Past adult lead exposure is associated with longitudinal decline in cognitive function

B.S. Schwartz, MD, MS; W.F. Stewart, PhD, MPH; K.I. Bolla, PhD; D. Simon, MS; K. Bandeen-Roche, PhD; B. Gordon, MD, PhD; J.M. Links, PhD; and A.C. Todd, PhD

Article abstract—*Objective:* To determine whether adults with past exposure to neurotoxicants have progressive declines in cognitive function years after exposure has ceased, and whether tibia lead is a predictor of the magnitude of change. *Methods:* A total of 535 former organolead manufacturing workers with a mean age of 55.6 years, a mean duration of 16 years since last occupational lead exposure, and low blood lead levels at the first study visit and 118 controls were evaluated with neurobehavioral tests two to four times over 4 years. "Peak" tibia lead levels, estimated from current levels measured by X-ray fluorescence, were used to predict changes in cognitive function over time. *Results:* In former lead workers, peak tibia lead ranged from −2.2 to 98.7 μg Pb/g bone mineral. Compared to controls, former lead workers performed worse over time for three tests of visuo-constructive ability and verbal memory and learning ($p < 0.05$). In former lead workers, peak tibia lead predicted declines for six tests of verbal memory and learning, visual memory, executive ability, and manual dexterity ($p < 0.05$ for four tests and < 0.10 for two additional tests). On average, for these six tests, an increase of 15.7 μg/g of peak tibia lead was equivalent in its effects on annual test decline to 5 more years of age at baseline. *Conclusions:* These are the first data to suggest that cognitive function can progressively decline due to past occupational exposures to a neurotoxicant.

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There is a high level of interest in whether adult exposure to neurotoxicants can cause long-term, progressive declines in CNS function beyond what would be expected due to normal aging alone. This question has important implications for understanding the causes of decline in cognitive function that occur as we age. Among putative neurotoxicants, lead has arguably been the most well studied.[1-7] Whereas lead exposure early in life is associated with cognitive and behavioral consequences in early adulthood,[1] no studies have successfully examined the late life neurobehavioral effects of lead exposure received primarily as an adult. Several studies have examined the neurobehavioral effects of current lead exposure, but no study, to date, has evaluated whether past, cumulative adult lead exposure is associated with long-term declines in cognitive function.[7]

To determine whether past exposure to lead as an adult can cause progressive changes in cognitive function, we conducted a 4-year longitudinal study of 535 former organolead manufacturing workers with past exposure to organic and inorganic lead. Change in cognitive function in former lead workers was compared to that in 118 nonexposed controls from the same neighborhoods as former lead workers, and also evaluated in relation to cumulative lead absorption, estimated by measuring tibia lead content by X-ray fluorescence.[8-12]

In a cross-sectional analysis of neurobehavioral test scores from one year of the study, tibia lead was a consistent predictor of poorer neurobehavioral test scores in the cognitive domains of manual dexterity, executive ability, verbal intelligence, and verbal memory and learning.[13] However, evaluation of longitudinal change in cognitive function in relation to lead absorption is of critical importance because such analysis allows assessment of the presence and rate of change over time (i.e., the persistence or progression of effects), is less subject to the influence of selection bias and confounding, and has not been successfully studied to date.

By including subjects from 40 to 70 years of age without current occupational exposure to lead, the study has important implications regarding the pro-

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From the Divisions of Occupational and Environmental Health (Drs. Schwartz and Stewart) and Radiation Health Sciences (Dr. Links), Department of Environmental Health Sciences, and the Departments of Epidemiology (Drs. Schwartz, Stewart, and Simon) and Biostatistics (Dr. Bandeen-Roche), Johns Hopkins School of Hygiene and Public Health; Departments of Medicine (Dr. Schwartz) and Neurology (Drs. Bolla and Gordon), Johns Hopkins School of Medicine; Neuropsychology Division, Department of Cognitive Sciences (Dr. Gordon), Johns Hopkins University, Baltimore, MD; and Department of Community and Preventive Medicine (Dr. Todd), Mount Sinai Medical Center, New York, NY.

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Address correspondence and reprint requests to Dr. Brian S. Schwartz, Division of Occupational and Environmental Health, Johns Hopkins School of Hygiene and Public Health, Room 7041, 615 North Wolfe Street, Baltimore, MD 21205; e-mail: bschwart@jhsph.edu

gression of cognitive decline after cessation of occupational lead exposure, and the relative contributions of normal aging and past lead exposure to change in cognitive function.

Methods. *Study design and subject recruitment.* A 4-year prospective evaluation of cognitive function was conducted in former employees of a chemical manufacturing facility in the eastern United States that produced tetraethyl and tetramethyl lead.[13-15] At the time the study was initiated, all subjects had ceased occupational exposure to lead, an average of 16.0 years before the first study visit. The study was approved by the Committee for Human Research at the Johns Hopkins School of Hygiene and Public Health, and all subjects provided informed, written consent.

Details of the selection and recruitment of study subjects have been reported elsewhere.[14,15] Former lead workers were eligible for recruitment if they were ever employed in the lead facility on or after January 1, 1950, were men, and were between 40 and 70 years of age in 1995. Of the estimated 968 eligible former workers who we attempted to contact, 73% enrolled into the study.[14,15] Limited data available on refusals suggested that the mean age and work duration of refusals did not differ from subjects who were enrolled. For comparison, community-based nonexposed control subjects were also recruited for the study. A database of telephone numbers in the residential areas of former lead workers was purchased from a commercial vendor. Numbers in the exchanges of former lead workers were randomly selected and telephoned to identify households with eligible men who were then frequency-matched to former lead workers for age, education, and race.

Subjects were enrolled from June 1994 to October 1997 and completed two to four annual visits in which cognitive function was assessed. A total of 703 former lead workers and 130 nonexposed controls were enrolled in the study. For former lead workers, the current report is based on 543 subjects on whom tibia lead levels were measured during the third year of the study. Tibia lead measurements were completed on 84% of eligible former lead workers (i.e., the denominator did not include those who were too ill, deceased, or had moved out of the area by the third year of the study).[14,15] Tibia lead measurements were not performed in nonexposed controls.

Follow-up status. The 543 former lead workers were enrolled over a 3-year period, with 403 (74.2%) enrolled in the first year, 101 (18.6%) in the second year, and 39 (7.2%) in the third year. All but one former lead worker had at least one follow-up visit (99.8%); 393 (72.4%) subjects had four visits, 99 (18.2%) had three visits, and 51 (9.4%) had two visits. The nonexposed controls were also enrolled over a 3-year period, with 119 (91.5%) in the first year, 7 (5.4%) in the second year, and 4 (3.1%) in the third year. A total of 91.6% of controls had at least one follow-up visit; 92 (70.2%) had four visits, 13 (9.9%) had three visits, and 15 (11.5%) had two visits. The mean ± SD (range) time intervals in years between visit one to visit two, visit two to visit three, and visit three to visit four were 1.05 ± 0.34 (0.60 to 2.78), 0.89 ± 0.21 (0.54 to 2.19), and 0.92 ± 0.17 (0.33 to 1.81).

Data collection. A well-constructed neurobehavioral battery consists of tests assessing a wide range of cognitive domains, including intelligence, verbal and visual learning and memory, visuo-constructive and organizational skills, executive functioning, reaction time, and motor performance. The vocabulary subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS-R)[16] was used as a measure of verbal intellectual functioning. Verbal learning and memory were assessed with the Rey Auditory Verbal Learning Test (RAVLT)[17,18] and the serial digit learning task,[19] whereas visual learning and memory skills were determined using the symbol digit paired associate learning test[20] and the Rey-Osterrieth complex figure, delayed score (hereafter referred to as Rey complex figure).[21] The Rey complex figure, copy[21] was used to measure visual planning and organization, whereas the block design subtest of the WAIS-R[16] assessed both visual organization and visuo-construction. Trail making tests A and B (Trails A and Trails B),[22] as well as the digit symbol subtest from the WAIS-R[16] and the Stroop test (A form minus C form),[23] assessed mental flexibility, executive functioning, and visual scanning. The choice reaction time task evaluated reaction time and response discrimination (computer administered test with a "1" or "2" appearing at random intervals ranging from 1 to 10 seconds for a total of 100 trials, the first 17 of which were practice).[24] Olfactory function was measured with the University of Pennsylvania Smell Identification Test (UPSIT).[25] The finger tapping task[22] (five trials each hand alternating from one to the other) was used to measure motor performance, whereas the Purdue pegboard[26] was used to assess manual dexterity. Subjects also completed the Center for Epidemiologic Studies–Depression Scale (CES-D),[27] a measure of depressive symptomatology, and the Symptom CheckList-90 (SCL-90), a measure of the frequency and magnitude of psychological symptoms.[28] Herein, "neurobehavioral tests" refers to the entire test battery and "cognitive tests" refers to all tests except the neuropsychiatric symptom scales and the smell identification test.

After obtaining consent, data were collected in the following order: SCL-90, blood pressure, height, weight, an initial interview, neurobehavioral testing, and detailed occupational history. Information on physician diagnosis of CNS disease, including neurodegenerative disease and head injury, and psychiatric disorders was obtained at all study visits.

Biologic measurements. Blood lead levels were measured by a commercial laboratory during the first year of the study on former lead workers by the standard addition method of the National Institute of Occupational Safety and Health.[29] During the third year, current tibia lead levels were measured (in units of μg lead per gram of bone mineral, hereafter referred to as μg/g) by ^{109}Cd-induced X-ray fluorescence (XRF) to fluoresce K-shell X-rays from lead.[8-10,30] This was performed at the left mid-tibia shaft via a 30-minute measurement with a back scatter geometry.

Because lead is eliminated from bone over time, we were concerned that the large differences among individuals in time since last occupational exposure to lead could obscure true differences in cumulative lead absorption as assessed by current tibia lead levels. Moreover, preliminary analysis revealed that years since last exposure was a strong predictor of decline in neurobehavioral test scores (6 of 19 cognitive tests had p values for years since last exposure ≤ 0.05), and the coefficients for interaction terms be-

tween current tibia lead levels and years since last exposure were consistently negative (9 of 19 cognitive tests had p values for the interaction term <0.05). Years since last exposure was not a biologically plausible predictor of declines in neurobehavioral test scores, and years since last exposure to lead and age were only moderately correlated (Pearson's $r = 0.33$, $p < 0.01$), so age did not explain these observations. These theoretical concerns and empirical observations thus motivated us to use years since last exposure to estimate tibia lead levels at the time of last occupational exposure to lead, termed peak tibia lead. Current tibia lead levels were extrapolated back using a clearance half-time of lead in tibia of 27 years,[9] assuming first-order (mono-exponential) clearance from tibia.[15]

Statistical analyses. Before data analysis, all neurobehavioral test results were reviewed by a neuropsychologist. The complete study records of all subjects with outlying values on the neurobehavioral measures were evaluated for possible explanations of unusually poor performance. One former lead worker was missing information on years since last exposure, and nine subjects (seven former lead workers and two controls) were excluded because they developed medical conditions not considered to be related to past lead exposure but which could adversely affect test performance (e.g., carpal tunnel syndrome, stroke, demyelinating or neurodegenerative disease). Thus, a total of 535 former lead workers and 118 controls were included in the analysis.

Neurobehavioral test change scores were calculated by subtracting the neurobehavioral test score at the first study visit from all subsequent scores ($Y_i - Y_1$, where i = 2, 3, or 4 and Y_1 = score at the first study visit). For each test, subjects could thus contribute one, two, or three change scores to the analysis. Change scores were then divided by the time between measurements to derive measures of change per year. This method assumes that the annual changes for each measure were equivalent from year to year. Tests were standardized for direction so that a negative coefficient indicated a relative decline in performance with increasing peak tibia lead.

All analyses of neurobehavioral test performance were made using linear regression models of annual change scores on a given test in terms of lead and other predictor variables. Because each regression model involved repeated measures on individuals over time, the analyses needed to account for the intrasubject correlation among repeated measures. Generalized estimating equations fitting was used for this purpose, for all the regression models described below.[31,32] The analysis was performed under an exchangeable correlation assumption. Thus, regression coefficients had the interpretation of predictor effects on mean neurobehavioral change per year, and standard errors and confidence intervals correctly accounted for correlations among repeated measures within subjects.

First, using linear regression models as just described, annual change scores were compared in former lead workers and controls, adjusting for age at the first study visit, education (less than high school, high school graduate, some college, college graduate), testing technician (four different technicians), number of previous visits (to control for practice effects), and neurobehavioral test score at the first study visit (to control for regression toward the mean). Next, to determine if age-related declines in cognitive function differed between former lead workers and nonexposed controls, cross-product terms of age at the first study visit and former worker versus control status were added to the regression models.

The influence of peak tibia lead levels on annual change for each of the 22 neurobehavioral tests was investigated in 22 separate regression models. Each regression model controlled for confounding by age at the first study visit, educational level, testing technician, number of previous visits, and neurobehavioral test score at the first study visit. Associations of blood lead levels obtained at the first study visit with annual change scores were also evaluated in separate regression models.

The influence of self-reported health conditions and tobacco and alcohol use were also assessed in the final models but were not included because such use neither predicted annual change scores nor confounded relations between lead exposure and annual change scores. To evaluate nonlinear (curvilinear) relations between peak tibia lead and neurobehavioral test scores, both linear and quadratic terms for peak tibia lead were evaluated.[33] Plots of the relations were examined to be certain that the models described the data accurately and the associations were not driven by outlying points. All significance testing was two-sided.

The XRF system provides a continuous unbiased estimate of the concentration of lead in bone that oscillates around the true concentration, so estimates below zero can be obtained when the true concentration is close to zero.[34] Seven subjects had negative current tibia lead estimates, which were retained in the analysis because this method minimizes bias and does not require censoring of data.[34] One subject had an extreme value of peak tibia lead (117.9 μg/g) and was excluded on statistical grounds before modeling neurobehavioral outcomes; exclusion of this subject did not significantly influence the regression results.

Results. The 535 former lead workers included in the analysis were primarily white (93.1%), and had a mean (±SD) age at the first visit of 55.6 ± 7.4 years (median 55.5 years, range 39.9 to 71.4 years) and mean peak tibia lead level of 22.6 ± 16.5 μg/g (range −2.2 to 98.7 μg/g) (table 1). Former lead workers had low blood lead levels measured in the first year of the study, with a mean of 0.22 ± 0.13 μmol/L (4.6 ± 2.6 μg/dL) and a range of 0.05 to 1 μmol/L (1 to 20 μg/dL). Controls were slightly older than former lead workers at the first study visit and had lower average education levels, but were similar in race, tobacco use, and alcohol use (see table 1). Although controls were older at enrollment and had lower education levels than did former lead workers, former lead workers and controls had similar neurobehavioral test scores at the first study visit (for additional data, please access www.neurology.org and click on the title link for the issue).

As expected, age at the first study visit was a consistent and strong predictor of change in neurobehavioral scores, directly associated with a greater decline in test scores over time for all but three neurobehavioral tests. Test scores at the first study visit were inversely related to change scores for all neurobehavioral tests, suggesting regression toward the mean at subsequent visits. There was also evidence of a practice effect; subjects with three or

Table 1 *Summary of selected characteristics of former lead workers who completed tibia lead measurement and nonexposed controls at the first study visit*

Variable	Former lead workers	Nonexposed controls
Number	535*	118*
Age, y, mean (SD)	55.6 (7.4)	58.6 (7.0)
Current blood lead, μmol/L, mean (SD)	0.22 (0.13)	Not applicable†
Current tibia lead, μg Pb/g bone mineral, mean (SD)	14.4 (9.3)	Not applicable†
Current tibia lead measurement uncertainty, μg/g, mean (SD)	5.2 (1.0)	Not applicable
Peak tibia lead,‡ μg Pb/g bone mineral, mean (SD)	22.6 (16.5)	Not applicable
Exposure duration, y, mean (SD)	8.1 (9.7)	Not applicable
Duration since last exposure, y, mean (SD)	16.0 (11.7)	Not applicable
White race, %	93.1	90.7
Educational level, %		
Less than high school	7.7	13.6
High school graduate	58.7	57.6
Some college	28.6	17.8
College graduate	5.0	11.0
Tobacco consumption, %		
Never	27.5	27.1
Previous	53.2	53.4
Current	19.3	19.5
Alcohol consumption, %		
Never	3.2	8.5
Previous	24.3	29.1
Current	72.5	62.4

* A total of 543 former lead workers completed tibia lead measurement; 535 are included in the longitudinal analysis because one was missing information on years since last exposure to lead and seven were excluded because of the development of health conditions that could affect test performance (see Methods). Blood lead was measured in the first year of the study, and current tibia lead was measured in the third year. Of the 130 controls, 120 had at least one follow-up visit, and two were excluded due to the development of health conditions that could affect test performance.

† Nonexposed controls did not have blood lead or tibia lead measurements.

‡ Current tibia lead levels were extrapolated back to the estimated tibia lead levels at the termination of occupational lead exposure using years since last exposure to lead and an estimated clearance half-time of lead in tibia of 27 years (see Methods).

four study visits had better change scores relative to subjects with only two study visits.

Former lead workers exhibited greater annual declines in adjusted test scores than did controls for 17 of 19 cognitive tests, achieving significance for Rey complex figure copy, RAVLT immediate recall, and RAVLT recognition. In addition, age-related annual declines in test scores were larger for lead workers, compared to controls, for 14 of 19 cognitive tests, achieving significance for block design, digit symbol, serial digit learning, and finger tapping nondominant hand, and borderline significance ($p < 0.10$) for Trails A.

After controlling for confounding variables, peak tibia lead was a consistent predictor of decline in test scores over time. The annual declines in neurobehavioral scores were larger with increasing peak tibia lead levels. The beta coefficients for peak tibia lead were negative for all 19 cognitive tests (table 2). Borderline or significant associations were observed between peak tibia lead and declines in symbol digit ($p = 0.04$), Rey complex figure delayed recall ($p = 0.07$), RAVLT immediate recall ($p < 0.01$), RAVLT delayed recall ($p = 0.01$), Purdue pegboard nondominant hand ($p = 0.01$), and the Stroop test ($p = 0.06$). Notably, in contrast to peak tibia lead, blood lead levels obtained in the first year of the study were not consistent predictors of annual change scores.

To interpret the magnitude of the annual declines in neurobehavioral test scores associated with peak tibia lead, we compared the magnitudes of these annual declines to those associated with age at the baseline visit (mutually adjusted in a single model). For these comparisons, the change scores were standardized (by z-transformation, expressed in SD units) so that the effects could be directly compared. Specifically, the annual declines in test scores associated with an increase of 20 μg/g in peak tibia lead (approximately the median value) were compared to the annual declines associated with a five year age difference at the baseline visit (see table 2). For many tests, the annual declines associated with a 20 μg/g difference in peak tibia lead were comparable in magnitude to the annual declines associated with a 5-year age difference at baseline. On average, for the six cognitive tests associated with peak tibia lead (p values ≤ 0.10), an increase of 15.7 μg/g of peak tibia lead was equivalent in its effects on annual test decline to 5 more years of age at the baseline visit.

Discussion. This study provides the first evidence that progressive and ongoing decline in cognitive function, particularly functions such as learning and memory, is associated with adult lead exposure long after exposure ceases. There has been a longstanding debate as to whether toxic exposures or other insults during adulthood can have long-term consequences in the CNS, but only rarely has this question been studied rigorously, and only in the context of head injury.[35] However, overt causes of damage to the CNS such as head injury differ in many ways from the more subtle effects of chemical neurotoxicants. The current study provides evidence that cognitive decline greater than would be expected due to aging alone is a more general phenomenon, occurring after toxic exposure. This evidence is of three types: former lead workers had larger annual declines in neurobehavioral test scores than did nonexposed controls; former lead workers had larger age-related cognitive declines compared to controls; and peak

Table 2 *Comparison of average annual declines (90% CI) in neurobehavioral test scores (expressed in standard deviation units†) for an increase in peak tibia lead of 20 μg/g and for an increase of 5 years in age at baseline in former lead workers*

Domain and neurobehavioral test	Annual decline (90% CI), in SD‡ units, per:	
	20 μg/g of peak tibia lead	5 years of baseline age
Visuo-construction/visuo-perception		
Block design (WAIS)	−0.06 (−0.14, 0.01)	−0.09 (−0.14, −0.05)**
Rey complex figure, copy	−0.05 (−0.11, 0.01)	0.01 (−0.03, 0.04)
Verbal memory and learning		
Serial digit learning	−0.02 (−0.09, 0.04)	−0.01 (−0.05, 0.03)
RAVLT, immediate recall	−0.13 (−0.20, −0.05)**	−0.06 (−0.10, −0.02)**
RAVLT, recognition	−0.01 (−0.09, 0.06)	−0.06 (−0.10, −0.02)**
RAVLT, delayed recall	−0.10 (−0.17, −0.04)**	−0.08 (−0.13, −0.04)**
Visual memory		
Symbol digit (WAIS-R)	−0.08 (−0.14, −0.01)**	−0.09 (−0.13, −0.05)**
Rey complex figure, delayed recall	−0.07 (−0.13, −0.004)*	−0.06 (−0.11, −0.02)**
Executive ability		
Digit symbol substitution	−0.01 (−0.09, 0.06)	−0.16 (−0.23, −0.09)**
Trail making, part A	−0.07 (−0.14, 0.001)	−0.10 (−0.14, −0.06)**
Trail making, part B	−0.002 (−0.07, 0.07)	−0.10 (−0.15, −0.06)**
Purdue pegboard, assembly	−0.04 (−0.12, 0.03)	−0.16 (−0.20, −0.11)**
Stroop (C form − A form)	−0.10 (−0.18, −0.01)*	−0.03 (−0.07, 0.01)
Manual dexterity		
Finger-tapping, dominant hand	−0.04 (−0.11, 0.02)	−0.14 (−0.18, −0.09)**
Finger-tapping, nondominant hand	−0.05 (−0.13, 0.02)	−0.15 (−0.19, −0.10)**
Purdue pegboard, dominant hand	−0.06 (−0.12, 0.01)	−0.12 (−0.16, −0.07)**
Purdue pegboard, nondominant hand	−0.11 (−0.18, −0.04)**	−0.10 (−0.15, −0.06)**
Purdue pegboard, both hands	−0.05 (−0.12, 0.03)	−0.11 (−0.15, −0.06)**
Psychomotor		
Complex reaction time, ms	−0.04 (−0.12, 0.04)	−0.06 (−0.11, −0.01)*
Neuropsychiatric symptom scales		
CES, depression scale	0.02 (−0.04, 0.08)	0.02 (−0.02, 0.06)
Symptom CheckList–90 global severity index	0.002 (−0.05, 0.05)	0.01 (−0.03, 0.05)
Olfactory function		
University of Pennsylvania Smell Identification Test	−0.02 (−0.13, 0.09)	−0.08 (−0.13, −0.02)**

* $p \leq 0.10$; ** $p \leq 0.05$.

† Annual neurobehavioral change scores were z-transformed before modeling, so the magnitude of change for an increase of 20 μg/g of peak tibia lead could be directly compared to an increase of 5 more years of age at baseline. Wechsler Adult Intelligence Scale—Revised (WAIS-R) vocabulary score was only measured during the first and third study visits, so annual change was not evaluated.

‡ Four standard deviations includes 95% of the change scores.

RAVLT = Rey Auditory Verbal Learning Test; CES = Center for Epidemiologic Studies.

tibia lead levels predicted annual declines in cognitive function among former lead workers.

For 6 of the 19 cognitive outcomes studied for associations with peak tibia lead, the associated p values were less than or equal to 0.10, and for four of these the associated p values were less than or equal to 0.05. At the $p = 0.05$ significance level, one significant association of peak tibia lead with a neurobehavioral change score was expected by chance. It should be noted that all of the coefficients for peak tibia lead as a predictor of change in neurobehavioral test scores were negative, a finding that would be highly inconsistent with the notion of a spurious association. Moreover, prior animal and human data suggested that verbal and visual memory tests would be important a priori outcomes associated with lead exposure. Finally, consistent associations were observed comparing the former lead workers to nonexposed subjects recruited from the general population. The strength and consistency of this evi-

dence supports a casual relation between past occupational lead exposure and prospective decline in cognitive function.

An important consideration is whether the number of associations we observed is greater than would be expected due to chance alone, given that the neurobehavioral outcomes are correlated to varying degrees with each other. As discussed by Ingraham and Aiken, this intercorrelation would lower the probability of finding concurrent associations if lead had no effect on neurobehavioral test performance.[36] These authors presented a model based on a binomial probability distribution for evaluating the expected number of abnormal test results in an assessment battery. Using this model, we would conclude that our observed results are very unlikely to be due to chance.

To date, longitudinal studies of the neurobehavioral effects of adult lead exposure, generally in the occupational setting, have been unsuccessful, plagued by poor follow-up rates, follow-up periods of short duration, small sample sizes, and inadequate measures of cumulative dose.[3-6] In four published longitudinal studies, the median sample size was 80 subjects, the median follow-up duration was 2 years, the median 2-year follow-up rate was 38%, and none of the studies used bone lead as a measure of cumulative lead dose. More generally, there are no published studies of any occupational neurotoxicant that reveal cognitive function can decline years after cessation of exposure to the agent as a function of cumulative dose. Lead and hydrocarbon solvents[37] are perhaps the two best studied occupational exposures suspected of causing chronic neurobehavioral effects, but studies of neither neurotoxicant have been able to address this issue.

The subjects in this study had past exposure to both inorganic and organic lead.[13] Tetraethyl and tetramethyl lead are dealkylated to inorganic lead in vivo; organic lead is not stored in bone, but its ultimate metabolite, inorganic lead, likely accumulates in bone just as if the exposure had been to inorganic lead. After injection of tetraethyl lead in rabbits, degenerative changes and neurofibrillary tangles have been observed in the pyramidal cells of the frontal cortex and hippocampus.[38-40] Studies in animals and clinical observations in humans suggest that organolead compounds may be selectively toxic to areas of the limbic system, involved in modulation of behavior, emotionality, motivation, learning, and memory.[39-41] Inorganic lead also concentrates in the hippocampus,[42] and glial acidic fibrillary protein, a cell-specific cytoskeletal intermediate filament protein used as a marker of number and size of astrocytes, has been observed to increase in the hippocampus of animals dosed with either organic or inorganic lead.[43,44] In the current study, many of the effects were seen in tests that involved declarative new learning, which is known to require the hippocampus and related structures.[45]

The current study was designed to evaluate longitudinal effects, not cross-sectional effects. We previously reported that peak tibia lead levels were consistently associated with poorer neurobehavioral test scores in a cross-sectional analysis of data from one study visit.[15] Overall, the results of the two analyses are consistent. It is likely that more significant associations emerged from the cross-sectional analysis because the results reflect change from the time of initial exposure to the time of testing, a longer period, on average (i.e., 26 years, the mean duration of lead exposure plus the mean duration since the termination of lead exposure), than the 3 years of follow-up in the longitudinal analysis. However, the longitudinal analysis focuses on decline in later life, when it may be more rapid.

Our information on study participants and nonparticipants would suggest that the findings of the cross-sectional analysis were not likely to be due to selection bias, but it was still a theoretical concern, motivating the need for longitudinal assessment. The longitudinal results confirm that selection bias and confounding are unlikely to account for the cross-sectional results, and furthermore, indicate that declines are progressive in some cognitive domains. Taken as a whole, the results of the two analyses allow an inference to be made that manual dexterity and executive functions are primarily affected early and without progressive decline, verbal memory and learning are affected early with progressive decline, and visual memory is affected later with progressive decline. Furthermore, over a relatively short follow-up period of 3 years, the magnitude of the effect of lead on the annual change scores was comparable to the effect of aging itself. Although these estimates of the magnitude of the effect have to be interpreted with some caution, our data would suggest that the magnitude of the lead effect is large relative to the age effect.

Two limitations of the study are 1) follow-up rates were high, but not complete; and 2) the change models made the simplifying assumption that the influence of peak tibia lead on change scores was constant over the time frame of the study. Both in the case of dropout and in the case of our simplifying assumption that peak tibia lead effect on neurobehavioral change rate is constant over the study course, we believe that our reported analyses capture the substantively important aspects of the association between lead absorption and progressive neurobehavioral change in our population of former workers.

Lead may thus exert progressive effects long after initial adult occupational exposure. Whether this is a consequence of the particular storage and mobilization of lead, or whether it is a more general effect of neurotoxicants, remains to be determined.

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