only the transfer of lead derived from mother to fetus associated with the mother's exposures during her pregnancy but also the transfer of lead stored in the mother accumulated over her prior history of lead exposure.

In addition, the mobilization of lead from bone during pregnancy and lactation may have toxic effects

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upon the mother. Lead toxicity must reflect the pharmacodynamic interactions of lead with its intracellular sites of toxic action; the more frequently and intensively atoms of lead pass by these receptors, the more likely cell and organ level toxicity will be produced. From the perspective of the receptor, a recycled atom of lead is the same as a newly absorbed atom. Mobilization of bone lead into the circulation increases the amount of lead in the proximately bioavailable compartment of the plasma.

This paper will discuss evidence for the hypothesis that mobilization of maternal lead stores occurs during pregnancy and that this mobilization is an important factor in overall fetal exposure and potential toxic effects to both mother and fetus. Although the focus of this paper is on maternal-fetal lead toxicokinetics and toxicity, it is not meant to imply that these are the only effects of significance related to lead and perinatal development. Male-mediated exposures and effects of lead on male reproduction are not considered in this paper, but may well be of importance in assessing the overall significance of relatively low-level lead exposures on reproduction and child development.

The paper will review available data on lead kinetics during pregnancy and lactation from both clinical and experimental studies and the few case studies of effects observed in mothers and children. It will also review what is known of mineral metabolism during pregnancy since the factors regulating mineral metabolism that respond to the physiological and hormonal changes during these periods also affect lead storage and bioavailability.

Lead Toxicokinetics during Pregnancy and Lactation

Human Data

Our information on the toxicokinetics of lead during pregnancy is indirect. As noted by Miller (*8*), kinetic studies in pregnancy must account for complex interrelationships involving three compartments: the mother, the fetus, and the placenta. For studies involving postnatal exposure via lactation, the child and the additional compartment of breastmilk must be included. In clinical studies, these three compartments are not readily available at the same time for sampling and analysis. Unfortunately, in most experimental studies, these compartments have not been studied in an integrated manner.

For lead, within humans, both mother and fetus, there are several compartments of kinetic importance: blood, soft tissue, and bone (*9*). As discussed by Rabinowitz (*6*), each of these compartments may have several binding and storage sites with internal fluxes that regulate overall intercompartmental fluxes and eventually maternal-fetal lead kinetics.

Two types of studies of maternal blood lead levels have been conducted during pregnancy: cross-sectional and longitudinal. The cross-sectional studies of women at different stages of pregnancy show a tendency for decreased blood lead from the first to second trimester and relatively little change thereafter (*10,11*). However, these cross-sectional studies may be confounded by age, which is a significant factor in determining blood lead levels and which may influence mineral metabolism (see below). The longitudinal studies, following cohorts over pregnancy, have not shown clear trends (*12,13*). Studies of blood lead at delivery, based upon sampling fetal blood from the umbilical cord, indicate that lead is readily transferred across the placenta. The correlations between maternal blood lead levels and those in cord blood are almost 1.0 (*5*).

Lead absorption and retention by the fetus has been extensively studied by Barltrop (*12*). He found significant increases in lead content (but not concentration) in fetal bone and organs over gestation. A more recent study concluded that lead did not accumulate in human fetuses during the first trimester (*14*), which is not inconsistent with what is known of mineral metabolism over pregnancy (see below).

Two case studies provide evidence that there can be significant mobilization of lead from bone during pregnancy. One case study suggests that the mobilization of lead during pregnancy can result in relatively high-dose exposure with overt toxicological consequences for the infant (*15*). Over the course of pregnancy, one woman's blood lead levels increased dramatically to 74 μg/dL, with clinical signs of intoxication and her baby's blood lead level was 55 μg/dL. There was no evidence of increased exposure to external lead sources over this period of time. The authors determined that she had had excessive lead exposure as a young child, over 30 years prior to this pregnancy.

In another case study, Manton measured his wife's blood lead and speciated it by stable isotopic ratio. He reported changes in stable isotopic ratios that indicated contributions to blood lead over pregnancy from a pool that did not correspond to the external source of lead at the time of measurement (*16*).

We have investigated changes in bone lead stores somewhat more directly by using the NHANES II dataset (*17*). In a group of postmenopausal women, we found significant increases in blood lead concentrations as compared to premenopausal women, after controlling for age, calcium intake, and other variables potentially related to both external lead exposure and mineral metabolism (Table 1). Of relevance to this topic, we also found that in postmenopausal women who had ever been pregnant, the extent of the postmenopausal increase in blood lead was significantly less than that in nulliparous postmenopausal women (Fig. 1). These data suggest that during prior pregnancies (and possible lactation), there was some mobilization of bone lead such that less was subsequently available for mobilization during demineralization after menopause. Alternatively, nulliparous women may be more at risk for postmenopausal bone demineralization, although epidemiological studies of postmenopausal osteoporosis have not clearly shown this (*18*).

Table 1. Variables entered in univariate and multivariate analyses.

Lead-related variables
Age (in years)
Age squared
Race[a]
Income[b]
Degree of urbanization[c]
Lead used in gasoline (10^6 g/day)
Number of cigarettes per day
Alcohol drinker (greater than one drink/week)
Variables related to osteoporosis
Dietary calcium (mg/day)
Hypertensive medication
Body mass index[d]
Subscapular skinfold (cm)
Dietary phosphorus (g/day)
Dietary protein (g/day)
Tricep skinfold (cm)
Recreational exercise[e]
Hypothesis variables
Menopause status
Years since menopause
Pregnancy history
Race

[a] 1 = black, otherwise 0.
[b] 1 = less than $5000/year; 2 = $5000–15,000/year; 3 = $15,000/year.
[c] 1 = cities over 3,000,000 to 8 = rural under 2500.
[d] Weight/height^2.
[e] 1 = little or none; 2 = moderate; 3 = heavy.

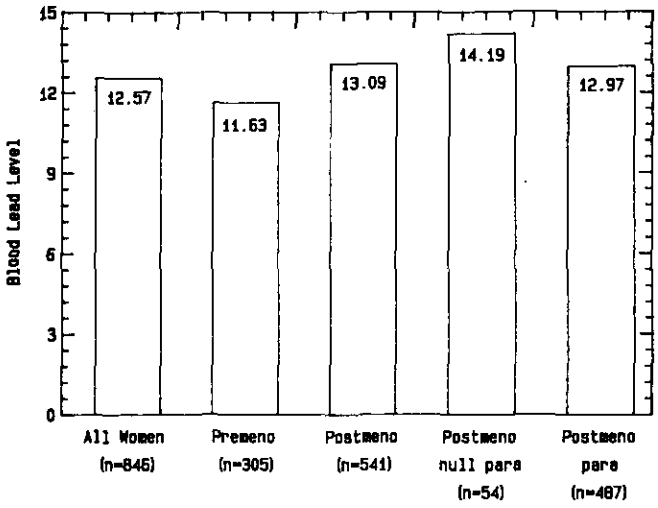

FIGURE 1. Blood lead concentrations in black and white women, aged 40 to 60 years (n = numbers in sample used for analysis). Premeno, premenopausal women; postmeno, postmenopausal women; postmeno null para, postmenopausal women with no prior pregnancies; postmeno para, postmenopausal women with at least one pregnancy. Data from NHANES II survey; see Silbergeld et al. (*17*) for details of analyses.

Lead is also secreted in breastmilk in a range from 0.24 to 35 mcg/dL. External exposures influence breastmilk lead levels, as expected, such that urban populations in general have higher levels than rural populations (*19*). Lead is found in concentrations higher than those found in plasma at the same time (*20*). Breastmilk lead concentrations may increase over lactation, although no comprehensive studies have been done. Women older than 30 years had significantly higher levels of breastmilk lead than women between 20 and 30 years of age (*11*). This may reflect the general increase in stored and circulating levels of lead as a function of age or altered mineral metabolism during lactation in older women.

Experimental Data

Only a few studies of experimental animals exposed to lead have examined lead kinetics over pregnancy. These studies are further limited in interpretation because of incomplete design and because rodents may not be adequate models for the physiology of pregnancy in humans. These studies have confirmed that lead is rapidly transferred from mother to fetus, particularly during the late stages of gestation. Moreover, after midgestation in the rodent, the flux of lead from maternal to fetal circulation favors the placental and fetal compartments (*21*). Total fetal lead content of the fetus increased with time but concentration tends to decrease [as noted by Barltrop in humans (*12*)] because of the relatively greater rate of fetal growth during this period.

Two experimental studies have examined the potential for redistribution of lead from the mother to the fetus and infant during pregnancy and lactation. Buchet et al. (*22*) found that in rats exposed to lead for 150 days, whose exposure was then discontinued for 50 days prior to mating, there was a substantial mobilization of lead from mother to fetus. This transfer was more pronounced in the discontinuous exposure group than in groups in which lead exposure was continued up to or through gestation, which the authors interpreted to reflect differences in bone resorption rather than lead dosage.

Keller and Doherty (*23*) examined lead kinetics with radiotracer lead (^{210}Pb) in female rats over gestation and lactation. They found that the major period of bone lead mobilization occurred during lactation rather than gestation. This involved both the lead administered to lactating mothers and the mobilization of lead stored in maternal bone from prior exposure. This latter source of lead transfer from maternal bone paralleled the measured decrease in bone mineral content over the same period. However, not all this lead was transferred to the sucking infant via milk; maternal excretion of lead was also increased during lactation.

Because of the relative lack of clinical data and unavailability of information from primate models of lead toxicokinetics during these periods, interpretation of these results must be guarded. It is appropriate to conclude that there is evidence that lead metabolism changes during pregnancy and lactation and that the transfer of lead to the fetus and neonate is likely to be enhanced.

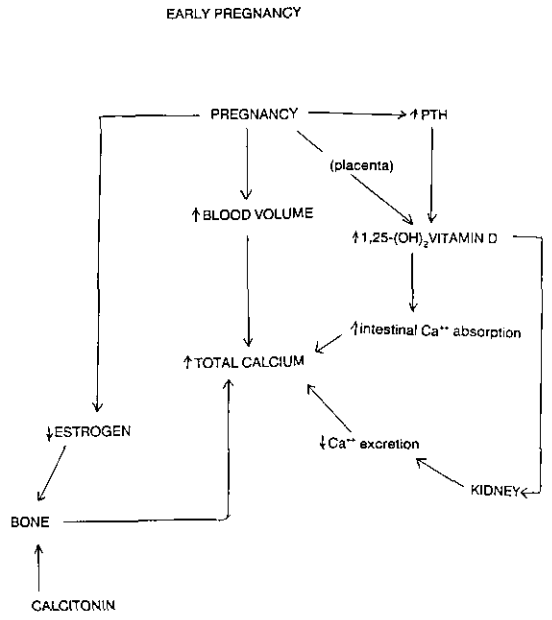

FIGURE 2. Calcium metabolism in early pregnancy. A major physiological change influencing calcium metabolism is the increase in maternal blood volume during this period; as a consequence, in order to maintain circulating levels of calcium, total calcium in the blood compartment is increased primarily through increasing intestinal calcium absorption and reducing renal calcium excretion. It is also possible that the decreased production of estrogen in pregnancy affects bone cell status through estrogen receptors in a manner similar to that observed in postmenopausal osteoporosis, that is, to increase bone resorption. The major hormonal signals governing these changes are parathyroid hormone and 1,25-dihydroxyvitamin D, both of which are increased in the circulation.

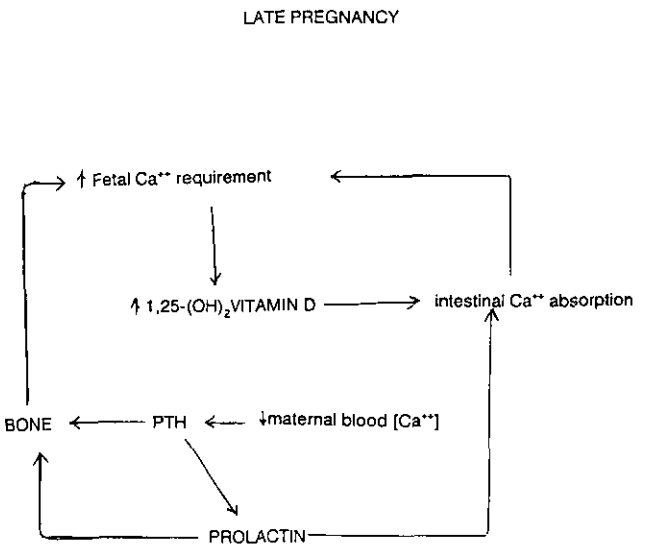

FIGURE 3. Calcium metabolism in late pregnancy (third trimester). During this period, fetal ossification becomes a driving factor in altering maternal calcium metabolism. Calcium is supplied to the fetus, and maternal calcium metabolism is regulated by vitamin D, parathyroid hormone, and prolactin.

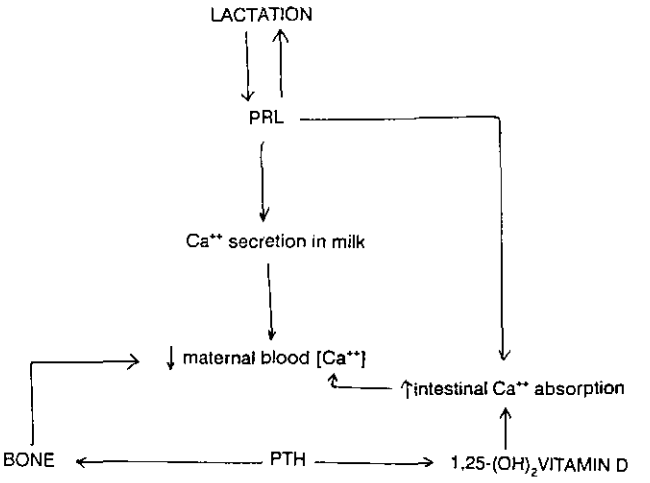

FIGURE 4. Calcium metabolism during lactation. During this period, the stress on maternal calcium metabolism is qualitatively greatest, and the extent of bone demineralization is potentially the largest. Prolactin, parathyroid hormone, and vitamin D all regulate changes in calcium metabolism during lactation.

Mineral Metabolism during Pregnancy and Lactation

Pregnancy and lactation place significant demands on the availability of calcium from the diet and from physiological stores in mineralized tissue (*24,25*). As shown in Figures 2 and 3, during pregnancy, two major changes affect calcium physiology: first, blood volume significantly increases, which requires increased circulating calcium to maintain normal [Ca^{2+}], and second, the fetus exerts a demand for calcium for ossification and growth. This second requirement for calcium is greatest during the third trimester when the fetus obtains about 20 g of the total intrauterine requirement of 30 g of calcium (*25,26*). During lactation, an additional and even greater demand is placed upon maternal sources of calcium for the secretion of this essential mineral in breast milk (Fig. 4). These demands of the developing organism and mother have only two possible sources of supply: increased dietary sources through a change in diet and enhanced retention of exogenously derived calcium, or a draw upon calcium in bone through the modification of bone turnover to favor resorption. During pregnancy, however, along with increased calcium absorption (about twice normal levels), calcium excretion is also increased (*24*).

Calcium requirements for pregnant and lactating women are much greater than those for adult men. During the last trimester, the fetus retains about 250 mg of calcium per day, generating a maternal daily intake requirement of about 1100 mg/day. During lactation, about 400 and 1600 mg/day is secreted in breastmilk each day (*24*). The recommended daily intake of calcium is even greater, about 1300 mg/day (*25*). At this time, both calcium absorption increases and calcium is drawn from bone stores.

However, there is still some controversy over calcium

requirements during pregnancy. It has been assumed that adequate dietary intake of calcium will prevent demineralization of maternal bone (*25*). However, the clinical data are still incomplete, in that many studies were not controlled for calcium intake or measurement of calcium balance. Physiologically, maternal metabolism adapts during pregnancy to exploit both external and internal sources of calcium. Dietary calcium is conserved by increasing gut absorption of calcium and decreasing renal excretion. Hormonal changes are the major factors controlling these adaptations. There is a steady and significant increase in circulating levels of 1,25-dihydroxyvitamin D during pregnancy in humans (*27,28*) and circulating levels of parathyroid hormone may also be increased (*24*). Prolactin is another major hormonal mechanism for modifying calcium metabolism during pregnancy and lactation, increasing calcium absorption and placental transfer of calcium (*29,30*). However, in many pregnant and lactating women, bone may be an additional source of calcium as evidenced by changes in bone formation rate, loss of bone mineral, and frank osteoporosis in some cases (*31,32*). Some studies have found as much as 10% loss of bone mineral in lactating women whose diets were only somewhat calcium deficient (about 900 mg/day) (*33*). In rats with adequate calcium and vitamin D intake, between 15 and 40% of bone mineral can be lost during lactation (*34*).

More detailed studies have demonstrated the complexity of bone physiology during pregnancy (Figs. 2 and 3). Purdie et al. (*35*) reported increased rates of resorption in early pregnancy, followed by increased rates of formation in late pregnancy, a finding paralleled by experimental studies in rats (*34*). This biphasic change in bone mineral status, which may result in part from changes in circulating estrogen levels could reflect a storage mechanism to provide calcium for the greater demands of lactation (Fig. 4). There is also some suggestion that different parts of bone are differentially mobilized during different phases of bone resorption, which may be of importance in estimating relative availability of lead stored in specific regions or types of bone (*36*).

Important Factors in Bone Lead Mobilization

It seems reasonable to conclude that bone lead is a potential source of lead for the fetus and neonate and that the kinetics of lead in bone follow those of calcium in bone during the periods of pregnancy and lactation. If this is the case, it is important to determine those factors modulating the movement of lead from bone in human pregnancy. Some of these factors are discussed below.

Lead Exposure. Integrated, cumulative lead exposure is obviously important in determining fetal and neonatal exposure from both stored lead and concurrent external exposures (*7*). Also, the dose rate of lead exposure may influence the location and concentration of lead in bone and its later availability for mobilization, as suggested by Rabinowitz (*6*).

Maternal Age. In addition to determining body lead burden and concentrations in bone, maternal age may influence mineral metabolism. Adolescent mothers with inadequate calcium metabolism have relatively high bone loss during lactation (*33*). Given the prevalence of dietary deficiencies in this population and the increasing rate of pregnancy among adolescents, particularly in groups at high risk for environmental lead exposure (*37*), the coincidence of these two highly correlated factors, age and nutrition, may be very important for lead exposure. In another age-related observation, older women appear to secrete higher levels of lead in breastmilk than do younger women, but this may reflect general trends in lead exposure and body lead burden.

Gestational Age. Gestational age clearly influences mineral metabolism in both mother and fetus. The fetus produces 1,25-dihydroxyvitamin D and hence regulates its own active calcium uptake across the placenta (*26,38*). The most active phase of calcium transfer to the fetus occurs in the last trimester of pregnancy, a period that coincides with the critical phases of neurodevelopment in which synaptogenesis and arborization of the cortex and cerebellum occur (*39*). This coincidence is unfortunate because of the effects of lead to inhibit synaptic formation (*40*) and to block neurotransmitter-directed cytoarchitectural development of the brain (*41*).

Maternal Nutritional Status. As noted above, maternal nutrition is a major determinant of maternal mineral metabolism during pregnancy and lactation. Calcium- and vitamin D-deficient diets during these periods result in substantial bone demineralization (*33*). Maternal nutritional status will also affect the absorption and retention of lead; although it is not clear that supplementing the diet with calcium can reduce lead absorption or affect lead kinetics, deficiencies clearly enhance the absorption of lead (*42*).

Parity. Little is known of the influence of number of pregnancies upon maternal mineral metabolism. In epidemiological studies, parity number is confounded by age and weight, variables that also affect mineral physiology (*43*). We found that parity influenced the magnitude of postmenopausal increases in blood lead levels (*17*), as discussed above, but we could not examine the impact of number of pregnancies due to small sample size available for analysis of this variable. Parity is a complex variable in studies of postmenopausal osteoporosis, and number of pregnancies as well as age at pregnancy are important, although incompletely understood, factors (*18*).

Race. For demographic and socioeconomic reasons primarily, race is a determinant of lead exposure in American populations (*37*). Nutritional status also varies with race in the U.S., and calcium-deficient diets are more common among poor, disadvantaged minority women than among other groups. Race is also a variable in mineral metabolism, with black women ex-

periencing much lower incidence of postmenopausal osteoporosis than white women (*18*). We found a significant difference between white and black women in the relative increase in blood lead levels following menopause, consistent with a decreased loss of bone mineral in black women. Among Asian and Turkish women, osteomalacia has been diagnosed during and after pregnancy of sufficient severity to increase the risks of fractures during pregnancy and rickets in their infants (*44*). This condition may be due to inadequate intake of vitamin D in these populations and hence to socioeconomic and cultural factors rather than genetics.

Summary and Research Needs

This conference has focused on bone lead primarily as an improved dosimeter for determining cumulative lead exposure in specific groups at risk, primarily children and workers. However, given the lability of bone mineral stores, there are additional toxicological concerns about the potential for release of lead from bone stores during normal physiological conditions that increase bone mineral loss. Of major importance for public health is the potential mobilization of lead from bone during pregnancy and lactation, with potential toxic consequences for both the mother and the neonate.

Most attention has been paid to the potential exposure of the fetus; however, the remobilization of lead during pregnancy and lactation may have toxic consequences for the mother as well, as lead is returned to the bioavailable compartment (plasma) and may be redistributed to such target organs as brain, heart, and kidney.

The available data are sparse. Some experimental data confirm that both dietary and stored lead are transferred to the fetus avidly and that maternal bone stores of lead may be mobilized, particularly during lactation. In humans, there is at least one case of maternal intoxication during pregnancy due to mobilization of significant bone lead stores (*15*). Indirect evidence for such mobilization was also found in a large population-based survey of the U.S. population, in which postmenopausal women were found to have significant increases in blood lead, but this increase was diminished by prior pregnancy (*17*).

If bone lead stores are a potential source of lead for the fetus, there are several important implications for the medical management of lead exposure and intervention as well as needed areas for research. First, the possible contribution of prior lead exposure, resulting in increased bone lead, must be evaluated in epidemiological studies associating lead dose with outcome in infants and young children. Second, the prior history of lead exposure may be important to determine in evaluating individuals and populations at risk. Third, determinants of bone status during pregnancy may be important not only for preventing osteomalacia, hypocalcinemia, hyperphosphatemia, and other mineral-related problems of pregnancy and the fetus, but also to prevent untoward mobilization of lead from bone. Fourth, methods for determining the overall toxicokinetics of lead during pregnancy, particularly the flux of lead from bone to the fetus, must be developed.

There is a consensus as to the research needed in order to develop feasible implementation of bone lead measurements for better estimation of lead dose—the influx term (*36*). For the purpose of estimating potential exposure to bone lead—the efflux term—somewhat different research strategies may be important. For dosimetry, a stable compartment that reflects accumulation of lead over time is important; for mobilization, it is important to be able to measure lead in unstable compartments of mineral tissue and to be able to estimate rates of bone formation/absorption at the same time.

The field of lead toxicology may be transformed by the availability of new technology for measuring lead stores in bone, the major pool for lead in the body. Bone lead may prove to be a vast improvement in dosimetry and, as such, advance our understanding of the dose-response relationships of lead at low dose and the long-term consequences of low level lead exposure. That there are children with very high bone lead stores suggests that they may be persons at considerable risk of lead toxicity whose risk is not adequately assessed by measurements of blood lead levels or chelatable lead in urine (*45*).

In certain populations at risk for bone demineralization for reasons of normal physiological change, aging, or disease, it may be important to determine bone lead stores as a determinant of potential risk of toxicity from mobilized lead during these periods. However, it is clear that much needs to be known about mineral metabolism and bone physiology during such periods as pregnancy and lactation in order to evaluate the potential risk of lead stored in bone for such persons.

In addition, the possibility that lead may affect the endocrinological signals regulating mineral metabolism and bone cell function requires further investigation, as suggested by Pounds (*46*). It may be that bone cells containing lead respond differently to the hormonal signals accompanying pregnancy, lactation, and menopause, which appear to be the determinants of altered bone status. We have suggested that lead may enhance processes of demineralization by inhibiting activation of vitamin D, decreasing calcium absorption, and interfering with hormonal signals, such as prolactin (*17*). Finally, these studies may at last focus attention upon bone as a target for lead toxicity. It has been remarkable that this compartment, in which the overwhelming majority of lead is stored, has long been considered as an inert depot into which lead is transferred and in which no biological response to this very toxic element was thought to occur. Advances in mineralized tissue physiology, not least the finding that most hormones that regulate bone cell status are shared by, among other organs, the brain (*47*), should serve to direct research toward understanding the endocrinological effects of lead and the cellular conse-

quences of lead in bone for bone itself and for the control of mineral flux that is regulated by bone. It has been proposed that lead-calcium interactions are the fundamental molecular mode of lead toxicity (*41,48*), yet little attention has been paid to that physiological system with the highest concentrations of calcium and lead and its interactions with such major functions as growth, development, reproduction, and senescence.

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