Final Performance Report

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"Vascular Effects of Chelation in Lead-Exposed Workers"

Principal Investigator: Michael J. Kosnett, MD, MPH*

Division of Occupational and Environmental Medicine
Box 0843
University of California, San Francisco 94143

* Current address:
Division of Emergency Medicine, B215
University of Colorado Health Sciences Center
Denver, CO 80262

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List of Abbreviations

KXRF = K X-ray fluorescence

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Significant findings

1. Using normative x-ray fluorescence data collected on 101 subjects with limited occupational lead exposure, an age and sex adjusted model of bone lead concentration has been established. Our cross-sectional data revealed that bone lead increases at the same rate in men and women between the age of 20 to 55 years, and thereafter increases at a faster rate in men. In addition to the variables age and sex, the best fitting multiple regression model for bone lead concentration ($R^2 = .66$, $P \leq .0001$) revealed a positive correlation with total pack years of cigarette smoking, and a negative correlation with a history of having nursed an infant for longer than two weeks. These data help to establish a reference range for assessing the lead burden of other populations with environmental or occupational lead exposure.

2. In four subjects in whom the influence of lead chelation on vascular reactivity was investigated, the magnitude of the change in blood pressure response to infused norepinephrine (as assessed by the dose-response slope) was not consistently diminished post-chelation. The magnitude of the change in blood pressure response to norepinephrine during placebo cycles was unexpectedly similar to that seen during chelation cycles. Although the low subject enrollment in this component of the research limited statistical power, the data did not provide evidence that lowering blood lead concentration by chelation exerts a significant impact on vascular reactivity.

3. In 28 lead-exposed workers undergoing K x-ray fluorescence measurements of lead in bone, blood lead measurement, and urinary measurement of lead post-chelation ("chelation challenge"), the K x-ray fluorescence measurements appeared superior to the chelation challenge tests as markers of longterm lead exposure. The bone lead values, but not the chelation challenge results, correlated with lifetime hours of high intensity lead exposure estimated by a detailed, blinded questionnaire. In a multivariable model, bone lead added little to the variance in urinary lead post-chelation explained by blood alone.

Usefulness of Findings

Noninvasive measurements of lead in bone by KXRF appears superior to blood lead as a biomarker of longterm, cumulative lead exposure in populations with both occupational and environmental lead exposure. The present study demonstrates that in the absence of substantial occupational lead exposure, KXRF measurements of bone lead concentration may be significantly influenced by variables relating to age, sex, cigarette consumption, and lactation. In future studies, KXRF measurements of bone lead concentration may have value in comparing the cumulative lead exposure of populations subjected to a variety of occupational and environmental lead sources. For most lead-associated pathology in adults, such as peripheral neuropathy, neuropsychological dysfunction, nephropathy, anemia, hypertension, or disordered spermatogenesis, the extent of cumulative exposure associated with the onset of illness has yet to be determined. The availability of in vivo KXRF as a quantitative biomarker of cumulative lead exposure may facilitate investigation of these dose-response relationships. Future longitudinal studies may also explore the impact of osteoporosis, pregnancy and lactation, hyperthyroidism, and other endocrinological conditions on the redistribution of lead from bone to sensitive soft tissues. The present data help to establish a reference range for assessment of bone lead concentration in populations and individuals, and identify key covariates to examine in future studies.

There has been growing evidence from epidemiological and animal studies that low-level exposure to lead may result in increased blood pressure, a major risk factor in the development of cardiovascular, cerebrovascular, and renovascular disease. Experimental data has suggested that lead may exert its pressor effects by potentiating the effect of catecholamines on vascular smooth muscle. In exploring the mechanism of this potential effect, the current study did not find that a chelation induced reduction in the blood lead concentration of lead-exposed, hypertensive workers results in a significant decline in vascular reactivity. In our experimental model, we found that the blood pressure response to norepinephrine infusion varied considerably during placebo (i.e. non-chelation) cycles. Blood pressure response to norepinephrine has been shown in other studies to be influenced by other factors, such as dietary sodium and emotional stress, that may dominate the effects of lead. Controlling for these variables requires an extended in-patient stay that is difficult to achieve in populations with occupational lead exposure. Although our experience does not in any way rule out the link between lead and blood pressure, it suggests that outpatient epidemiological studies, using multiple blood pressure measurements over time, may offer a more feasible approach in the future.

Urinary excretion of lead following a single challenge dose of a chelating agent (usually EDTA) has often been cited as a diagnostic test that is superior to blood lead as an indicator of total body lead burden or longterm lead exposure. We found that the urinary excretion of lead following a single DMSA chelation challenge does not correlate with either lifetime hours of high intensity lead exposure, or bone lead concentration assessed by K x-ray fluorescence. This finding, together with the results of two related investigations, lends serious doubts to the utility of chelation challenge tests in assessing body lead burdens, or in ultimately assessing the relationship of lead exposure to disease states.

Abstract

Background: Epidemiological and experimental evidence has associated occupational and environmental lead exposure with elevated blood pressure, possibly by potentiating the action of catecholamines on vascular smooth muscle. We sought to investigate this relationship by examining the impact of lead chelation on vascular reactivity as assessed by the change in blood pressure response to infused norepinephrine. Because blood lead concentration may be an unreliable biomarker of the longterm, cumulative exposure possibly responsible for lead's adverse health effects, two other potential biomarkers of lead exposure were also investigated: bone lead concentration (assessed by noninvasive K x-ray fluorescence), and urinary lead following a chelation challenge. Methods: To investigate the vascular effects of chelation, lead exposed workers underwent inpatient dietary equilibration, and received a stepped-dose infusion of norepinephrine immediately before and after an experimental intervention (EDTA chelation or placebo). For each subject, the change in slope of the norepinephrine-blood pressure response relationship pre and post chelation, a measure of the change in vascular reactivity, was compared between a chelation and a placebo cycle. Each subject also underwent a noninvasive assessment of bone lead concentration using the new technique of noninvasive K x-ray fluorescence. To establish age and sex adjusted normative data for bone lead concentration, 101 subjects between the ages of 10 to 78 years underwent noninvasive KXRF bone lead measurements and blood lead measurements, and were administered a questionnaire assessing potential sources of lead exposure and medical conditions affecting bone metabolism. To investigate the relationship of urinary lead after chelation challenge ("mobilizable lead") to bone lead and blood lead, 28 lead exposed workers underwent bone and blood lead measurements, and measurement of urinary lead in timed, overnight collections before and immediately following a single oral dose of 10 mg/kg DMSA. In a final component, additional work was undertaken to increase the precision of bone lead measurements by instituting hardware and software revisions. Results: In four subjects completing the vascular effects of chelation protocol, the change in the slope of the regression line relating norepinephrine infusion to change in blood pressure was not consistently different between the chelation cycle and the placebo cycle. Data generated during K x-ray fluorescence measurements of 101 subjects with limited occupational lead exposure yielded a piece-wise linear regression model in which bone lead concentration showed no significant change up to age 20, increased with the same slope in men and women between age 20-55, and then increased at a faster rate in men older than 55. In addition to the variables age and sex, the best fitting multiple regression model for bone lead concentration ($R^2 = .66$, $P \leq .0001$) revealed a positive correlation with total pack years of cigarette smoking, and a negative correlation with a history of having nursed an infant for longer than two weeks.

Twenty eight subjects with occupational lead exposure underwent bone lead measurements, blood lead measurements, and measurement of urinary lead post chelation. Lifetime hours of high intensity lead exposure, as estimated by a detailed, blinded questionnaire, correlated ($p < .01$) with patella lead concentration ($r = .71$), tibia lead concentration ($r = .53$), and blood lead ($r = .47$), but not with urinary lead concentration post chelation. Urinary lead concentration post chelation was highly correlated with blood lead ($r = .84$). In a multivariable model, bone lead added little to the variance in urinary lead post chelation explained by blood alone. Adjustment of urinary lead concentration by creatinine or baseline urine lead yielded similar results. Conclusions: Although limited by low statistical power, our model investigating the vascular effects of lead chelation did not observe a significant effect of chelation on vascular reactivity in lead exposed, hypertensive workers. In the 101 subjects with limited occupational lead exposure undergoing bone lead measurement, the age and sex related increases in bone lead concentration found by K X-ray fluorescence concur with published postmortem studies of bone lead concentration, and are consistent with both the kinetics of bone turnover, and secular trends in lead exposure. These data help to establish a reference range for assessing the lead burden of other populations with environmental or occupational lead exposure. The results obtained from the workers undergoing the single dose chelation challenge are consistent with other findings suggesting that lead mobilized into the urine by chelation predominantly reflects lead present in blood (and possibly other soft tissues), and not the major body burden of lead in bone. KXRF measurements therefore appear superior to chelation challenge tests as markers of longterm lead exposure.

Body of Report

1. Introduction and Background

There has been growing evidence from epidemiological and animal studies that low-level exposure to lead may result in increased blood pressure, a major risk factor in the development of cardiovascular, cerebrovascular, and renovascular disease.[1-9] From both a physiologic and public health standpoint, black adults have appeared particularly susceptible to the hypertensive effects of lead, and constitute a key target group for initial clinical investigation. In our group's recent cross-sectional study of San Francisco busdrivers, a strong relationship between lead and blood pressure was found exclusively in black subjects. [10] Other studies have found black hypertensives to have an elevated pressor response to infused catecholamines, [11] and to have higher intracellular stores of calcium, [12] the same mechanisms experimentally implicated in lead's blood pressure effects. Although black adults constitute a key susceptible group, large epidemiological evaluations, such as NHANES II, have found a positive association between lead and blood pressure in non-black subjects as well. [3]

Most investigations of the effect of lead on blood pressure and other health outcomes have relied on blood lead as a biomarker of exposure. However cumulative lead exposure may be better assessed by measurement of lead in bone, where greater than 95% of the adult body lead burden occurs with a half-life of several years.[13] The availability of K x-ray fluorescence as a noninvasive quantitative measurement of the lead concentration of cortical and trabecular bone may enhance the investigation of dose-response relationships in lead-associated disorders. [14,15]

The recent availability of the oral chelating agent 2,3 dimercaptosuccinic acid (DMSA) permits implementation of an outpatient chelation challenge test to investigate the relationship between bone lead stores and the "mobilizable" pool of lead that may be most closely associated with toxic effects on target tissues.[16] If both bone lead measurements and chelation challenge tests are performed on subjects whose lifetime occupational and avocational lead exposure has been carefully characterized by a detailed questionnaire, the relative utility of these tests as biomarkers of longterm, cumulative lead exposure may be determined.

2. Specific aims

The *initial* specific aims of the research program sought to experimentally investigate the role of lead exposure in the pathogenesis of human hypertension by studying the impact of lead chelation on the blood pressure

response to infused norepinephrine. Because prior studies have suggested that racial factors may interact with lead in the causation of hypertension, black hypertensives with occupational lead exposure were particularly targeted as research subjects. Difficulties in recruiting black hypertensives with occupational lead exposure for the extended inpatient protocol, the variability in blood pressure results encountered in the initial subjects enrolled, and the availability of bone lead measurements as a promising new biomarker of lead exposure resulted in an expansion of the specific aims. The *expanded* specific aims sought to a) investigate the utility of noninvasive K x-ray fluorescence measurements of lead in bone as a biomarker of lead exposure by determining the influence of demographic, exposure, and medical factors on the bone lead concentration of subjects with background (nonindustrial) environmental lead exposure; and b) to assess the relationship of urinary lead concentration post chelation, a frequently used measurement of "mobilizable lead", to the major body burden of lead present in bone.

3. Methods and procedures

To investigate the effect of lead chelation on vascular responsiveness, asymptomatic subjects with blood lead concentrations between 15 and 80 μg/dl were recruited as subjects from industries, unions, and occupational and environmental health clinics. Black adult men were specifically targeted for recruitment. Subjects with diastolic blood pressure between 85 and 105mmHg on two consecutive screenings, indicative of borderline to moderate hypertension, were admitted to the UCSF General Clinical Research Center, concurrent with outpatient and inpatient stabilization of dietary sodium. In each of two 5-day, inpatient cycles, subjects received a stepped-dose infusion of norepinephrine (known to generate a linear blood pressure response), immediately before and after an experimental intervention. The slope of the increase in blood pressure to norepinephrine was assessed. In one cycle, the intervention consisted of a 48-hour lead chelation with i.v. EDTA, in the other matched i.v. placebo. The order of the two cycles was assigned in a double blind, balanced manner. For each subject, the change in slope between the pre- and post-intervention NE infusion, a measure of the change in pressor sensitivity [11], was compared between the chelation and placebo cycles. If reduction in soft-tissue lead by chelation resulted in a decline in the reactivity of vascular smooth muscle, then the slope of norepinephrine-blood pressure response relationship would be expected to decline between the two norepinephrine infusions of chelation cycle, but remain relatively unchanged between the two infusions of the placebo cycle.

Noninvasive measurement of lead in bone was initially determined using an Abiomed Body Lead Analyzer. In this technique, the tibia (representative of cortical bone) and the patella (representative of trabecular bone) were sequentially irradiated with low energy photons from a ^{109}Cd source, and a

germanium detector linked to an amplifier and a multichannel pulse-height analyzer quantified the energy spectrum of the fluorescent x-rays. The lead fluorescence signal was normalized to the elastic, or coherently scattered x-ray signal, yielding a measurement of bone lead concentration expressed as micrograms of lead per gram of bone mineral (ppm). Additional details of the experimental approach, including the selection of subjects to obtain normative data, are described in a publication arising from this research.[17]

Blood lead concentrations were measured by anodic stripping voltammetry. An administered questionnaire designed for this project assessed a subject's lifetime occupational and avocational lead exposure, as well as medical conditions affecting bone metabolism. A copy of this unique interview instrument, which is being applied in future studies of lead exposure, is included as appendix *A*.

To assess the relationship between bone lead burden, and the "labile" pool of lead mobilized into the urine during chelation, subjects with occupational lead exposure collected urine specimens before and after an outpatient chelation challenge. Subjects with occupational lead exposure were recruited by referring physicians, the San Francisco Bay Area Regional Poison Control Center, or investigator-initiated contact with unions or industries whose occupational activities involved exposure to lead. In a manner analogous to the EDTA challenge tests now common in clinical practice [18], subjects underwent measurement of urinary lead excretion before and after a single dose of the oral chelating agent DMSA (dimercaptosuccinic acid; succimer). Baseline urinary lead excretion was first measured during a timed, overnight period. Urine specimens were collected by subjects at their homes. Subjects were asked to eat dinner at ≈ 6:00 to 7:00 pm. The site and content of the meal was left to the subject's discretion, provided that the following food and utensils were avoided: imported ceramics, leaded crystal glassware, imported canned food, wine or beer. Subjects were instructed to refrain from eating food after the 7:00 pm meal until 8:00 am the following morning, but were free to consume beverages. Three hours after the evening meal, subjects emptied their bladder. Using a supplied, labeled container, they then collected all urine voided during the next 10 hours, up to and including a final bladder emptying void performed between 7:00 to 8:00 am the following morning. Subjects completed a time log that reported the time interval of urine collection, and the content of meals and beverages consumed during the test. A baseline K-XRF measurement was scheduled for the morning or afternoon following the baseline urine lead measurement.

Measurement of urinary lead excretion after the DMSA challenge occurred during a similar timeframe beginning later that evening. Subjects again consumed and recorded dinner, beverages, and utensils as described above. Three hours after the evening meal, subjects emptied their bladder. They then immediately ingested a designated number of 100 mg DMSA capsules to deliver a dose of 10 mg/kg (rounded upward to the nearest 100 mg increment). Using a labeled container, they collected all urine voided during the next 10

hours, up to and including a final bladder-emptying void performed between 7:00 to 8:00 am the following morning. Specimens were delivered by subjects to the investigators' laboratory or picked up from subjects at their residence. The urine specimens were analyzed for lead by atomic absorption spectroscopy, and for creatinine by standard spectroscopic methods.

In an effort to improve the precision of the noninvasive measurements of bone lead concentration obtained in our laboratory, our final efforts on the grant included a modification of our K x-ray fluorescence hardware and software originally obtained through Abiomed, Inc. In consultation with collaborator Andrew Todd, PhD of the Mt. Sinai School of Medicine, we changed the configuration of our source-detector geometry to more closely approximate a 180 degree angle between incident and fluorescent photons. (The Abiomed geometry was approximately 160 degrees). This change reduced the magnitude of the Comptom background overlying the lead peaks in the fluorescence spectra. A smaller spot source of Cd109 was substituted for the larger disc source used in the Abiomed instrumentation, thereby reducing effective masking of the detector, and increasing potential count rate. A new analysis algorithm developed by Dr. Todd was also implemented that, compared to the Abiomed approach, increased the number of terms used to model the spectra background, and analyzed information in the lead beta peaks as well as the lead alpha peaks.

4. Results, discussion and conclusions

Three black subjects and one Caucasian subject completed the in-patient protocol examining the effect of lead chelation on vascular reactivity. The subjects included, respectively, a 51 year old construction worker, a 58-year-old scrap metal recycler, a 53-year-old machinist, and a 42 year old radiator repair mechanic. In each subject, the norepinephrine produced linear increases in blood pressure. An illustrative blood pressure-norepinephrine infusion response plot is depicted in Figure 1. Linear slopes were assessed on the basis of the change in either systolic or diastolic blood pressure per norepinephrine infusion rate, or plasma concentration of norepinephrine obtained from blood samples drawn at the end of each infusion rate. The slope data from the four subjects is presented in Table 1. Norepinephrine plasma assays were not run on subject IV and analysis on this subject is based only on the slope of the blood pressure increase versus norepinephrine infusion rate. Columns 5 and 6 indicate the *change* in slope (blood pressure response) associated with the placebo cycle and the chelation cycle, respectively. Column 7 was obtained by subtracting column 5 from column 6. If lead chelation were associated with a decline in vascular reactivity, the change in slope associated with the chelation cycle (column 6) would be expected to be larger than the change in slope associated with the placebo cycle (column 5) and hence the difference between the cycles (column 7) would be a positive value.

Inspection of the data reveals that the magnitude of *change* in slope found in the chelation cycle was not consistently greater than that found in the placebo cycle. Indeed, in some subjects, the variability between the two slopes of the placebo cycle was substantial. The experimental approach was patterned after the model of Dimsdale et al [11], which examined the effect of a change in dietary sodium on the change in slope of the blood pressure - norepinephrine infusion relationship. However, Dimsdale et al used only one norepinephrine infusion in the placebo cycle and one norepinephrine infusion in the intervention cycle to assess the effect of the intervention. By contrast, the present study used the difference between two infusions in each cycle (a total of four infusions) to assess the effect of the intervention. Although scientifically more rigorous, this latter approach must overcome greater statistical variability to discern a result. Given the lack of clear response to intervention in the first four subjects, it does not appear promising that the recruitment of the targeted number of subjects in this model would have yielded a result that was statistically significant.

Nevertheless, recruitment of additional subjects into the inpatient vascular effects of chelation protocol was vigorously attempted. In accordance with the hypothesis that race and lead may interact in the elevation of blood pressure, recruitment efforts focused on black males with an occupational lead exposure resulting in a blood lead concentration ≥ 15 μg/dL. The following steps partially illustrate the many approaches undertaken in recruitment: Subjects were sought in the course of medical surveillance performed on 51 lead workers from 5 different companies participating in lead surveillance at the San Francisco Occupational Health Clinic: of these, only two were black, and both failed to meet other enrollment criteria. A number of private employers and unions were contacted. Cleveland Wrecking, the largest demolition contractor in Northern California, agreed to cooperate with potential subject referrals for our lead research projects. Out of their entire lead exposed workforce, one black laborer with an elevated blood lead was successfully enrolled in the vascular effects of chelation protocol. The International Brotherhood of Iron Workers referred a cohort of 17 workers exposed to lead during torch demolition of a highway overpass for potential research participation. None of the workers were black, but five Caucasian workers did agree to participate in the DMSA chelation/bone lead measurement protocol. The workforce of Acme Steel, a strap-steel manufacturer with approximately 18 lead-exposed workers, was a source of subject referral for the DMSA chelation/bone lead measurement protocol, but again no eligible black workers were available for the vascular effects study. The commercial paint crew of UC Berkeley was the source of subject referral for six Caucasian subjects to the DMSA chelation protocol; however, none of the workers involved in lead paint abatement were black. Direct solicitation of five radiator repair shops in Berkeley, Richmond, and San Leandro, CA yielded referrals of two Hispanic and two non-Hispanic Caucasian radiator repairmen available for enrollment in the DMSA chelation/bone lead measurement protocol, but no black subjects were employed. Contact with the San Francisco

Police Department firing range resulted in recruitment of a Caucasian pistol range instructor for the DMSA chelation/bone lead measurement protocol, but no black range instructors with elevated blood lead concentration were available. Additional agencies and companies directly contacted in the recruitment effort included, in part, the paint crew of the California Department of Transportation; Redwood Painting, the Bay Area's largest structural steel painting contractor; Keystone Battery, the Bay Area's largest lead storage battery manufacturer; Trojan Battery, a large lead battery maintenance provider, and painters employed by contractors affiliated with the Northern California chapter of the Painting and Decorators Contractors Association. The University of California Press Office issued a press release on the vascular effects protocol to local and national media. Profiles that ran in several venues, including Bay Area black community newspapers, and the UCSF bulletin, generated several follow-up calls, but on screening, none of the black callers had documented lead exposures or blood lead concentrations > 10 μg/dL.

Bay Area occupational physicians on the clinical faculty of the Center for Occupational and Environmental Health were the source of referral of multiple non-black workers for the DMSA chelation/bone lead measurement protocol, but only one black worker, a machinist, was referred and enrolled in the vascular effects protocol. Referrals from the San Francisco Bay Area Regional Poison Control Center lead to the enrollment of two Caucasian lead workers (painters) to the DMSA chelation/bone lead measurement protocol. A 60 year old retired black male scrap metal worker was referred by the Poison Control Center as a potential candidate for the vascular effects study. Although he had a blood lead concentration of 35 μg/dL two years previously, his current blood lead of 10 μg/dL did not meet eligibility requirements. When eligibility requirements for enrollment in the vascular effects protocol were broadened to include non-black subjects, the Poison Control Center referred a hypertensive, white radiator repair worker who was enrolled in the study. However, this worker was successfully enrolled only because he had been terminated from his job. Many other actively employed lead workers, black and non-black, expressed interest in participating in lead research, but were unable to be away from work for the two 5-day inpatient cycles included in the vascular effects of chelation protocol. Consideration was given to diminishing the length of the inpatient stay to 3 days for each cycle by eliminating the first two inpatient days used for dietary and environmental equilibration. However, the variability encountered in the placebo cycles of the subjects enrolled for the full five days (see above) strongly suggested that elimination of these inpatient equilibration days would worsen the variability problem further.

Given the successful cultivation of referral sources and the identification of lead workers and others interested in participating in clinical research, subjects not eligible or available for the vascular effects protocol were enrolled in lead research protocols with related aims. Because the noninvasive measurement of lead in bone by K x-ray fluorescence appears superior to blood lead as a

biomarker of longterm, cumulative lead exposure [19,20] and because such longterm exposure may be important in the genesis of lead's adverse effects, the protocol to assess factors influencing bone lead concentration measured by K x-ray fluorescence was undertaken.

Full details regarding the protocol and its findings are presented in the attached publication from the Journal of the American Medical Association [17]. A total of 101 subjects (49 males, 52 females, age 11 to 78) were recruited from 49 of 123 households geographically located in a suburban residential neighborhood unexposed to a major source of industrial lead emissions. Following the exclusion of one outlier, log transformed bone lead concentration was highly correlated with age ($r = .71$, $P \leq .0001$). Bone lead concentration showed no significant change up to age 20, increased with the same slope in men and women between age 20-55, and then increased at a faster rate in men older than 55. In addition to the variables age and sex, the best fitting multiple regression model for bone lead concentration ($R^2 = .66$, $P \leq .0001$) revealed a positive correlation with total pack years of cigarette smoking, and a negative correlation with a history of having nursed an infant for longer than two weeks. Blood lead concentrations of the subjects were low (geometric mean 0.24 μmol/L, [4.9 ± 1.7 μg/dL]) and after log transformation were weakly correlated with log transformed bone lead concentration ($r = .23$, $P = .02$). In addition to measurement of lead in the tibia, a representative cortical bone, bone lead measurements were obtained in the patella, a representative trabecular bone. Log transformed patella lead concentrations were also highly correlated with age ($r = .65$, $P \leq .0001$), and increased at a faster rate in males than in females. [21] The age and sex related increases in bone lead concentration found by K X-ray fluorescence concur with published postmortem studies of bone lead concentration, and are consistent with both the kinetics of bone turnover, and secular trends in lead exposure. These data help to establish a reference range for assessing the lead burden of other populations with environmental or occupational lead exposure.

Adults with known occupational lead exposure were also recruited to undergo K x-ray fluorescence measurements of lead in bone, and to assess the relationship of bone lead to lead mobilized into the urine by a single dose of a chelating agent in a "chelation challenge test." K x-ray fluorescence measurements of lead concentration in the tibia and patella were obtained in 31 male workers (age 22 - 67) with a mean blood lead concentration of 17 μg/dL (range 2 - 48 μg/dL; geometric mean 11.3 μg/dL). Lifetime hours of high intensity occupational lead exposure, as estimated by a detailed, blinded questionnaire, correlated with log transformed tibia lead concentration ($r = .53$, $P = .002$) and with log transformed patella lead concentration ($r = .71$, $P = .0001$). A multiple regression model with terms in age, log transformed blood lead, and lifetime hours of high intensity occupational lead exposure accounted for two-thirds of the variance in log transformed patella lead concentration ($R^2 =$

.68, $P \leq .0001$; see Table 2). It is clear that bone lead reflects the impact of substantial lifetime occupational lead exposure, even after adjusting for current blood lead and age. This model confirms the utility of K x-ray fluorescence measurements as a unique biomarker of lead exposure. Although other investigators [19,20] have demonstrated the strong correlation ($r > .8$) of bone lead concentration with cumulative lead exposure estimated by integrated serial measurements of blood lead concentrations, the present study will be the first to report the detectable impact on bone lead burden of cumulative occupational lead exposure assessed by a quantitative, questionnaire-based approach. It is also the first model presented that simultaneously adjusts the relationship between bone lead and cumulative lead exposure using the key factors of age and current blood lead.

In 28 of the 31 lead workers, urinary lead content was measured in two timed, overnight collections obtained at baseline, and immediately following a single oral dose of 10 mg/kg DMSA. Mean baseline urinary lead excretion in a timed overnight collection (minimum 6.5 hours, maximum 11.25 hours) was 21 micrograms (range 1 - 101). Following a single oral dose of DMSA (10 mg/kg), mean overnight urinary lead excretion increased approximately 8-fold, to 173 micrograms (range 11 - 677). Urinary lead content after chelation was highly correlated with current blood lead concentration ($r = .84$, $P \leq .0001$), but not with lifetime hours of high intensity lead exposure ($r = .27$, $P = .17$). In a multivariable model, bone lead concentration added little to the variance in urinary lead post chelation that was explained by blood alone, (see Table 3). The data are consistent with findings by Schutz et al [22] and Tell et al [23] suggesting that lead mobilized into the urine by chelation predominantly reflects lead present in blood (and possibly other soft tissues), and not the major body burden of lead in bone. K x-ray fluorescence measurements of lead in bone appear superior to chelation challenge tests as markers of longterm lead exposure.

After implementing changes in the K x-ray fluorescence hardware and software intended to enhance the precision of the bone lead measurements, extensive calibration experiments were undertaken using 10 lead doped phantoms containing between 0 to 150 ppm lead. Excellent calibration lines were obtained with an R^2 of > .99, yielding an estimated lower limit of detection of approximately 3 to 6 ppm. Thirty human subjects with occupational or environmental lead exposure have undergone tibia and/or patella lead measurements with the new system, including 8 children (age 2 - 8 years) with a history of environmental lead exposure. Experiments to optimize in vivo spectra obtained with the new system have included repeated measurements on the same subject, altering the source to detector distance in a stepped progression from 20 mm to 60 mm. Work is in progress to optimize the in vivo measurement geometry and the analysis algorithms.

In conclusion, the data collected on the research protocols supported by this grant offer useful insights regarding the assessment of lead exposure and measurement of its effect on vascular reactivity. Although difficulties with subject recruitment limited our ability to reach statistically significant conclusions regarding the effects of lead chelation on vascular reactivity, the pilot data obtained suggest that the magnitude of such an effect, when considered within the context of this experimental model, is unlikely to be substantial, or to differ significantly from background variability. Our research does affirm the utility of noninvasive K x-ray fluorescence as a unique measure of lead exposure that is superior to blood lead and chelation challenge tests as a biomarker of longterm, cumulative lead exposure. The normative and occupational data collected will support the further use of this quantitative biomarker in assessment of dose-response relationships for elevated blood pressure and other adverse health effects of lead.

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Present and Possible Future Publications

a) Present Publications

1. Kosnett MJ. Unanswered questions in metal chelation. Clin Toxicol 30:529-547, 1992

2. Kosnett MJ, Becker CE, Osterloh JD, Kelly TJ. Assessment of body lead burden by K x-ray fluorescence measurement of lead in bone. [abstract] Vet Hum Toxicol, 34:355, 1992

3. Kosnett MJ, Becker CE, Osterloh JD, Kelly TJ, Pasta DJ. Factors influencing bone lead concentration in a suburban community assessed by noninvasive K x-ray fluorescence. JAMA, 271:197-203, 1994

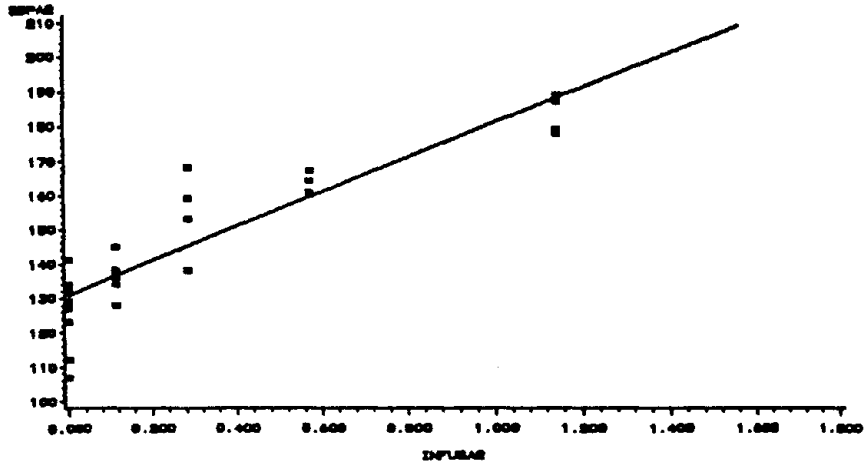
4. Kosnett MJ, Regan LS, Kelly TJ, Osterloh JD, "Interrelationships of urinary lead after DMSA challenge, bone lead burden, and blood lead in lead exposed workers [abstract] Vet Hum Toxicol, 36:363, 1994

5. Kosnett MJ. Noninvasive x-ray fluorescence measurement of lead in bone: Emerging applications of a new biomarker. Advances in X-ray Analysis [in press, 1995]

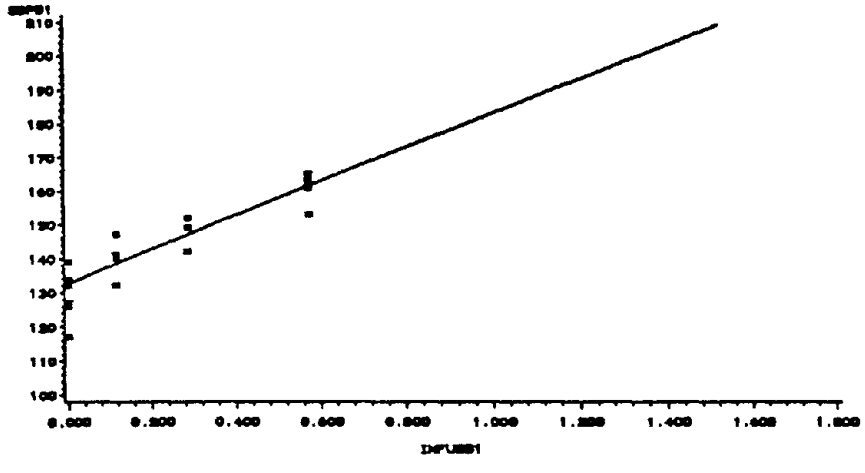
b) Planned future publication

1. Kosnett MJ, Regan LS, Kelly TJ, Osterloh JD, "Interrelationships of urinary lead after DMSA challenge, bone lead burden, and blood lead in lead exposed workers [abstract] Vet Hum Toxicol, 36:363, 1994 [full manuscript in preparation]

SBP by Infusion Rate



SBP by Infusion Rate



SBP by Infusion Rate

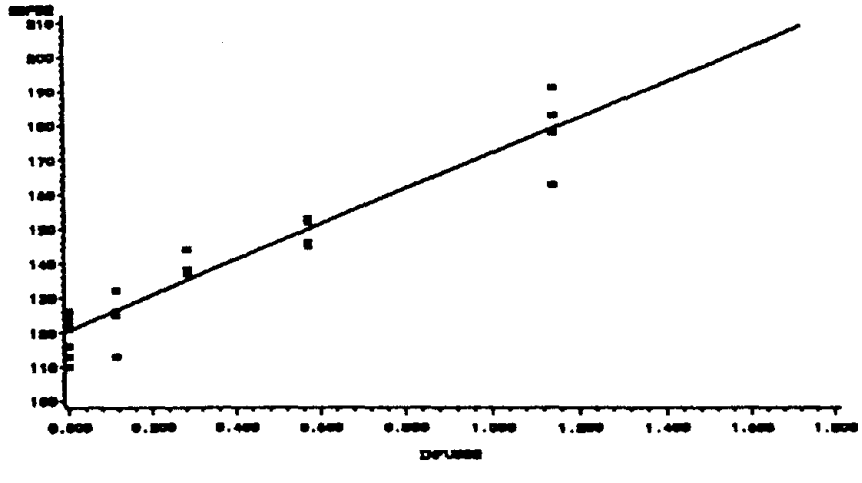


Table 1

Influence of Lead Chelation on the Systolic and Diastolic Blood Pressure - Norepinephrine response slope

Subject	Column 1 Pre- Placebo	Column 2 Post-Placebo	Column 3 Pre-EDTA chelation	Column 4 Post-EDTA chelation	Column 5: Δ Slope Placebo Cycle (Col 1 - 2)	Column 6 Δ Slope EDTA Cycle (Col 3 - 4)	Column 7 Difference in Δ Slope (Col 6 - 5)
A. Systolic blood pressure versus norepinephrine infusion rate							
I	.25065	.22390	.38550	.37016	.02675	.01534	-.01141
II	.11545	.13722	.14858	.11784	-.02177	.03074	.05251
III	.44347	.51135	.50939	.52864	-.06788	-.01925	.04863
IV	.16245	.39729	.23735	.22033	-.23484	.01702	.25186
B. Diatolic blood pressure versus norepinephrine infusion rate							
I	.06965	.04945	.12781	.09224	.02020	.03557	.01537
II	.05786	.03972	.07002	.07229	.01814	-.00227	-.02041
III	.15338	.14246	.17228	.15293	.01092	.01935	.00843
IV	.15248	.17229	.17050	.12318	-.01981	.04732	.06713
C. Systolic blood pressure versus plasma norepinephrine concentration							
I	.01317	.01301	.02114	.01516	.00016	.00598	.00582
II	.01584	.01695	.00937	.00997	-.00111	-.00060	.00051
III	.02579	.0426	.04117	.06219	-.01681	-.02102	-.00421
D. Diastolic blood pressure versus plasma norepinephrine concentration							
I	.00357	.00285	.00665	.00363	.00072	.00302	.00230
II	.00804	.00507	.00402	.00572	.00297	-.0017	-.00467
III	.00844	.01246	.01465	.01815	-.00402	-.0035	.00052

TABLE 2

Regression Model for Patella Lead concentration in workers (n = 31)

Variable	Parameter estimate	*t*	*P*
Hrs exp.	.00002	3.98	.0005
Log Pb blood	.196	3.50	.0016
Age	.012	2.27	.0314

$R^2 = .68$ ($P \leq .0001$)

TABLE 3

Bone lead adds little to the variance in chelated lead explained by blood alone

Dependent Variable: Urine Lead Excretion after DMSA Challenge

Variable	Parameter estimate	*t*	*P*
Blood Pb	11.2	5.64	.0001
Tibia Pb (ln)	16.12	0.18	.86

$R^2 = .71$

Study ID: ___ ___ ___ ___

UCSF XRF INTERVIEW

Interviewer's Name: _____ Intrv. ID: ___ ___ ___

Today's Date: ___ ___ / ___ ___ / ___ ___
MO DAY YR

Time Interview Started: ___ ___ : ___ ___ am / pm
(circle)

I want to thank you again for coming in today. We appreciate your taking the time to help us with our study. To help us evaluate your bone lead measurements we need to ask you some questions about your residence history, work history and certain health topics.

[GET WORK HISTORY FORM FROM R.]

1. [SEX BY OBSERVATION]

Male ..... [1]
Female ..... [2]

Let's begin.

2. What is your date of birth? ___ ___ / ___ ___ / ___ ___
MO DAY YR

I have some questions about your work and hobbies.

[TURN TO THE WORK HISTORY FORM. CHECK TO SEE THAT WORK HISTORY FORM IS COMPLETE AND LEGIBLE. NUMBER EACH JOB ENTRY. PLACE A DOUBLE LINE AT THE END OF R'S SELF-ADMINISTERED WHF TO SEPARATE FROM ADDITIONS]

4. Have you ever worked with or around lead, lead-based paint, or chemicals containing lead? Please include employment, unpaid jobs, military service, and hobbies.

Yes ..... [1]
No [SKIP TO Q5] ..... [2]
Don't Know [SKIP TO Q5] . [9]

4a. [Is this job/are those jobs] listed on your Work History Form?

[IF NO, FILL OUT WHF]

4b. In what activity of this job did you work with or around lead?

[BRACKET AND NUMBER EACH ACTIVITY WHICH INVOLVED LEAD, PLACE NUMBER IN COLUMN A ON WHF, ASK QUESTIONS 4c - 4e FOR THIS ACTIVITY]

4c. What years did you work as a [SPECIFY ACTIVITY]?

[RECORD CALENDAR YEARS IN COLUMN B ON WHF]

4d. We are interested in the percentage of time from [SPECIFY YEARS] that you were working as a [SPECIFIC ACTIVITY].

[ASK FOR EACH ACTIVITY] **[SHOW CARD 1]**
Please select the number on this card which best represents your answer

Never	1
1%	2
5%	3
25%	4
50%	5
75%	6
100%	7

In the years __to__ what percent of the time as a [MAIN JOB] did you spend [SPECIFY ACTIVITY]?

[RECORD LETTER FOR PERCENT TIME IN COLUMN %T ON WHF]

4e. While you were working as a [SPECIFY ACTIVITY] what percent of the time did you work with or around lead?

[RECORD LETTER FOR PERCENT TIME IN COLUMN %P ON WHF]
[RETURN TO WHF AND CLARIFY ANY AMBIGUOUS JOB DESCRIPTIONS. GO OVER ANY POTENTIAL LEAD JOBS WITH RESPONDENT STARTING WITH QUESTION 4b]

4f. While you were working as a [SPECIFIC ACTIVITY], how often would you encounter visible dust or fumes?

[Read aloud choices] Never ..... [1]
Sometimes ..... [2]
Most of the time or always [3]

4g. During this activity, how often would you use a respirator? By respirator I mean a face mask equipped with a replaceable cartridge, or a supplied air line.

[Read aloud choices] Never ..... [1]
Sometimes ..... [2]
Most of the time or always [3]

5. We may have already discussed some of these activities, however, I'd like to ask specifically, have you ever performed or assisted in any of the jobs, activities, or hobbies listed on this card?

[SHOW CARD 2. READ LIST ALOUD TO RESPONDENT]

	Ever Worked Yes=1, No=2	Number on WHF
Cutting, touching, or welding painted metal objects	___	_ _ _ _ _ _
Removing old paint from buildings or houses	___	_ _ _ _ _ _
Removing old paint from furniture	___	_ _ _ _ _ _
Sandblasting painted metal surfaces	___	_ _ _ _ _ _
Soldering	___	_ _ _ _ _ _
Lead, copper, or silver mining	___	_ _ _ _ _ _
Lead or copper smelting	___	_ _ _ _ _ _
Steel foundry work using lead for alloys	___	_ _ _ _ _ _
Brass,bronze or copper foundry work	___	_ _ _ _ _ _
Lead battery manufacturing or reprocessing	___	_ _ _ _ _ _
Mixing lead-containing chemicals or powder	___	_ _ _ _ _ _
Casting lead in molds, weights, or keels	___	_ _ _ _ _ _
Making lead bullets	___	_ _ _ _ _ _
Manufacturing or spraying lead pesticides (lead arsenate)	___	_ _ _ _ _ _
Galvanizing with lead	___	_ _ _ _ _ _
Lead abatement work	___	_ _ _ _ _ _
Automobile radiator work	___	_ _ _ _ _ _
Pistol or rifle range use	___	_ _ _ _ _ _

Lead crystal glass making	___	__	__	__
Stained glass or art glass work using lead came	___	__	__	__
Gemstone polishing or grinding using lead	___	__	__	__
Painting	___	__	__	__
Splicing/cutting jacketed electrical cable	___	__	__	__
Plumbing or pipefitting	___	__	__	__
Boat building and repair	___	__	__	__
Machininist and metal work	___	__	__	__
Punch and stamp press operation	___	__	__	__
Plastics manufacturing	___	__	__	__
Paint or pigment mixing or manufacturing	___	__	__	__
Enameling	___	__	__	__
Ceramics or pottery	___	__	__	__
Use of lead fishing weights	___	__	__	__
Imitation pearl manufacture	___	__	__	__
Commercial canning	___	__	__	__
Ammunition manufacturing	___	__	__	__
Gasoline refining	___	__	__	__
Hazardous waste disposal work	___	__	__	__
Scrap metal work	___	__	__	__
Printing press operation	___	__	__	__
Typesetting - linotype or handset lead type	___	__	__	__
Gasoline station attendant	___	__	__	__
Automobile repair (body work or mechanical)	___	__	__	__
Any other activity involving lead	___			
SPECIFY: 1 _____		__	__	__
2 _____		__	__	__
3 _____		__	__	__

DO NOT CODE (OTHER LEAD ACTIVITIES)
1 ___ ___ 2 ___ ___ 3 ___ ___

[IF NEVER WORKED AT ANY OF THE ABOVE JOBS, ENTER 2]: ___
----> [AND SKIP TO Q. 7]

[FOR EACH 'YES' ASK:]

5a. Is this job or activity part of one of the jobs previously listed or just entered on the WHF?

[CHECK FOR DUPLICATIONS]

[IF YES, DETERMINE APPLICABLE JOB AND ADD ACTIVITY]

[IF NO, CREATE NEW JOB FOR THIS ACTIVITY AND INCLUDE HOURS PER WEEK AND WEEKS PER YEAR]

[IF ACTIVITY DOES NOT FIT IN A JOB, WRITE "HOBBY" IN INDUSTRY COLUMN AND RECORD HOURS PER WEEK AND WEEKS PER YEAR FOR ACTIVITY, WRITE '1' IN THE 'H' COLUMN]

[BRACKET AND NUMBER EACH ACTIVITY WHICH INVOLVED LEAD, PLACE NUMBER IN COLUMN A ON WHF, ASK QUESTIONS 4c - 4e FOR THIS ACTIVITY AND RECORD NUMBER FROM WHF BESIDE APPROPRIATE ACTIVITY]

6. During the <u>past year</u> have you worked with lead as part of any job, hobby, military service or other activity?

Yes ..... [1]

(SPECIFY) _____ ___ ___ ___ (DO NOT CODE)

No [SKIP TO Q7] ..... [2]

6a. How long ago was it? [MOST RECENT] ___ ___
[DAY=1, WEEK=2, MONTH=3, YEAR=4] ___

6b. Have you ever had a blood lead test?

Yes ..... [1]
No [SKIP TO Q7] ..... [2]

6c. Has your current or most recent job had a blood lead monitoring program?

Yes ..... [1]
No ..... [2]

6d. What was your most recent lead level?

Date ___ ___ ___ (mo day yr) Level _____ Units_____ (if known)

6e. What were the results of your previous blood lead tests?

Date _____ Result _____
Date _____ Result _____
Date _____ Result _____
Date _____ Result _____

Date _____ Result _____

(After subject provides as much data as possible by recall, ask whether a record of these tests is available)

Source, if available:_____

6f. Have you ever been removed from work because of a high lead level?

Yes ..... [1]
No ..... [2]

6g. If yes, number of times removed from work ____

Date	Level	Amount of time off work [WEEKS..1, MONTHS..2, YEARS..3]		
_____	_____	____	____	_____
_____	_____	____	____	_____
_____	_____	____	____	_____

7. Counting only houses **built before 1960**, have you ever worked or assisted on home remodeling projects that involved scraping, stripping, burning, or sanding paint?

Yes ..... [1]
No [SKIP TO Q8] ..... [2]

7a. How many of these projects on houses built before 1960 have you worked on? __ __

7b. How many of these paint removing projects did you work on....

A.	Before 1980	__ __
B.	1981 through 1985	__ __
C.	1986 through 1989	__ __
D.	Since 1990	__ __

[VERIFY THAT TOTAL OF THREE COLUMNS EQUALS ANSWER IN 7a.]

Now I have some questions about other activities people sometimes engage in.

8. Have you smoked at least 100 cigarettes in your lifetime?

Yes ..... [1]
No [SKIP TO Q10] ..... [2]

8a. How old were you when you first started smoking cigarettes regularly? By regularly I mean at least one cigarette a week. __ __

[CODE '-3' IF R. HAS NEVER SMOKED AT LEAST ONE CIGARETTE A WEEK AND SKIP TO Q.10]

8c. We're interested in how your smoking patterns may have changed over time. When you first started smoking at age [number from Q. 8a] how many packs of cigarettes a day did you smoke?

[RECORD ANSWERS BELOW]

8d. And at what age did the number of packs change by at least a half a pack a day?

8e. And at that age, how many packs a day were you smoking?

[CONTINUE WITH QQ. 8d AND 8e UNTIL CURRENT AGE OR LAST SMOKING PATTERN HAVE BEEN DESCRIBED, CODE '96' FOR CURRENT AGE IN LAST PATTERN]

	Age 1st Smoked/ Changed	Packs Per Day
Pattern 1	__ __	__ . __
Pattern 2	__ __	__ . __
Pattern 3	__ __	__ . __
Pattern 4	__ __	__ . __
Pattern 5	__ __	__ . __

[PROBE FOR EVERY SMOKING PATTERN, INCLUDING PERIODS R. STOPPED, AND VERIFY THAT YOU ARE CURRENT UP TO TODAY OR UP TO R'S LAST CIGARETTE]

9. Have you smoked any cigarettes during the past month?

Yes ..... [1]
No [SKIP TO Q10] ..... [2]

9a. During the past month, on average how many packs of cigarettes did you smoke in one day? ___ . ___

10. Do you smoke pipes or cigars regularly. By regularly I mean at least once a day?

Yes ..... [1]
No [SKIP TO Q11] ..... [2]

10a. How many years have you been smoking pipes or cigars regularly? ___ . ___

11. These next questions are about drinking alcoholic beverages. By alcoholic drinks I mean drinks containing beer, wine, or liquor.

In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage? Do not count small tastes.

Yes ..... [1]
No [SKIP TO Q16] ..... [2]

11a. How old were you when you first started drinking alcoholic beverages regularly, regularly meaning at least one drink a month. ___ ___

[CODE '-3' IF R HAS NEVER DRANK REGULARLY AND SKIP TO Q 16]

11b. How many years in all have you drunk alcoholic beverages regularly? Don't count years when you didn't drink. ___ ___

11c. On the average, in the past 12 months, how many days per month did you drink alcoholic beverages? ___ ___

11d. On average, in the past 12 months when you did drink alcohol, how many drinks per day did you have? By a drink I mean a 12 oz. beer, a 4 oz. glass of wine, or an ounce of liquor. ___ ___

[SHOW CARD 3]

11e. Which letter best represents the percentage of drinks in the past 12 months which were wine? ___

None	1
1%	2
5%	3
25%	4
50%	5
75%	6
100%	7

11f. Was there ever a time or times in your life when you drank 5 or more drinks almost every day? ___

12. During your lifetime, have you ever had any moonshine? By moonshine I mean alcohol made in a homemade still.

Yes ..... [1]
No [SKIP TO Q17] ..... [2]

12a. How many total pints of moonshine have you had in your lifetime?

Less than one pint ..... [1]
One to 10 pints ..... [2]
11 to 100 pints ..... [3]
More than 100 pints ..... [4]

Now I have a few questions about your medical background.

17. Has a doctor ever told you that you had lead poisoning?

Yes ..... [1]
No [SKIP TO Q18] ..... [2]
Don't know ..... [9]

17a. How many episodes of lead poisoning were diagnosed? __ __

17b. In what year were you (first/next) diagnosed with lead poisoning?
[RECORD ANSWERS BELOW. FOR EACH EPISODE, ASK]:

17c. In this episode, were you hospitalized?

17d. In this episode, was blood drawn to measure the lead level?
[IF NO, SKIP TO Q18]

17e. What was the lead level in your blood?

17f. In this episode, what kind of treatment, if any, did you receive?

TREATMENT CODES-DO NOT READ	
NO TREATMENT	A
CHELATION	B
EDTA, VERSENATE	C
BAL	D
DMSA, CHEMET, SUCCIMER	E
PENICILLAMINE	F
INJECTION OR IV	G
OTHER:(SPECIFY)_____	H
TREATMENT NOS	I
DON'T KNOW	J

	17b. Year	17c. Hosp. 1=yes 2=no	17d. Blood Drawn	17e. Lead Level	17f. Treatment [ENTER UP TO 3 PER EPISODE]
1st	19__	__	__	__ __ __	__ __ __
2nd	19__	__	__	__ __ __	__ __ __
3rd	19__	__	__	__ __ __	__ __ __

18. Have you ever had bullets or buckshot lodged in your body for more than one week?

Yes ..... [1]
No [SKIP TO Q19] ..... [2]

18a. What is the TOTAL amount of time you have had bullets in your body? __ __

[WEEKS...1, MONTHS.....2, YEARS....3]

18b. Do you still have bullets or buckshot in your body?

Yes ..... [1]
No [SKIP TO Q19] ..... [2]

18c. Where is the bullet located? _____

19. Has a doctor ever told you that you had (disease)...

[FOR EACH YES, ASK QQ. 19a AND 19b]:

19a. In what year were you diagnosed with ( )?
19b. What treatment or medication did you receive?

	19. Ever had	19a. Year Diag.	19b. Treatment [ENTER UP TO 3 CODES PER DISEASE]	DO NOT CODE
Arthritis	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ _____ 19__ __ _____ 19__ __ _____		___ ___ ___
Osteoporosis/ thinning bones	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ _____ 19__ __ _____ 19__ __ _____		___ ___ ___
Osteomyelitis or bone infection	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ _____ 19__ __ _____ 19__ __ _____		___ ___ ___
Bone cancer	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ _____ 19__ __ _____ 19__ __ _____		___ ___ ___

	19. Ever had	19a. Year Diag.	19b. Treatment	DO NOT CODE
Any Cancer spreading to bone	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
(Specify: _____)			(___ ___) DO NOT CODE	
Specify other treatment:		19__ __ 19__ __ 19__ __	_____ _____ _____	___ ___ ___
Paget's disease (metabolic bone disease)	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ 19__ __ 19__ __	_____ _____ _____	___ ___ ___
Other Bone disease	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
(Specify: _____)			(___ ___) DO NOT CODE	
Specify other treatment:		19__ __ 19__ __ 19__ __	_____ _____ _____	___ ___ ___
Hyperthyroidism / overactive thyroid	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ 19__ __ 19__ __	_____ _____ _____	___ ___ ___
Parathyroid disease	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ 19__ __ 19__ __	_____ _____ _____	___ ___ ___

	19. Ever had	19a. Year Diag.	19b. Treatment	DO NOT CODE
Gout	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ _____ 19__ __ _____ 19__ __ _____		___ ___ ___
Kidney failure (≥ 2 months duration)	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ _____ 19__ __ _____ 19__ __ _____		___ ___ ___
Iron Deficiency	___	19___ ___ 19___ ___	___ ___ ___ ___ ___ ___	
Specify other treatment:		19__ __ _____ 19__ __ _____ 19__ __ _____		___ ___ ___

TREATMENT CODES - DO NOT READ			
A	ALLUPURINOL	B	ANTIBIOTICS
C	ANTIINFLAMMATORY	D	CALCIUM
E	CALCITONIN		
F	CHEMOTHERAPY	G	DIALYSIS
H	ESTROGENS	I	ETIDRONATE(DIDRONEL)
J	FLUORIDE	K	IRON TABLETS/INJEC
L	KIDNEY TRANSPLANT	M	**MEDICATION NOS**
N	PARATHYROID HORMONE	O	RADIATION
P	RADIOACTIVE IODINE	Q	SURGERY
R	**TREATMENT NOS**	S	VITAMIN D
T	**NO TREATMENT**		
U	OTHER (specify)_____		

20. Have you ever broken a bone?

Yes ..... [1]
No [SKIP TO Q21] ..... [2]

[SHOW CARD 4]

20a. Please take a look at this list of bones. Which bone or bones have you broken?

[READ LIST SLOWLY. ASK QQ. 20b AND 20c FOR EACH YES]

20b. How many times did you break ( )?
20c. In what year did you (most recently) break ( )?

	20. Ever brk. 1=Y 2=N	20b. How many times did you break ( )?	20c. In what year [RECORD MOST RECENT]
Skull or any bone in head	___	___ ___	19___ ___
Clavicle or collar bone	___	___ ___	19___ ___
Spine or Vertebra	___	___ ___	19___ ___
Rib or Sternum	___	___ ___	19___ ___
Scapula (shoulder blade)	___	___ ___	19___ ___
Bone in hand or wrist	___	___ ___	19___ ___
Bone in your arm	___	___ ___	19___ ___
Hip	___	___ ___	19___ ___
Femur (upper leg)	___	___ ___	19___ ___
Kneecap	___	___ ___	19___ ___
Tibia or fibula (lower leg)	___	___ ___	19___ ___
Ankle	___	___ ___	19___ ___
Foot or toe	___	___ ___	19___ ___

21. Have you ever been immobilized or completely bedridden for 3 consecutive months or longer?

Yes ..... [1]
No [SKIP TO Q26 .....[2]

21a. During what time period (month and year) did this occur?

[RECORD MOST RECENT 3 OCCURRENCES]

[MO / YEAR TO MO / YEAR]

1. ___ ___ / ___ ___ to ___ ___ / ___ ___
2. ___ ___ / ___ ___ to ___ ___ / ___ ___
3. ___ ___ / ___ ___ to ___ ___ / ___ ___

22. Have you regularly experienced any of the following symptoms within the last six months? By regularly I mean at least once a week for at least three weeks during the last six months.

	yes	no	don't know
unintended weight loss > 5 lbs	___	___	___
night sweating	___	___	___
tire easily	___	___	___
lose temper easily	___	___	___
change in personality	___	___	___
nightmares	___	___	___
poor memory	___	___	___
difficulty reading	___	___	___
poor appetite	___	___	___
constipation	___	___	___
diarrhea	___	___	___
stomach cramps	___	___	___
depression	___	___	___
trouble concentrating	___	___	___
weakness of hands or feet	___	___	___
muscle pain	___	___	___
joint pain or swelling	___	___	___
metallic taste in mouth	___	___	___
numbness or tingling in hands	___	___	___
dizziness or fainting spells	___	___	___
swelling of legs of feet	___	___	___
shortness of breath	___	___	___
difficulty hearing	___	___	___
fast or irregular heartbeat	___	___	___
loss of interest in sex	___	___	___
headaches	___	___	___

26. Have you ever taken any of the following medications or dietary supplements for 4 consecutive weeks or longer? Please do not include multivitamins.

[FOR EACH YES, ASK QQ. 26a, 26b, 26c, AND 26d]:

26a. In what year did you first take ( )?
26b. In what year did you last take ( )?
26c. Are you currently taking ( )?
26d. Not counting the years you may have stopped, how long have you taken ( )? [DAY=1 WEEK=2 MONTH=3 YEAR=4]

	26 Ever Taken		26a Year 1st Taken	26b Year last Taken	26c Taking Now	26d How Long
Calcium supplements	___	(19)	___ ___	___ ___	___	___ ___ ___
Vitamin D	___	(19)	___ ___	___ ___	___	___ ___ ___
Prednisone, cortisone, or other steroids; do not include anabolic steroids taken for body building:	___	(19)	___ ___	___ ___	___	___ ___ ___

Have you ever taken any of the following diuretics or water pills for high blood pressure or other reasons?

Dyazide	___	(19)	___ ___	___ ___	___	___ ___ ___
Hydrochlorothiazide	___	(19)	___ ___	___ ___	___	___ ___ ___
Chlorthalidone	___	(19)	___ ___	___ ___	___	___ ___ ___
Moduretic	___	(19)	___ ___	___ ___	___	___ ___ ___
Any other high blood pressure medications	___ *[IF YES SPECIFY]:					
1_____		(19)	___ ___	___ ___	___	___ ___ ___
2_____		(19)	___ ___	___ ___	___	___ ___ ___

DO NOT CODE (OTHER DIURETICS)
1 ___ ___ ___ 2 ___ ___ ___ 3 ___ ___ ___

[SHOW CARD 6, AND READ THROUGH FOR R.]

27. Please take a look at this card and tell me, on average, during the past 12 months, which number on the card best describes your level of physical activity:

WALK LESS THAN 1 BLOCK OR CLIMB LESS THAN ONE FLIGHT OF STAIRS A DAY; NO SPORTS OR EXERCISE ..... [1]
WALK MORE THAN ONE BLOCK OR CLIMB MORE THAN ONE FLIGHT OF STAIRS A DAY; SOME SPORTS OR EXERCISE ..... [2]
ENGAGE IN VIGOROUS SPORTS OR STRENUOUS EXERCISE FOR MORE THAN ONE HOUR A DAY FOR AT LEAST 6 DAYS A WEEK ..... [3]

28. During last year's gardening season, how many days during the month did you eat vegetables from your garden or from a garden in your neighborhood? __ __

29. During the gardening season 5 years ago, how many days during the month did you eat vegetables from your garden or from a garden in your neighborhood? __ __

Now I have some questions about places you have lived.

30. In what decade was your current residence built?

_____

31. How long have you lived at your current residence?

___ ___
___

[WEEKS... 1, MONTHS... 2, YEARS... 2]

32. How would you describe the condition of the paint?

NOT PEELING ..... [1]
SOMEWHAT PEELING ..... [2]
EXTREME PEELING ..... [3]

33. Did you ever live within 400 yards (1/4 mile) of ( )?

[IF YES]:
33a. During what years did you live there?

	Ever live near	Years
A lead or copper smelter?	___	19 ___ ___ to 19 ___ ___

A lead battery reprocessing plant? ___ 19 ___ ___ to 19 ___ ___

Now I have a few final questions.

34. What is the highest year or grade of regular school you have completed or received credit for? Include college, but not trade or vocational school. ___

[COLLEGE = 13 THROUGH 16; POSTGRAD FROM YEAR 17]

35. How many years of vocational or technical school have you attended? ___
[ENTER '00' IF NONE]

[SHOW CARD 7]

36. Please look at this card and tell me which letter on the card best describes your ethnic or racial group.

White non-Hispanic ..... [1]
Hispanic..... [2]
Black..... [3]
Asian (INC. PACIFIC ISLAND) .. [4]
Native American Indian..... [5]
OTHER: _____ .... [6]

[SHOW CARD 8]

37. Please take a look at this card and tell me which letter on the card best describes your total household income in 1991 before taxes:

Less than $9,999 ..... [1]
10,000 to 19,999 ..... [2]
20,000 to 34,999 ..... [3]
35,000 to 59,999 ..... [4]
60,000 and over ..... [5]

38. How many people were supported by this income in 1991? __ __

That's the end of the questionnaire. Thank you again for taking the time to help us today.

Time Ended: ___ ___ : ___ ___ (am/pm)
(circle)

DO NOT ASK: INTERVIEWER COMMENTS:

A. Was anyone else present during this interview?

Yes ..... [1]
No [SKIP TO C] ..... [2]

B. Who was present?

[CODE ALL THAT APPLY]

Mother ..... [1]
Father ..... [2]
Other adult relative .... [3]
Other relative < 16 yrs . [4]
Attorney ..... [5]
Observer ..... [6]
Other: (_____).. [7]

C. How confident do you feel about the validity of R's answers?

Completely confident [SKIP TO F] ..... [1]
Some doubts ..... [2]
No confidence ..... [3]

IF ANY DOUBTS:
E. Which data do you have doubts about, and why?

_____
_____
_____
_____

F. Did R. have any difficulty in understanding or responding to the questions?

Patient alert, no difficulties ..... [1]
Some difficulty ..... [2]
Patient had difficulty ..... [3]

G. Is there anything else about this interview or its circumstances which seems significant to you?

Yes [SKIP TO H] ..... [1]
No ..... [2]

H. Please describe:

_____

Interviewer Edit: ___ ___ / ___ ___ / ___ ___ ___ ___ ___

2nd Edit: ___ ___ / ___ ___ / ___ ___ ___ ___ ___

Coding: ___ ___ / ___ ___ / ___ ___ ___ ___ ___

First (A) Entry: ___ ___ / ___ ___ / ___ ___ ___ ___ ___

2nd (B) Entry: ___ ___ / ___ ___ / ___ ___ ___ ___ ___

UCSF XRF INTERVIEW

Subject ID: ___ ___ ___ ___

Subject Information

Name _____

Address _____

_____

Phone # _____

Referred or Recruited by:

Name _____

Address _____

_____

Phone # _____

Circle Referral Category:

Physician Attorney Govt. Agency Co-Worker

Insurance Friend/Family Self Other _____

Most recent lead industry employment:

Company _____

Address _____

_____

Type of Industry _____

WORK HISTORY

__ __ __ __

We are interested in every job you have ever held for longer than 1 month. For each job please answer the following questions starting with the most recent position. Please include only jobs you have held since the age of 12 and include military service. An example has been provided.

What Industry/ Business did you work in?	What were your activities/duties? (exactly what did you do)	What Years did you work at this job?	What were your average		Please Leave Blank								
			Hours per Week	Weeks per Year	A	B	T	P	D	R	Pr	I	H
Most Recent		Start 19 __ __ End 19 __ __	__ __	__ __		__ __ to __ __							
						__ __ to __ __							
						__ __ to __ __							
		Start 19 __ __ End 19 __ __	__ __	__ __		__ __ to __ __							
						__ __ to __ __							
						__ __ to __ __							
		Start 19 __ __ End 19 __ __	__ __	__ __		__ __ to __ __							
						__ __ to __ __							
						__ __ to __ __							
		Start 19 __ __ End 19 __ __	__ __	__ __		__ __ to __ __							
						__ __ to __ __							
						__ __ to __ __							
		Start 19 __ __ End 19 __ __	__ __	__ __		__ __ to __ __							
						__ __ to __ __							
						__ __ to __ __							

(Continued on Reverse)

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4. Title and Subtitle Vascular Effects of Chelation in Lead-Exposed Workers			5. Report Date 1995/10/19
			6.
7. Author(s) Kosnett, M. J.			8. Performing Organization Rept. No.
9. Performing Organization Name and Address Occupational Health Clinic, Division of Occupational and Environmental Medicine, University of California, San Francisco, California			10. Project/Task/Work Unit No.
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15. Supplementary Notes

16. Abstract (Limit: 200 words) The effect of chelation in lead (7439921) exposed, hypertensive workers on vascular reactivity as monitored by changes in blood pressure response to infused norepinephrine was investigated. Three black workers and one Caucasian worker who had been exposed to lead underwent inpatient dietary equilibration, and were given a stepped dose infusion of norepinephrine just before and just after each experimental intervention of EDTA chelation or placebo. Each subject also underwent a noninvasive assessment of bone lead concentration. There was no significant effect of chelation on vascular reactivity in these lead exposed, hypertensive workers. K-X-ray fluorescence measurements of lead in bone were made in 31 male workers with known lead exposure, and a chelation challenge test was performed in 28. The K-X-ray fluorescence measurement was found to be a better marker of long term lead exposure than the chelation test. In a group of 101 individuals with only limited occupational lead exposure, the age and sex related increases in bone lead concentration were consistent with the kinetics of bone turnover and secular trends in lead exposure. The author concludes that K-X-ray fluorescence measurements are superior to chelation challenge tests as markers of long term lead exposure.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms NIOSH-Publication, NIOSH-Grant, Grant-Number-K01-OH-00108, End-Date-03-30-1995, Cardiovascular-system-disorders, Lead-poisoning, Occupational-exposure, Biological-monitoring, Chelating-agents

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages 46
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(See ANSI-Z39.18) *See Instructions on Reverse*

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