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''Severe Chronic Lead Insult That Maintains Body Burdens of Lead Related to Those in the Skeleton'': Observations by Dr. Clair Patterson Conclusively Demonstrated[1]

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INTRODUCTION

As a geochemist, Clair Patterson studied trace occurrences of lead in the earth and oceans. As an unique and far-reaching extension of these studies, he examined the quantitative contribution of industrial lead contamination to babies, children, and adults (Patterson, 1965) many years before the first definitive cross-sectional (Needleman *et al.* 1979) and prospective studies (Bellinger *et al.*, 1987) were published, which, collectively, linked lead at low levels to adverse neurotoxic effects on the central nervous system (National Research Council, 1993). In so doing, he developed the unassailable concept that the average American was exposed to toxic levels of lead. Thus, large U.S. populations were being subjected ''to severe chronic lead insult'' (Patterson, 1991) (Fig. 1). These conclusions were based upon a series of isotope dilution mass spectroscopy analyses of lead (in an ultraclean laboratory) in the skeletons of prehistoric humans (Patterson, 1965; Settle and Patterson, 1980; Patterson, 1980; Ericson *et al.*, 1979; Patterson *et al.*, 1991; Mancea-Krichten *et al.*, 1991). Collectively, these pioneering studies unequivocally demonstrated that the total body burden of lead in Americans today is about 1000 times greater than that measured in ancient cultures. Furthermore, Clair cogently reasoned that classical lead poisoning is only one extreme of a continuum of responses to this toxic metal. In view of these brilliant insights, within the context of his integrity and his dedication to the health of all humans, Clair singlehandedly challenged and successfully amended the narrow and self-serving industry-led view of lead toxicity.

In addition, his studies (Patterson, 1965, 1980; Ericson *et al.*, 1979) successfully and cogently undermined the industry view that the body burden of lead was adequately and fully defined by only measuring lead in blood. Patterson surmised, correctly, that circulating lead reflected recent absorption of lead, and the skeletal reservoir of lead also provided a reentry site of endogenous lead into the blood steam and to the rest of the body, including the brain. Clair concluded that the net result is to ''maintain levels of lead in the body related to those in the skeleton'' (NRC, 1980). Current evidence directly linking release of lead from bone to blood is conclusive.

The main purpose of this article is to demonstrate, using recently reported data in contemporary Americans, that Clair's pioneering concepts and observations have been definitively confirmed. Rather than an extensive review of bone lead studies based upon L-line X-ray fluorescence (LXRF) and K-line X-ray fluorescence (KXRF) methodologies, we have decided to discuss a few, selected reports; from some of these, we have singled out values to provide a basis for biokinetic modeling of current body burdens of lead compared to those in ancient humans. More specifically, the focus of this article is to: (a) selectively review measurements of bone lead carried out in current American populations by LXRF and KXRF methodologies (values from some of these reports provide the basis for modeling current body burdens of lead compared to those in ancient humans); (b) model bone and blood lead data from moderately and heavily lead-exposed adults today in comparison to measurements reported in ancient humans by Patterson and co-workers; and (c) summarise conclusive data relating to the release of lead from bone to blood and thus to other soft tissues.

[1] Quote from Patterson *et al.*, 1991.

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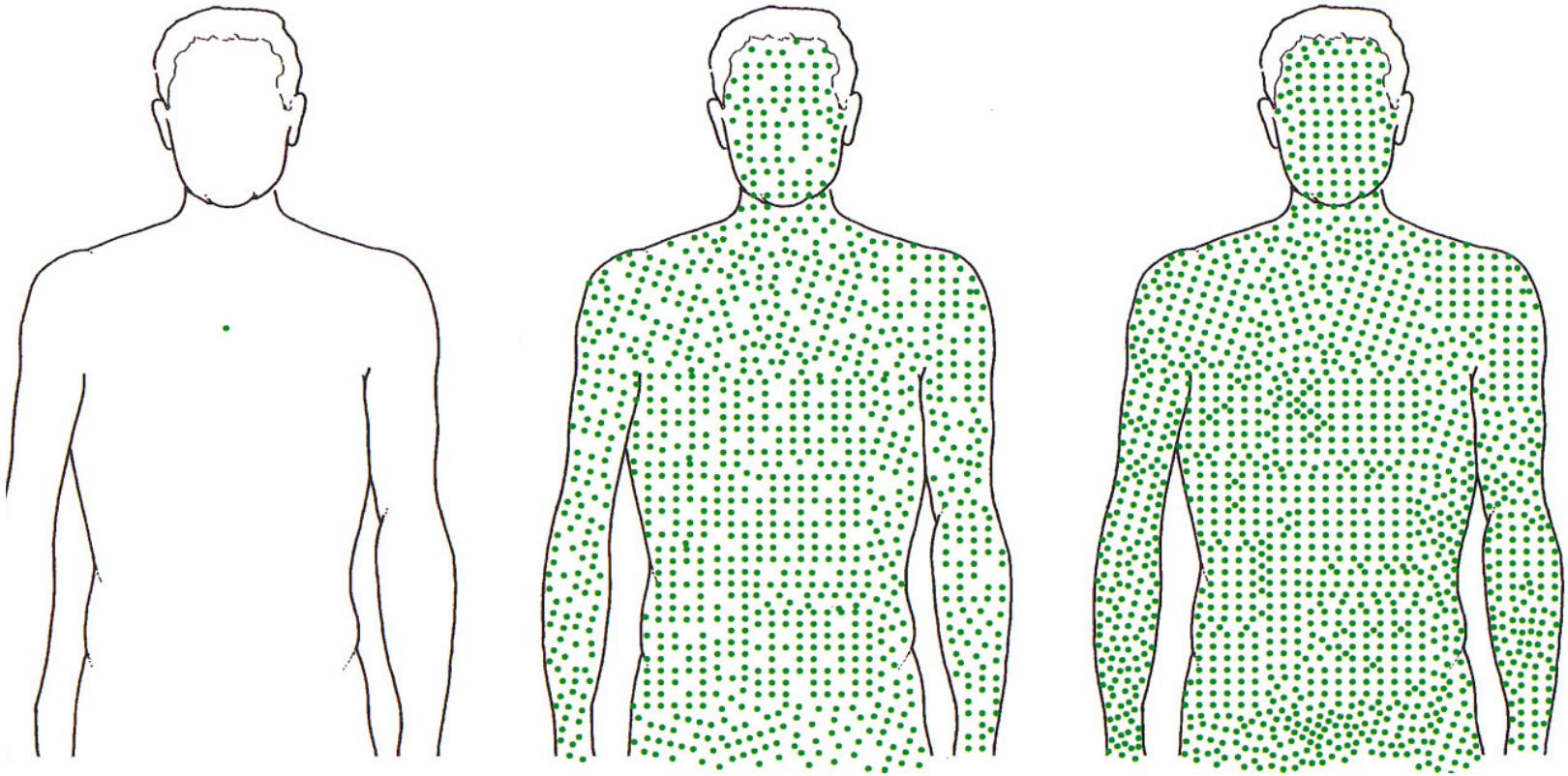

FIG. 1. Each dot represents 40 μg Pb/70 kg person, with one dot on the left (ancient people), 1000 in the middle (typical Americans), and 4000 in the right figure (clinical lead poisoning). Adapted from Patterson *et al.*, 1991.

MEASUREMENT OF LEAD IN THE SKELETON

Several factors impair facile understanding of the distribution and kinetics of lead in the skeleton. The skeleton is a complex and dynamic organ. The skeleton includes bone, bone marrow, periosteum, cartilage, teeth, and the blood vessels found in these tissues. Bone is primarily composed of cortical or hard dense bone with a slower remodeling rate and trabecular bone with a higher porosity and a faster remodeling rate. The bone of adults is approximately 80% cortical and 20% trabecular bone, although the composition of individual bones varies considerably. Furthermore, many bones are heterogenous with respect to structure, composition, and function on a scale of millimeters. The IRCP's reference skeleton document is a valuable description of the component parts (ICRP, 1995).

Numerous analytical procedures are used to measure the lead content of bone. Common analytical procedures include atomic absorption spectroscopy (AAS) or anionic stripping votametry (ASV) applied to biopsy and cadaver samples and KXRF and LXRF, usually applied to measurements of bones *in vivo*. Although these analytical procedures each report lead measurements in units of micrograms Pb, the amount of lead is normalized to a confusing array of values. For example, AAS and ASV measurements are commonly normalized to 1 g fresh wet bone, 1 g dry bone, or 1 g dry, defatted bone. The XRF measurements, which are superficially identical, also use disparate normalization. LXRF expresses lead levels as microgram Pb/gram fresh bone and KXRF measurements are expressed as micrograms Pb/grams mineralized bone, micrograms Pb/grams bone mineral, or micrograms Pb/grams calcium. All of these data are typically presented as ppm Pb; however, it is often difficult to appreciate from the published description of the methods which normalization is being used.

SUMMARY OF RELEVANT LXRF DATA

The clinical applications of the LXRF technique have focused mainly on assessing bone lead content in young children poisoned by lead-based paint (Rosen *et al.*, 1989, 1991; Rosen and Markowtiz, 1993; Rosen, 1995, 1997).

We extended our data (Rosen *et al.*, 1989) relating to LXRF and blood lead values (BPb) to predict $CaNa_2EDTA$ lead mobilization (Pb-MT) outcomes in 201 children (Rosen, 1995, 1997). The same protocol for carrying out the Pb-MT was used as previously reported (Rosen *et al.*, 1989). When bone lead values were above the median (11 ppm) and BPb levels were >35 μg/dl, the Pb-MT outcome was predicted correctly in 83% of children (r values: LXRF/BPb, 0.688; LXRF/PT-MT, 0.701, both P values <0.0001). When age was included as a variable (children <36 months and >36 months), LXRF and BPb values predicted the Pb-MT result in 89% of children. Hence, it is reasonable to surmise that the toxicokinetics of lead in tibial bone sampled by LXRF differs according to age (Rosen, 1995, 1997). Age-related bone mineralization, resorption, and formation rates may differ within structures and regions of cortical bone including the periosteal surface of the tibia. Lead in this area may "act" more like that of trabecular rather than cortical bone. These data indicate that age can be a highly significant variable in the interpretation of values obtained by X-ray fluorescence techniques.

Among children poisoned by lead paint who are 1–6 years of age and undergoing chelation therapy with calcium disodium EDTA, bone lead values, as measured by LXRF, decrease in children who qualified for and received one course of chelation therapy (Table 1) (Rosen *et al.*, 1989; Rosen and Markowitz, 1993). In Children treated twice or three times with 5-day courses of $CaNa_2EDTA$, the decreases in bone lead did not reach statistical significance (Table 1). However, in children who did not qualify for chelation therapy as a result of a negative Pb-MT, and whose homes underwent prompt remediation, as in the other groups, bone lead values did not change over a period of 6 months. Prompt remediation of the home environment prevents further accumulation of excessive lead in bone.

Based upon these data in children poisoned by lead paint, whose average age was 33 months and

TABLE 1

Bone Lead Values at Enrollment (T1) and 6 Months Post-enrollment (T3) in Chelated and Nonchelated Children

	Group I[a]		Group II[b]		Group III[c]		Group IV[d]	
	T1	T3	T1	T3	T1	T3	T1	T3
No. of children	87		33		27		19	
Bone Pb (ppm)	12	11†	15	11*	17	10†	19	16†

Note. Adapted from Rosen and Markowitz, 1993.

[a] Not chelated.

[b] Chelated once.

[c] Chelated twice.

[d] Chelated three times.

* $P<0.05$.

† Not significant.

who weighed approximately 15 kg, bone lead values (Table 1) approximated those in adult workers (active and inactive) in lead industries (Somervaille *et al*., 1988; Schutz *et al.*, 1987A; Gerhardsson *et al*., 1993; Erkkila *et al*., 1992). These data clearly indicate that young children in this category have already achieved bone lead values characteristically observed in 70-kg men excessively exposed to lead (Tables 1–4) and have undergone "severe chronic lead insult that maintains body burdens of lead related to those in the skeleton" (Patterson *et al.*, 1991).

Generally, although the primary site of lead chelation by $CaNa_2EDTA$ is believed to be bone (Hammond, 1973), $CaNa_2EDTA$ treatment failed to decrease mean bone lead values below about 10–11 ppm 6 months after enrollment in any treatment group. This mean value, reached in all groups of $CaNa_2EDTA$-treated children except those treated three times, suggests that there may be two or more compartments of lead in cortical bone: one with a short residence time of a few weeks to months (perhaps that pool accessible to $CaNa_2EDTA$) and a second with a long residence time of several years (perhaps inaccessible to $CaNa_2EDTA$). Christofferson and co-workers (1986), using the KXRF methodology, have characterized two compartments of lead in bone of industrially exposed workers: the shorter-term pool had a residence time of a few months to a few years, whereas the longer-lived compartment had a residence time of 7–12 years. Lead in a more rapidly exchangeable pool may be the primary source of lead chelated by $CaNa_2EDTA$ in children. Ongoing lead paint exposure, albeit at lower levels, may contribute to the limited efficacy of $CaNa_2EDTA$ to remove lead from bone. A third alternative is that $CaNa_2EDTA$ may be more effective in removing lead from bone within a very short time frame, and subsequent redistribution of lead from soft to skeletal tissues may ultimately replete bone lead content posttreatment.

We have also measured bone lead values in children, teenagers, and adults from an excessively lead-exposed suburban community (Throop, Pennsylvania) compared with a non-lead-exposed town (Moosic, Pennsylvania) with a very similar population (years in school, income, ethnicity) (Rosen *et al*., 1993) 8 miles distant from Throop. Throop is a valley community of about 4100 residents who live within 1 mile of a battery recycling factory where Pb was the primary toxicant; the factory and smelter were in operation from 1963 to 1981. Throop was designated as a "Superfund site," and remediation began in 1988. The mean bone lead value in 269 residents of Throop (15 ppm) was three-fold higher than in residents of the reference suburb, Moosic (5 ppm). Average LXRF-measured bone lead concentrations in residents of Throop approximated estimated values in lead industry workers (Rosen *et al.*, 1993).

Thus, children 5–12 years of age (average weight 29 Kg; range 20–38 Kg) and teenagers 13–17 years of age (average weight 55 Kg; range 45–57 Kg) (Harriet Lane Handbook, 1995) have already achieved bone lead values observed in 70-kg men excessively exposed to lead (Somervaille *et al*., 1988; Schutz *et al*., 1987a; Gerhardsson *et al*., 1993; Erkkila *et al*., 1992). Hence, these children and teenagers who live within 1 mile of a lead smelter (Tables 1–4) are subject to "severe chronic lead insult that maintains body burdens of lead related to those in the skeleton" (Patterson *et al.*, 1991).

Upper limit cut-off values for bone lead, at the 95% confidence interval, were established for each of three age groups in the control town of Moosic by summing the mean and twice the SE, which yielded cut-offs of 6, 8, and 7 ppm for 5–12, 13–17, and ≥ 18 year old age groups, respectively. Although BPb concentrations in Throop and Moosic were both below 5 μg/dl, within the current United States average, for each age group in Throop, the mean BPb value was about 2 μg/dl higher than that for the comparable age group in Moosic ($P < 0.0001$) (Rosen *et al*., 1993).

SUMMARY OF RELEVANT KXRF DATA

KXRF clinical studies have focused on excessively exposed lead workers in industry (Schutz *et al*., 1987a,b; Somervaille *et al*., 1988; Christoffersson *et al.*, 1986; Borjesson *et al*., 1997; Nilsson *et al*., 1991, Gerhardsson *et al.*, 1993; Erkkila *et al.*, 1982) (Table 3).

The duration of industrial lead exposure (above citations) was 12 to 32 years in active workers; retired workers generally had higher bone lead content as a result of longer exposure. Trabecular bone lead reflected more recent exposure, whereas tibial bone lead content best reflected cumulative exposure (Schutz *et al*., 1987a; Gerhardsson *et al*., 1993; Erkkila *et al.*, 1992). This suggestion is further suggested by correlation coefficients (r) between trabecular (calcaneus) and cortical (tibia) bone. Erkkila *et al.* (1992) found the r value between lead in the calcaneus and tibia to be 0.503 in active workers, compared with 0.928 in retired workers. The latter value also supports the concept of length of exposure and intensity of exposure being expressed concurrently in long-time workers.

TABLE 2

Bone measured (units)	Bone Pb (ppm) Active	Retired	Bone Pb–BPb relationship integrated BPb	Average half-times	Reference
Finger (wet weight) (μg/g)	40 (means)	83		7 years	Schutz *et al.*, 1987a
Tibia (μgPb/g bone mineral)	31–35 (means) Three factories		$r = 0.82$–0.86		Somervaille *et al.*, 1988
Finger (μg/g, wet wt)	93 (means)	72	Strong	7 years, active and retired workers	Christoffersson *et al.*, 1986
Finger (μg/g, wet wt)	5–100		Strong	14 years	Barjeson *et al.*, 1997
Finger (μg/g, wet wt)	85 → followed for 7.2–17.7 years (median)		Strong	34 days, 1.2 and 13 years	Nilsson *et al.* 1991
Tibia	13	39.3	$r = 0.60$	27	Gerhardsson *et al.*, 1993
Calcaneus (Both: μgPb/g bone mineral)	48.6 (medians)	100.2	$r = 0.44$	16	
Tibia	21.1	32.4	Active: Strong relationship	Retired: Stronger relationship	Erkkila *et al.*, 1992
Calcaneus (Both: μgPb/g) bone mineral)	76.6 (means)	73.5			

In all the studies in Table 2, robust correlations were observed between time-integrated blood lead values and bone lead concentrations. In active workers, the *r* value between integrated BPb levels and lead in the calcaneus was 0.535, and the *r* value for BPb and tibial lead was 0.667. However, in retired workers, these values became more robust: BPb/tibial lead, 0.794; BPb/calcaneus lead, 0.871 (Erkklia *et al.*, 1992).

It was first estimated by Schutz *et al.* (1987b) that about 50% of circulating lead in blood of retired workers was derived from the skeleton. Nilsson *et al.* (1991), using software that simultaneously fits a family of exponential curves, reported half-times for lead in cortical bone of 34 days, 1–2 years, and 13 years. The shorter half-times of lead in the calcaneus probably result from the more rapid turnover of lead in trabecular bone (Gerhardsson *et al.*, 1993) compared with cortical bone lead in the tibia.

The skeleton contains at least two metabolic components of lead, trabecular and cortical bone, and the anatomical compartments and composition of different bones vary. The fingerbones contain more cortical than trabecular bone (Nilsson *et al.*, 1991), and, in the middle phalanx of the finger, the fraction of trabecular bone is lower than at its ends. Other parts of the skeleton, such as the calcaneus or vertebrae, which contain mostly trabecular bone, also have a more rapid bone lead turnover rate, whereas

TABLE 3

Age-Dependent Lead Exposure Scenarios Used for Physiological-Based Pharmacokinetic Modeling as Defined by Patterson (NAS, 1980)

	Age-dependent lead intake to Blood (μg Pb/d)				
Scenario	0–2[a]	2–10	10–20	20–50	50–60
Prehistoric man	0	0.07[b]	0.21	0.21	0.21
Contemporary man	0	10.0[c]	29.0	29.0	29.0
Occupationally exposed man[d]	0	10.0	29.0	100	29.0

[a] Years 0–2 are not modeled.

[b] Input for years 2–10 of age is set to 1/3 of adult Prehistoric Man by analogy to contemporary man.

[c] Input for 2–10 years of age is the mean of IEUBK defaults for ages 2–7. Note that this value, 10 μg/day, is 1/3 of contemporary man's adult daily intake.

[d] Input for 2–10, 10–20, and 50–60 years of age are equivalent to contemporary man. Input for age 20–50 is set to 100 μg/day to give a PbB of approximately 40 μg/dL.

TABLE 4
Patterson's Measured and Calculated Lead Levels in Ancient and Modern Humans Compared to the ICRP Model Predicted Lead Levels[a]

	Patterson				ICRP model: predictions					
	Ancient humans		Modern humans		Ancient humans		Modern humans		Occupationally exposed humans	
Age (years)	Young adult[b]	Middle-aged	17[b]	45	17	45	17	45	17	45
Blood lead (μg/dL)	N/R[c]	N/R	N/R	N/R	0.09	0.11	12.4	15.3	12.4	40.1
Bone lead (μg/g bone ash)	0.004	0.013	4.7	14	0.003	0.008	4.3	11.1	4.3	33.4
Body burden (mg)	0.013	0.040	13.3	40	0.100	0.250	14.6	35.1	14.6	105.8

[a] Patterson did not calculate lead uptake to blood for infants or children; thus, the ICRP model predicitions are not presented here.
[b] The lead values for "young adults" is calculated as 0.333, the bone lead concentrations at age 45, according to Barry (1979).
[c] N/R, not reported. Patterson did not calculate PbB levels resulting from natural lead exposure.

the tibia, which contains relatively more cortical bone, appears to have a slower half-time. Long bones also contain significant amounts of marrow. Hence, although individual bones may reflect more one type of bone anatomically and metabolically, qualifiers are indicated for individual bones (and their lead content) because individual bones are not anatomically homogeneous.

Of great relevance to the pioneering studies of Dr. Patterson, total body burdens of lead have been estimated, based upon KXRF data in lead workers, "mildly" exposed office workers at the same factory, and a control population (Erkklia *et al.*, 1992). The estimated total body burden of lead for workers was 107.9 $\pm$ 104 mg (mean $\pm$ SD) of lead, calculated using KXRF measurements expressed as lead/gram bone mineral. In mildly exposed office workers, the total body burden was 24 $\pm$ 27.7 mg; in the control population the value was 7.8 $\pm$ 26.6 mg (Erkklia *et al.*, 1992). Hence, even the control population contained a body burden of lead approximately 200 times Patterson's estimated burden of 40 μg in ancient humans. In office workers and in industrial workers, Patterson's estimated value is exceeded by three orders of magnitude.

Needleman *et al.* (1996) reported that at 7 years of age, borderline associations existed between higher hextiles of lead in bone and antisocial behavior. However, by 11 years of age, bone lead values in the higher hextiles were associated with a higher risk of attentional problems, aggression, delinquency, and externalizing and internalizing behaviors. These data systematically extended an earlier report by Denno (1990), who found that lead poisoning in male subjects was the most significant predictor of delinquency and adult criminality.

RELEASE OF LEAD FROM THE SKELETON TO BLOOD

Based upon the behavior of lead in bone (Patterson, 1980; Mushak, 1993) and factors affecting bone lead kinetics, it is evident that bone lead is in equilibrium with and undergoes release to the blood and other soft tissues. Currently, evidence linking bone lead release to blood is compelling. Studies of lead workers, particularly when there is a change in exposure, as with retirement, have demonstrated release of lead from bone to blood (Nilsson *et al.*, 1991; Christofferson *et al.*, 1986; Schutz *et al.*, 1987; Gerhardsson *et al.*, 1993). Although half-lives for lead loss from bone have differed somewhat between studies, the half-life for the contribution from intrabecular bone has been shown to be shorter than that from cortical bone (Schutz *et al.*, 1987a). Blood lead concentrations in retired workers are strongly influenced by bone lead content, and at least two distinct kinetic contributions to blood lead from skeletal lead have been documented (Nilsson *et al.*, 1991; Christoffersson *et al.*, 1993; Gerhardsson *et al.*, 1993; Schutz *et al.*, 1987a), perhaps reflecting differences in metabolism of lead (and calcium) in trabecular compared to cortical bone. Generally, bone compartments have half-lives of about 1 and 13 years, although another compartment has been shown to have a half-life of only 34 days (Nilsson *et al.*, 1991). Significant contributions to blood lead from bone stores have been documented during pregnancy

(Ward *et al.*, 1987; Zaric *et al.*, 1985; Bonithon-Kopp *et al.*, 1986), and even in non-pregnant women, skeletal lead may account for 45–70% of blood lead (Gulson *et al.*, 1995). Release from bone lead stores has also been reported in postmenopausal women (Silbergeld *et al.*, 1988) and in immobilized children, casted for long bone fractures, who were previously lead poisoned (Markowitz and Weinberger (1990). Moreover, in children poisoned by lead paint, there is a strong relationship between bone lead content assessed by LXRF and the results of the $CaNa_2EDTA$ mobilization test, as well as blood lead values (Rosen *et al.*, 1989, 1993). Chelatable lead is considered to be the best toxicological measure of the toxic potential of lead in young children (Chisolm, 1976).

Elevations in bone lead content correlate with renal disease in adults (Kijewski and Lowitz, 1982) and with neurobehavioral-cognitive deficits in children (Needleman *et al.*, 1979). These studies have been further supported by observations in normal adult volunteers, treated with stable isotopes of lead (Rabinowitz *et al.*, 1977) or assessed by natural isotopic differences (Manton, 1985; Smith *et al.*, 1995), indicating that bone lead is in equilibrium with blood lead and that alterations in exposure modify the bone–blood equilibrium (Rabinowitz *et al.*, 1977; Manton, 1985; Smith *et al.*, 1995). Based upon these data, it is reasonable to conclude that, in populations excessively exposed to lead months to years prior to assessment by LXRF or KXRF, noninvasive measures of lead in bone could serve to identify those at risk for future adverse health effects of lead. Moreover, these data, obtained by LXRF and KXRF, demonstrate the marked extent of "chronic lead exposure" (Patterson *et al.*, 1991), as proposed by Dr. Patterson in 1980 (NAS, 1980) and in 1991 (Patterson *et al.*, 1991).

BIOKINETIC MODELING OF LEAD IN PREHISTORIC POPULATIONS

To further illustrate Patterson's thesis that contemporary exposure levels of lead were more comparable to those in occupationally exposed workers than to those in prehistoric humans, we have used an age-dependent biokinetic model to compare these exposure scenarios. Physiologically based, pharmaokinetic and biokinetic models are developing into powerful tools for risk assessment (Anderson *et al.*, 1995; van Vliet and de Jongh, 1996), because they describe the absorption, tissue distribution, and elimination of a chemical toxicant using mathematical forms to describe complex, interactive biological processes, including age-dependent measures of growth and toxicant dynamics.

The ICRP model (Leggett, 1993a, b) was used, because the age-dependent physiological components of the model are included for adults to age 60 years. Thus, modeling is not restricted to children but can include lifetime or occupational exposure scenarios. The second important advantage is that the user has versatile and nearly complete access to almost all model input and output parameters. The major disadvantage of the ICRP model is that lead input is defined in micrograms/day to the gastrointestinal tract (Table 3), respiratory tracts, or directly to the blood. This disadvantage is not critical when the Pb uptake is experimentally defined or the situation is hypothetical.

Patterson determined the Pb content of ancient bones to be about 0.04 and 0.08 μg Pb/g dry wt bone in young adults and mature adults, respectively. These data then define the natural value in ancient humans as 0.013 μg compared with 14 μg Pb/g bone ash in modern humans. From these data, Patterson estimated that ancient man's lead uptake to blood was 0.21 μg Pb/day and that of contemporary man (1960s) was 29.0 μg/day (NAS, 1980). We have used Patterson's estimated Pb dose to blood in the ICRP lead model to further explore and illustrate the lead body burden between ancient and modern humans (Table 4). The ICRP model predictions for total lead body burden and lead concentration in bone ash of contemporary humans are about 20% less than Patterson's values. The ICRP model predicted the total lead body burden to be 250 μg Pb or about six times Patterson's estimate of 40 μg Pb in prehistoric humans. The model-predicted total body burden for an occupational exposure, 106 mg, is virtually identical to that recently derived from K-XRF measurements of lead workers, 107 mg (Erkklia *et al.*, 1992). The ICRP model-predicted blood lead levels for adult ancient humans are identical to the 0.11 μg/dl predicted by the IEUBK biokinetic model for preindustrial children eating a mixed diet (Mushak, 1993). Our model-predicted PbB levels are about sixfold higher than the natural blood lead concentration of 0.016 μg/dL, predicted by linear extrapolation of bone and blood lead concentrations in humans and experimental animals (Smith and Flegal, 1992). In contrast, the linear extrapolation estimates lead concentrations of 0.013 μg/g in bone ash, which is about 50% higher than those predicted by the ICRP model. Nonetheless, the model predictions are in very good agreement with Patterson's measurements and with each other, considering the limitations of the models discussed below.

Lifetime model predictions to age 60 years for PbB (μg/dL) and cortical and trabecular bone lead (μg/g

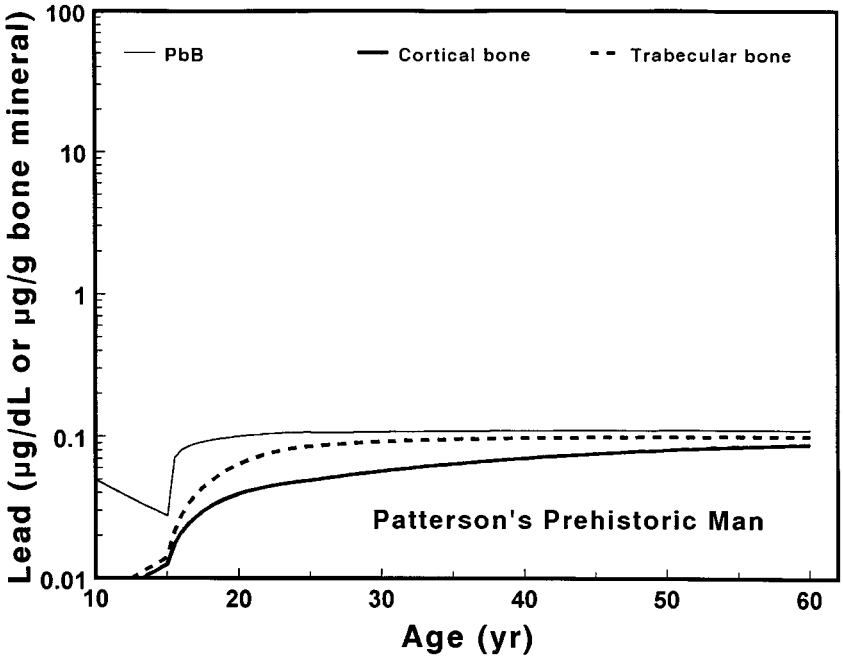

FIG. 2. Lifetime ICRP model-predicted blood and cortical and trabecular lead concentrations for Patterson's prehistorical man. Lead input to blood was as described in Table 1.

bone mineral) are presented in Figs. 2 to 4. These model predictions graphically illustrate Patterson's thesis that lead burdens of occupationally exposed and non-excessively exposed contemporary human populations are more similar to each other than to those at prehistoric levels. The predicted blood and bone levels are reasonable and consistent with literature values for occupational exposure in humans

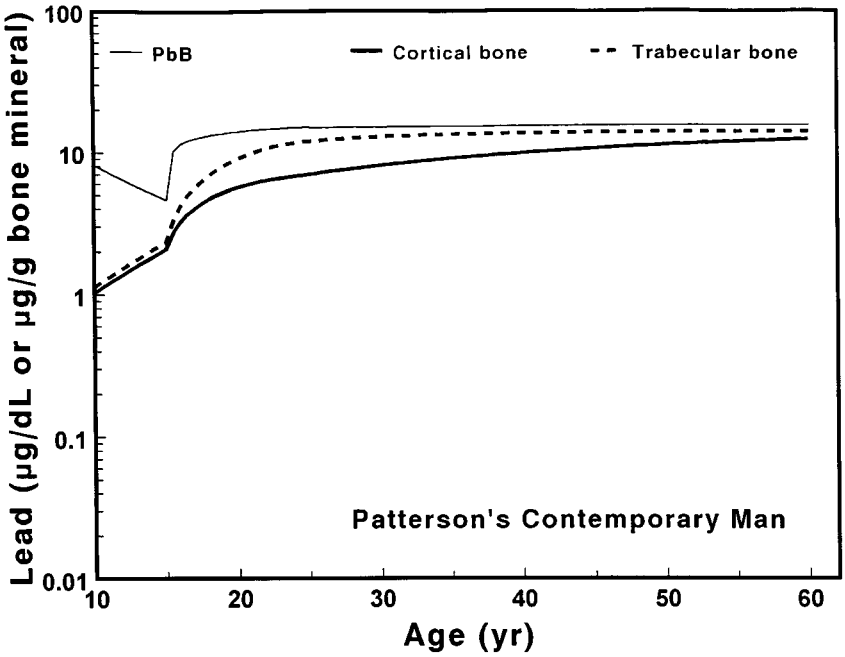

FIG. 3. Lifetime ICRP model-predicted blood and cortical and trabecular lead concentrations for Pattersons' comtemporary man. Lead input to blood was as described in Table 1.

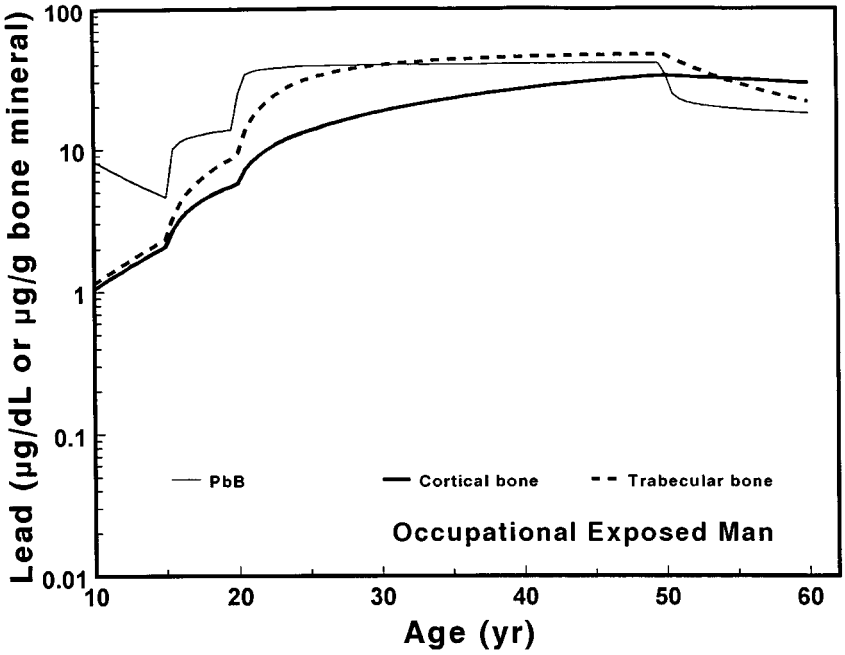

FIG. 4. Lifetime ICRP model-predicted blood and cortical and trabecular lead concentrations for a simulated occupational exposure. Lead input to blood was as described in Table 1 and was selected to result in PbB levels about 40 µg/dL during occupational exposure.

and thus inspire some confidence in the validity of the conclusions (Christoffersson *et al.*, 1986; Nilsson *et al.*, 1991).

This simulation has several obvious but minor limitations for simulating the kinetics of lead in ancient populations. First, the ICRP, like other biokinetic models for lead, was developed using data from contemporary humans with high lead levels. The nonlinear toxicokinetics of lead absorption and partitioning of lead in blood into the cellular and noncellular constituents is well documented at PbB between 10 and 50 µg/dL and greater. These nonlinearities are included in the ICRP model. However, if blood lead is nonlinear with exposure between 10 and 50 µg/dL, it is logical to anticipate that PbB levels from 10 to 0.10 µg/dl and lower may be nonlinear as well. However, in the absence of data, lineality is assumed. Second, prehistoric man was more active and had a different diet than contemporary humans.

INITIATIVES TO EXPLORE AND TO ALLEVIATE LEAD POISONING: METHODOLOGICAL AND PUBLIC HEALTH CONSIDERATIONS

Recommendations

Methodologic

(1) It is evident that, anatomically, a single bone is not wholly representative of cortical or trabecular bone. For example, the calcaneus has a cortical sheath, other bones have substantial marrow compartments, and subperiosteal bone, sampled together with cortical bone, may "act" metabolically more like trabecular bone. Hence, XRF calibration standards, ideally, should simulate the complexity of the anatomical configuration of bones. If such standards fail to meet the complexity of the anatomy of individual bones, the use of such standards may be limited to assessing the day-to-day instrument variation, instead of replicating, realistically, the anatomy of bone structures. In this regard, by either biopsy or autopsy studies, marrow, cartilage, bone sheaths, and periosteal bone (as examples) should be assessed for lead content by state-of-the-art analytical methods.

(2) Microlocalization of lead in bone requires considerably more intensive and systematic studies. Sensitive techniques, such as proton-induced X-ray emission, should be employed to assess lead levels in thinly sectioned bone samples (less than 50 µm).

(3) There is a need to develop and to recognize sensitive outcome measures, clinically and biochemically, as related to XRF values. To accomplish this task also involves associating (or not associating) adverse health outcomes as related to the biomarker of lead concentrations in different areas of the skeleton. Collectively, it is important to enhance the capability of XRF values to predict specific outcome measures.

(4) We suggest that modeling techniques should be more extensively applied in the bone lead field. Such endeavors should include integrating XRF data into biokinetic models for childhood, adult, and geriatric lead kinetics.

(5) Previous articles in the XRF field have appropriately defined the methodological minimum detection limit (MDL) within the context of relying upon the MDL to be sufficiently precise to yield a satisfactory quantitative estimate (Currie, 1968; Irgolic, 1994; Eaton, 1994). Examples of appropriate MDLs include $\sqrt{3}$ background counts, $\sqrt{2}$ background counts, 2 times the SD of the background, 3 times the SD of the background, $2\sqrt{2} \times$ SD of the background, 2 times the observed median error, and 1 times the SD of the background (Schutz *et al.*, 1987a; Christoffersson *et al.*, 1986; Somervaille *et al.*, 1985; 1988; Chettle *et al.*, 1989; Rosen *et al.*, 1989; Borjesson *et al.*, 1997; Nilsson *et al.*, 1991; Gerhardsson *et al.*, 1993; Price *et al.*, 1992; Hu *et al.*, *et al.*, 1989; Bellinger *et al.*, 1994; Hu *et al.*, 1991; Roels *et al.*, 1995).

In contrast, recent reports have substituted epidemiological approaches to determine a counting instrument's MDL. In these reports, because all epidemiological data (far below previously reported MDLs, including negative "values") have been used to define an analytical counting instrument's MDL, the net result yields extremely low detection limits (MDL) and population values which are separate from satisfactory quantitative estimates (Kim *et al.*, 1995a, b, 1996; Hoppin *et al.*, 1995; ATSDR, 1996). This new definition of a counting instrument's (KXRF) MDL yields population values, for example, of 1.38, 4.24, 5.25, and 7.49 μg Pb/g bone mineral in different age groups from the exceesively exposed town of Kellogg, Idaho (Landrigan *et al.*, 1976; Schwartz *et al.*, 1988, 1990; Ragaini *et al.*, 1977). In 1974, 170 of 172 children living within 1.6 km of the Kellogg smelter had BPb ≥ 40 μg/dl, and 38 (22.1% of those tested) had BPb levels ≥ 80 μg/dl, the highest being 164 μg/dl (above citations). As another example, bone lead values (μgPb/g bone mineral) have been reported in normal adult college students within the range of <1, 1–4, and >4 (Hoppin *et al.*, 1995), despite a "precision [MCL]...acceptable in diagnosing individual lead levels in bone... greater than 10 μg g^{-1}" (Kim *et al.*, 1995a).

We suggest that the inappropriate defintion of an instrument's detection limit (a true limit that one may decide whether or not the result of an analysis indicates detection), based upon epidemiological values, as a substitute for a MDL (cited in 14 references above), yields bone lead values that are artifically low and wholly inconsistent with the pioneering observations of Dr. Clair Patterson, as described and confirmed above. It is our view that a group, such as the International Committee of Radiation Protection, should assess this new definition of a counting instrument's MDL as well as data thus obtained.

Public Health

To further alleviate lead poisoning in American populations considered to be highly susceptible to lead toxicity, we are hopeful that the following recommendations will be seriously considered by public health and regulatory agencies.

(6) The CDC's 'Strategic Plan For the Elimination of Childhood Lead Poisoning" (1991) should be instituted to remediate about 3 million tons of extant leaded paint in American residential housing (NAS, 1993).

(7) Regulatory actions, initiated by the U.S. EPA, should be started to restrict and control the manufacturing and use of leaded products for which there are known and feasible substitutes.

(8) During infrastructure repairs, such as bridges and subways, such repairs should be carried out to fully protect the health of nearby susceptible populations, including community facilities (schools, parks, playgrounds).

In closing, we suggest that implementation of several of these recommendations will fulfill the dreams and expectations that Dr. Patterson expressed to ensure the health of the American population.

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