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Effects of Lead on the Adult Brain: A 15-Year Exploration

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Background *Historically, there has been minimal concern about the effect of adult lead exposure on the brain. Evidence from recent longitudinal studies raise concerns about the long-term effects of past exposure.*

Methods *We initiated three independent longitudinal studies to determine whether cumulative lead exposure was associated with persistent or progressive brain effects. The studies include 1,109 former U.S. organolead manufacturing workers, 803 current and former inorganic lead workers in Korea, and 1,140 50- to 70-year-old Baltimore residents with environmental lead exposure. The organolead workers had past exposure to inorganic and tetraethyl lead (TEL); in the other two studies, exposure was to inorganic lead. In each of these studies, we measured blood lead and tibia and patella lead by ^{109}Cd K-shell-induced X-ray fluorescence.*

Results *Higher tibia lead was consistently associated with poorer measures of cognitive function. Longitudinal analysis of the Korean and organolead cohort indicate that the effect of lead is persistent. Moreover, MRI data on organolead workers indicates a possible progressive effect from past exposure; higher tibia lead was associated with lower brain volume. The latter study indicates that a difference in tibia lead equivalent to about one-sixth of the overall range was associated with a mean difference in these cognitive tests that was equivalent, on average, to what was observed for a five-year age difference.*

Conclusions *Our data suggest that a significant proportion of what is considered to be "normal" age-related cognitive decline may, in fact, be due to past exposure to neurotoxicants such as lead.* Am. J. Ind. Med. 50:729–739, 2007. *© 2007 Wiley-Liss, Inc.*

KEY WORDS: lead; occupational; environmental; longitudinal; neuropsychology; MRI; white matter; gray matter; adult

INTRODUCTION

Historically, concerns about the health effects of lead have been singularly focused on perinatal and childhood exposure. In children, the evidence of short- and long-term adverse cognitive and behavioral effects is consistent and compelling. Adult exposure to lead has not motivated a similar concern. In fact, to the contrary, it has been assumed for decades that there were no serious long-term cognitive consequences from past lead exposure among adults. Until recently, numerous studies of occupational groups exposed to lead offered little in the way of convincing evidence for or against associations between cumulative lead dose and

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cognitive dysfunction or decline [Balbus-Kornfeld et al., 1995]. Studies were underpowered, focused on acute effects in current workers, and lacked a measure of cumulative exposure or dose. Even when significant associations between lead exposure and cognitive measures were observed, studies failed to separate the acute or transient effects of recent lead exposure from the chronic effects of cumulative exposure. More recent evidence [Stewart et al., 1999; Schwartz et al., 2000, 2001, 2005; Wright et al., 2003; Weisskopf et al., 2004; Bleecker et al., 2005; Winker et al., 2005, 2006; Shih et al., 2006] from larger comprehensive studies reveals a consistent concern about the chronic effects of cumulative lead exposure on the adult brain.

We began to examine questions about adult lead exposure in 1990, work that eventually expanded to the study of three distinct populations (Table I); over time, each study has offered evidence complementary to the others. Starting in 1994 we began to follow a cohort of former organolead manufacturing workers (''organolead study'') examining the relation between past exposure to organic and inorganic (i.e., tetraethyl, tetramethyl) lead and brain-related outcomes. Given an average of more than 16 years between last occupational exposure to lead and brain-related outcomes, this cohort offered unique opportunities to learn about the long-term effects of a neurotoxicant on both brain functional and structural outcomes. Because of the manufacturing process, we cannot state with certainty that the brain effects observed in this cohort are due to organic lead, inorganic lead, or both. We began to study another cohort with occupational exposure to inorganic lead to determine if our findings in the organolead study were generalizable. In 1997,we initiated a longitudinal study of 803 current and former Korean lead workers (''Korea lead study'') using a protocol for lead dose measurement (i.e., blood lead, bone lead by ^{109}Cd-induced K-shell X-ray fluorescence) and for cognitive function similar to that used in the organolead study. The Korea lead study raised questions of whether findings could be generalized to populations with only environmental lead exposures common to adults born after 1930. Beginning in 2000, we addressed this latter question in the Baltimore Memory Study (BMS), a longitudinal assessment of 1,140 residents between 50 and 70 years of age at enrollment. Again, in the BMS, similar methods were used to assess lead dose and cognitive function.

From the outset, we conceptualized hypotheses relevant to how cognitive function might change depending on the timing of exposure (Fig. 1). In ''ideal aging,'' cognitive function is stable across the lifespan (Fig. 1, panel A). A common trajectory, however, indicates that in many persons, cognitive function declines with age. Recognizing that there is considerable inter-individual variation, the expectation is that cognitive function is relatively stable in the first four to five decades of life, somewhat resistant to change; accelerated decline occurs in later life as the integrity of neural networks degrade (panel B). The age-specific change point and rate of change are likely to be influenced by genetic, lifestyle, general health risk factors (e.g., exercise, nutrition), and exposure to known neurotoxicants (e.g., alcohol). The

TABLE I. Summary of Three Ongoing Studies of Lead and Cognitive Function, 1990-Present

	Study		
Study description	**Organolead study**	**Korea lead study**	**Baltimore memory study**
Source of funding	NIA	NIEHS	NIA
Years of study	1993–2008	1997–2007	2000–2006
Study location	New Jersey	South Korea	Baltimore, MD
Source of exposure	Occupational	Occupational	Environmental
Sample size			
Occupational lead	1,109	803	0
Occupation—no lead	0	135	0
General population	132	0	1,140
Number of study visits	4–7	3	3
Lead biomarkers			
Blood lead	Once	Three times	Once
Tibia lead	Once	Two times	Once
Patella lead	Once	Once	Once
Other measures			
Phase I			Neighborhood assessment
Phase II	Brain MRI (n = 656)		
Phase III	Second MRI		

NIA, National Institute on Aging; NIEHS, National Institute for Environmental Health Sciences.

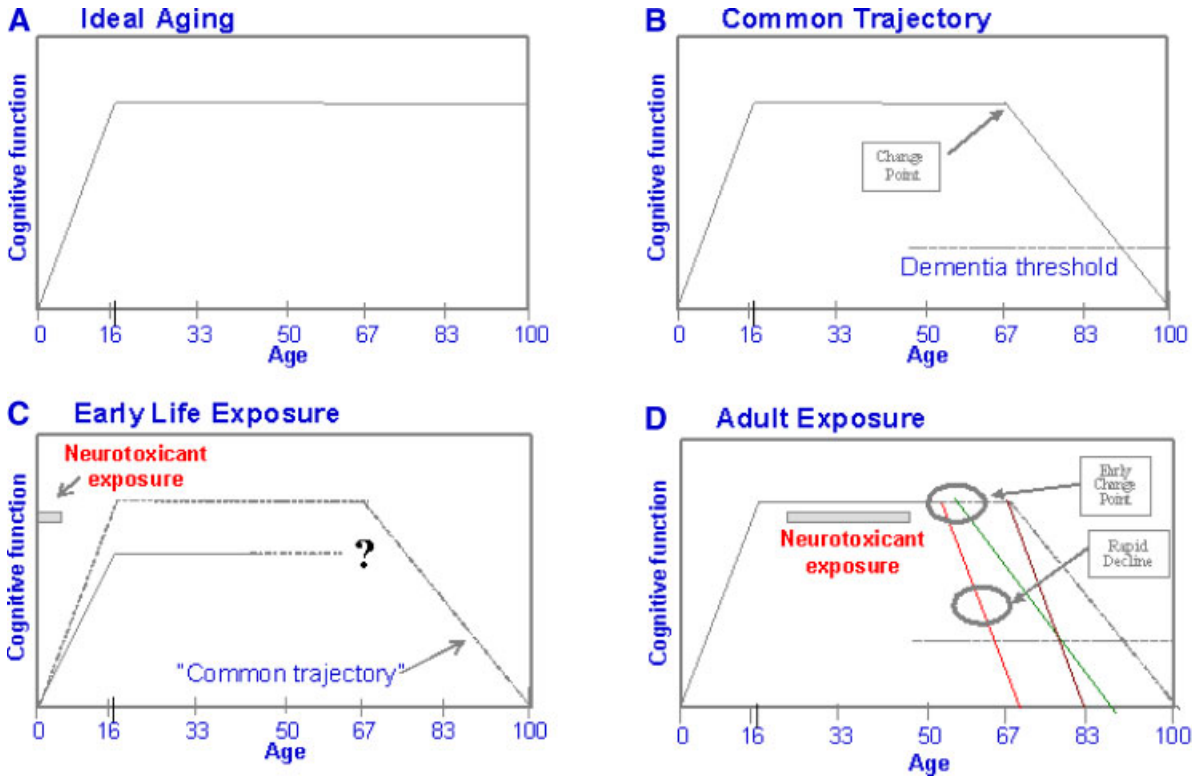

FIGURE 1. Patterns of change of cognitive function with aging. **A**: "Ideal aging," reflecting stable cognitive function across the lifespan. **B**: A commonly observed trajectory in which cognitive function declines with age beginning in the seventh or eighth decades of life. **C**: After early life neurotoxicant exposure, cognitive function does not reach the same plateau height, consistent with studies suggesting that mean IQ may be lower by five-seven points among those with early life lead exposure. **D**: The focus of our research interest, patterns of change in cognitive function with aging after adult neurotoxicant exposure. The three new lines indicate that cognitive function decline may begin earlier, occur more steeply, or both. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

age at which function declines below a disease-specific threshold (e.g., dementia) is a sentinel event. Early life exposure reduces cognitive function or reserve early in life, which may result in crossing a disease threshold at an earlier age than would otherwise occur (panel C). Studies of perinatal and childhood lead exposure were first initiated in the 1970s, too recent to test hypotheses about the late life brain consequences of this early life exposure. In contrast, adult exposure to a neurotoxicant (panel D) could modify the change point or rate of decline, either of which will influence the age at which cognitive function falls below the disease specific threshold. Given this framework, we summarize evidence from these three large studies and discuss the consistency of findings. In the discussion section, we consider disease progression models to explain our findings and specifically consider the possible link between past exposure to a neurotoxicant and chronic progressive brain diseases like Alzheimer's disease. We close with a consideration of existing gaps in knowledge and needs for future research summary of the findings from the three studies (Table II).

MATERIALS, METHODS, AND RESULTS

Organolead Study

Before its elimination from gasoline in the 1970s and 1980s, tetraethyl lead (TEL), commonly referred to as an

TABLE II. Summary of Key Findings in our Three Studies of Lead and Adult Cognitive Function, 1990-Present

Study	Cross-sectional findings	Longitudinal findings
Organolead	Cumulative dose [Stewart et al., 1999, 2006]	Cumulative dose [Schwartz et al., 2000; Links et al., 2001]
Korea	Recent dose [Schwartz et al., 2001]	Recent and cumulative dose [Schwartz et al., 2005]
Baltimore memory study	Cumulative dose [Shih et al., 2006]	

anti-knock agent, was used to increase fuel compression to minimize premature combustion (i.e., engine ''knocking or pinging''). TEL manufacturing workers were exposed to both inorganic lead (e.g., lead fumes from melting of lead bars before processing)) and organic lead (TEL and tetramethyl lead). Anecdotal reports in the medical literature began appearing shortly after TEL manufacturing began in earnest in the 1920s, and suggested severe acute toxicity and possible chronic effects [Norris and Gettler, 1925; Beattie et al., 1972; Walsh et al., 1986]. In the late 1980s, the TEL manufacturing area of the plant in southwest New Jersey was issued several citations for health and safety violations by the Occupational Safety and Health Administration (OSHA). In an unusual notification, OSHA recommended two health studies, one focused on cancer and the other on cognitive outcomes. Johns Hopkins University conducted the initial study of cognitive function [Schwartz et al., 1993]. In that first study, we examined relations of cognitive test scores with two traditional estimates of cumulative exposure: exposure duration and a cumulative exposure metric based on industrial hygiene data and occupational history interviews for dwell-time data in defined exposure zones in the plant. Performance on cognitive function tests was inversely related to both exposure measures. The observed associations in this cross-sectional study of currently exposed workers did not allow us to separate the acute and transient effects of lead exposure from its long-term persistent or progressive effects. In addition, we could not address potential challenges to interpretation of results attributable to survivor bias, a common concern with studies of current workers. A National Institute of Aging funded longitudinal study of former workers, which began in 1994, allowed us to address methodological concerns in the cross-sectional study. In this section, we describe the longitudinal study that continues to this day, key findings, and ongoing work.

A complete organolead cohort was assembled from a review of more than 45,000 personnel records of former workers. The plant produced a broad range of chemicals and only a minority of workers was ever employed in the TEL facility. Males 40 to 70 years of age in 1994 with potential exposure to the TEL facility on or after 1950 were specifically targeted [Stewart et al., 1999]. We were interested in a younger age cohort to understand, in part, when neurotoxic effects from past exposure might first begin to emerge. The long time period since last exposure (i.e., an average of more than15 years) posed challenges in tracking former workers. Of the 7,170 with possible exposure, we made specific efforts to locate a random sample of 3,223 individuals. A total of 15% were deceased or resided outside the study area, 35% could not be located, and another 9% refused interest. Of the 968 individuals who were eligible, 703 were initially enrolled in the study. In this initial study, data were collected on past exposure to lead, serial assessments of cognitive function, and detailed interview data on occupational history, health history, medications used, health habits, and other relevant measures. In addition, whole blood was obtained to measure blood lead and to bank DNA and serum [Stewart et al., 1999]. The cohort was predominantly white (92.8%), relatively young (62% were $<$60 years of age), with most (92%) having at least a high school education, while 33% had education beyond high school. There was wide variation in exposure; 58% had worked in the lead area of the plant for 3 or more years and 27% had 10 or more years.

As with most occupational cohorts, exposure assessment was the Achilles heel of the organolead study. Substantial amounts of air monitoring data were available from plant records along with floor plans of the plant. Moreover, the combination of personnel records and interview data about each occupation held in the TEL facility provided the means to develop a traditional exposure matrix (i.e., linking occupation to plant location to air monitoring data). While this method was suitable and adequate for the cross-sectional pilot study of current workers, we concluded that the exposure matrix method was too non-specific to derive reliable proxies for important dose metrics, including cumulative dose for former workers. Thus, individual measures of body burden or surrogates of cumulative dose were deemed essential. Two such measures were obtained: DMSA-chelatable lead and tibia lead. Blood lead was also included for comparison to previous studies, but was deemed the least useful, a priori, as it was assumed to represent current or recent dose rather than cumulative dose. We hypothesized that DMSA-chelatable lead would provide a proxy for current bioavailable lead stores (i.e., representing a proportional sample of lead extracted from long-term storage deposits). Tibia lead was measured with a 30-min measure using ^{109}Cd K X-ray fluorescence (XRF), expressed as μg Pb/g bone mineral [Todd et al., 1992; Todd and McNeill, 1993]. Given the long clearance half-time of lead from tibia (i.e., $t_{1/2} = 27$ years), this measure is an estimate of cumulative dose. However, in our cohort, there was a range of one to more than 20 years since last occupational exposure to lead, a factor that would account, in part, for inter-individual differences in the amount of lead remaining in bone. To control for these differences, we estimated what the individual tibia lead level would have been if it were measured on the last day of occupational exposure to lead. A measure termed ''peak tibia lead'' was estimated as:

$$\text{Peak tibia lead} = [\text{current tibia lead}) \times e^{(k \times t)}]$$

Where $k = (0.693/t_{1/2})$, $t_{1/2} = 27$ years, and $t =$ years since last exposure to lead. Compared to current tibia lead, peak tibia lead (PTL) was more strongly associated with measures of cognitive function [Stewart et al., 1999; Schwartz et al., 2000; Links et al., 2001]. Current tibia lead levels were between -1.6 (i.e., any value below 0 is effectively 0 and represents some degree of error) and 52 μg

Pb/g of bone mineral with a mean of 14.4 (SD = 9.3). PTL values were between −2.2 and 105.9 with a mean of 23.7 (SD = 17.4). The Pearson's correlation coefficient between current and peak tibia lead was 0.86, meaning that current tibia lead accounted for 74% of the variation in PTL; the remaining variation was explained by differences among former workers in their time since last exposure to lead. Mean (SD) blood lead levels were 4.6 (2.6) μg/dl with a range of 1 to 20.

The large cohort, XRF measures of lead in tibia, and the relatively long time period between last occupational exposure provided the means to clearly separate transient and acute effects of lead from persistent and possibly progressive effects of past exposure. In this ''cross-sectional'' analysis, all outcomes were standardized for directionality to simplify interpretation. Namely, regression coefficients could be interpreted in the same manner across tests. There were no meaningful findings for either blood lead or DMSA-chelatable lead with cognitive measures. The latter is explained by the recognition that DMSA primarily removes lead from bioavailable sources (e.g., soft tissue), not cortical bone. On the other hand, both before and after adjusting for covariates, all coefficients for PTL were negative in the regression models for each of the 19 measures of cognitive function, indicating that cognitive performance was worse for former workers with higher PTL levels. Eleven of the 20 coefficients were statistically significant ($P < 0.05$). A difference in PTL of 22 μg Pb/g bone mineral (i.e., approximately one-sixth of the overall range) was associated with a mean difference in these 11 tests that was equivalent, on average, to what was observed for a 5-year age difference, a substantial lead effect if it was real [Stewart et al., 1999].

Strictly speaking, the term ''cross-sectional'' refers to an assessment of the relation between current exposure and current outcome status. Cross-sectional evidence is typically given little weight. However, our initial study of former organolead workers was not a traditional cross-sectional study. PTL measured cumulative occupational dose, not current dose. Moreover, given the focus on former workers, inter-individual differences in measures of cognitive function could be viewed as an indirect measure of cumulative changes from lead exposure and aging since the time of last exposure, along with confounding from constitutional differences, changes attributable to other neurotoxicants (e.g., alcohol), and possibly selection bias (e.g., lower education being associated with higher exposure jobs). This retrospective-like study offered substantial statistical power because there was an average of more than 16 years between last exposure to lead and the initial cognitive measures, a substantial period of time for change to occur if lead was the causative agent. If past exposure to lead explained part of the inter-individual differences in cognitive measures, the above results indicated stronger associations with selected functions (i.e., strong associations for tests of executive ability, verbal learning and memory, and manual dexterity). However, a diversity of functions also appears to be associated with past exposure. The latter might be explained by pervasive distribution of lead in the brain, progressive changes since last exposure that affected other brain regions, or associations among the different functional tests.

We thus began to consider whether the pervasive effects were the product of progressive changes, where early specific insults spread to other brain regions in a progressive dying back process. The cohort was examined annually for the next 2-years. Longitudinal findings mirrored the prior cross-sectional results [Schwartz et al., 2000]. All coefficients for PTL as predictors of change in cognitive function in each of 19 regression models (using generalized estimating equations [GEE] methods because of the longitudinal data) were negative. Moreover, PTL was a significant predictor of decline in six tests (four at $P < 0.05$, two at $P < 0.10$), including verbal memory and learning, visual memory, executive ability, and manual dexterity. While the findings were less striking than those observed in the cross-sectional study, it is important to recognize that change was observed for only a 2-year period (vs. an average of over 24 years for the cross-sectional study, the sum of mean exposure duration and mean duration since last exposure) in relation to PTL. These results were important as they indicated changes in brain functions continued to unfold in relation to PTL, a cornerstone linking past neurotoxicant exposure to the notion of disease progression, not simply the persistent effect of a prior brain insult. Again, a difference in PTL of 15.7 μg Pb/g mineral bone (i.e., equivalent to comparing those at the upper and lower ends of the inter-quartile range of PTL) was associated with changes in measures of cognitive function similar to what was observed, on average, for a 5-year age difference.

We formalized testing of whether evidence from the organolead study supported a persistent or a progressive effect from past lead exposure. Applying linear systems theory, Links et al. [2001] evaluated relations of lead dose measures with longitudinal change in neurobehavioral function, concluding that the effect of lead on the brain was progressive (Fig. 2). By comparing associations of blood lead, current tibia lead, peak tibia lead, and estimated area-under-the-curve of tibia lead versus time, with longitudinal change in cognitive function scores, we were able to conclude that the effect of past lead exposure could not be explained by a reversible or persistent cognitive effect. Rather, only progressive changes could account for the observed associations. That is, in former workers with more than 16 years since last occupational exposure to lead, current blood lead levels were low. Presumably brain lead levels were also likely to be low. Lead must have gained access to the brain decades ago, caused brain lesions, and the functional effects of these lesions were progressive over the ensuing time period. We thought that such a functional effect of lead could only be a

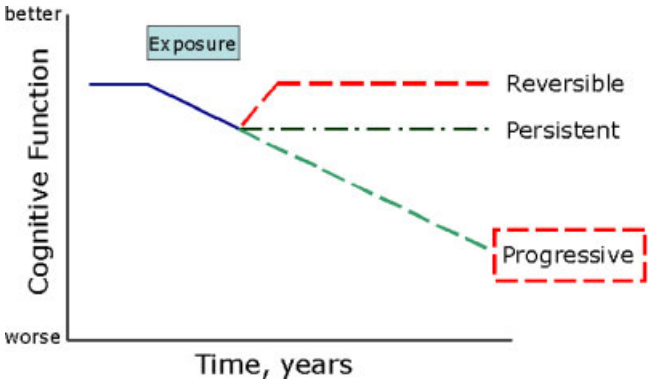

FIGURE 2. Schematic of reversible, persistent, and progressive health effects. In reversible health effects, after exposure ends, function returns to the pre-exposure baseline. Persistent health effects do not change, for better or worse, after the cessation of exposure. Progressive health effects get worse after the cessation of exposure. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

consequence of a persistent or progressive structural lesion(s), not short-latency changes in brain neurochemistry or effects of lead on brain macromolecules. This hypothesis motivated the next phase of study, involving continued assessment of cognitive function and the first structural measures obtained by brain MRIs. As previously mentioned, because tibia lead was associated with declines in a broad range of cognitive domains, we predicted a more global structural effect (e.g., cumulative lead dose may be associated with smaller volumes of larger structures such as total brain volume, frontal lobe, parietal lobe) and more specific associations with selected structures (e.g., specific structures involved in learning and memory such as limbic and perilimbic volumes).

MRIs were subsequently obtained on 532 former organolead workers, all completed at a single location with a GE 1.5 T Signa model [Stewart et al., 2006]. Analysis focused on both white matter lesions and on brain volumes of regional and more specific structures selected a priori. White matter (WM) lesions were graded using the Cardiovascular Health Study 10-point scale (no WM abnormalities [0] to all supratentorial WM involved excluding the corpus [9])[Fried et al., 1991]. MR images were segmented into gray matter (GM) and WM, and regional volumetric analysis was performed. While our hypotheses tested positive, the results were, nonetheless, somewhat startling. A total of 36% of individuals had WM lesion grade of 1 to 7 (0–9 scale). Increasing PTL was associated with increasing WM lesion grade ($P = 0.004$). The adjusted odds ratio for a 1 μg Pb/g increase in tibia lead was 1.042 (95% CI = 1.021, 1.063) for a CHS grade of 5 ($\geq$5 vs. <5). The adjusted odds ratio associated with an increase of PTL from 12.3 to 31.6 μg Pb/g (the inter quartile range for PTL) was 2.21. In linear regression models of the volumes of regions of interest (ROI) in the brain, the coefficient for tibia lead was negative for all structures, a finding that paralleled that observed for cognitive measures. Higher tibia lead was significantly ($P < 0.05$) related to smaller total brain volume, frontal and total gray matter volume, and parietal white matter volume. Of nine smaller specific regions of interest, higher tibia lead was associated with smaller volumes for the cingulate gyrus and insula.

Several different explanations could account for the above findings. Perhaps the most intriguing is the notion that lead could accelerate age-associated changes in WM. The effect of lead on cognitive function suggests, in part, that widely distributed neural networks involved in the integration of functions are affected. More specifically, lesions to cortical association areas would be consistent with our finding that the strongest associations with PTL were observed for verbal memory and learning, visual memory, and executive function [Benes et al., 1994; Schafer et al., 2005]. A growing body of evidence indicates that myelination continues into later life, [Bartzokis, 2004] but that this process is limited to selective brain regions (e.g., inferior temporal, prefrontal, and temporoparietal regions) [Bartzokis, 2004; Braak and Del Tredici, 2004]. Moreover, these regions include cells with long but small caliber projections in cortico-cortical association areas that may be particularly sensitive to oxidative stress and exogenous insults [Scahill et al., 2003]. The specificity of associations between PTL and selected regions (i.e., parietal WM and GM, temporal WM, and two relatively small paralimbic system structures) is consistent with the notion that lead could promote or accelerate an age-associated region specific neurodegenerative process in a locus relevant to dementing illnesses like Alzheimer's disease [Scahill et al., 2003; Braak and Del Tredici, 2004]. It is noteworthy that PTL was not associated with the occipital lobe and cerebellum, ROIs where myelination occurs early in life and where short axonal projections are relatively common [Scahill et al., 2003].

Korea Lead Study

The study of current and former inorganic lead workers in the Republic of Korea (South Korea) began in 1997 with funding from the National Institutes of Environmental Health Sciences. A total of 803 lead workers and 135 controls without occupational exposure to lead were enrolled between October 1997 and August 1999 [Schwartz et al., 2001]. Cohort members were followed annually, regardless of continued lead exposure. Given that the study was initiated with workers currently exposed to lead, we obtained measures that would allow us to separate the effects of recent from past exposure. To this end, serial measures of cognitive function and lead biomarkers were obtained. More specifically, by measuring blood lead (i.e., a measure of recent exposure) at each of the three study visits and tibia lead (i.e., a measure of cumulative does) at each of the first two, we

could specifically evaluate cross-sectional, historical, and longitudinal associations in our longitudinal models (Fig. 3).

At baseline, subjects had a mean (SD) age of 40.4 (10.1) years, job duration of 8.2 (6.5), blood lead of 32.0 (15.0), and tibia lead of 37.1 (40.3). A total of 79.6% of lead workers were male and 50.3% had a high school education or higher. In cross-sectional analysis, the regression coefficients for blood lead were negative for 16 of 19 neurobehavioral tests (i.e., similar to those used in the organolead study); 8 of the coefficients were statistically significant, including tests of executive abilities and manual dexterity [Schwartz et al., 2001]. In contrast, before controlling for job duration, tibia lead was not associated with neurobehavioral test scores. However, with adjustment for job duration, tibia lead was associated with four tests in the same domains as for blood lead. We believe the difference in the two models (i.e., with and without adjustment for job duration) is explained by selective loss of workers with longer duration exposure. Specifically, the longer one is exposed to lead the greater is the likelihood of a cumulative dose that could cause overt symptoms (e.g., headache, irritability, joint pain). Those who are more susceptible to these symptoms will also be more likely to change jobs resulting in selective loss associated with both exposure and outcome status. The adjustment for job duration accounts, in part, for inherent confounding attributable to the selective loss [Schwartz et al., 2001].

The longitudinal analysis offered the opportunity to examine four possible ways in which lead exposure could affect cognitive function: (1) cross-sectional blood lead and longitudinal blood lead would indicate a short-term, probably reversible, change associated with recent dose; (2) cross-sectional blood lead and historical tibia lead would indicate a longer-term, possibly irreversible or progressive change with cumulative dose (controlling for cross-sectional influence of recent dose); (3) cross-sectional tibia lead and historical tibia lead would indicate longer term, possibly irreversible or progressive change with cumulative dose (controlling for cross-sectional influence of cumulative dose); and 4) cross-sectional blood lead, historical tibia lead, and longitudinal blood lead would indicate both short-term change with recent dose and longer-term change with cumulative dose [Schwartz et al., 2005].

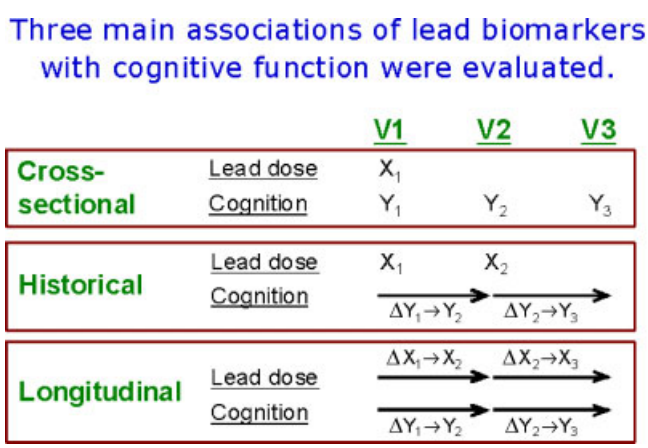

FIGURE 3. Summary of the three kinds of associations that were evaluated in the longitudinal analysis of the Korea lead study. By measuring biomarkers over time, this allowed detailed assessment of issues of recent and cumulative dose and acute and chronic health effects. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

In the longitudinal analysis of 576 lead workers who completed testing at all three study visits, there was a mean (SD) follow-up duration of 2.2 (0.5) years. Consistent associations were observed for blood lead with test scores at baseline (cross-sectional blood lead association) and of tibia lead with declines in test scores over the subsequent year (historical tibia lead association), mainly in executive abilities and manual dexterity. We believe the results support the conclusion that occupational exposure to inorganic lead can cause declines in cognitive function over time, indicative of both an acute effect of recent dose and a chronic effect of cumulative dose [Schwartz et al., 2005].

Baltimore Memory Study

In 2006, most adults aged 30 years and older were exposed to ambient and other sources of environmental lead exposure during long periods of their lifetimes. As such, it is logical to explore the relevance of our studies of the above two occupational cohorts to the general population, with a specific focus on environmental, not occupational, lead exposure. Environmental lead exposure was a problem for virtually all Americans over the age of 30 years, when lead was still extensively used in commercial products [Annest et al., 1983; Brody et al., 1994; Pirkle et al., 1994, 1998]. If outcomes observed in occupationally-exposed groups are relevant to the general population, public health concerns about environmental lead go well beyond the initial focus on peri-natal exposure, especially given the very large aging cohort of baby-boomers in Western countries.

There are substantial differences between the nature of occupational and environmental adult lead exposure. Even at their height, most environmental exposure levels to lead were considerably lower than occupational exposure levels. On the other hand, in the past, exposure to ambient environmental lead was continuous (i.e., not confined to working hours) and of considerably longer duration. For example, among adults born before 1940, who are currently 65 years of age and older, environmental lead exposures were significant until the 1980s, a duration of over 50 years. In contrast, the mean duration of lead exposure in our organolead and Korea lead study workers was 8 to 10 years.

With funding from the National Institute of Aging, we began in 2000 to study the effects of past environmental lead exposure on the aging brain. The study, known as the Baltimore Memory Study (BMS), involved 1,140 adults aged

50 to 70 years randomly selected from targeted neighborhoods in Baltimore City [Schwartz et al., 2004]. All participants completed a battery of cognitive tests similar to those in our other studies. Measures of blood lead and tibia lead (by XRF) were also obtained. Study subjects were each tested three times, with an average of approximately 14 months between study visits. Mean (SD) blood and tibia lead levels were 3.5 (2.4) μg/dl and 18.9 (12.5) μg lead per gram bone mineral, respectively; the average current blood lead levels are the lowest among our three study populations, but the tibia lead levels, from just environmental exposures in Baltimore, were intermediate between those observed in the organolead (lowest) and Korea lead (highest) populations.

In the BMS, we began to explore new methods for summarizing the diverse and numerous cognitive measures to simplify understanding of results and to minimize challenges from false positive associations due to multiple comparisons. Twenty cognitive test scores were collapsed into seven cognitive domains scores (language, processing speed, eye-hand coordination, executive functioning, verbal memory and learning, visual memory, and visuoconstruction). We found that higher tibia lead levels were consistently associated with worse cognitive function in all seven domains after adjusting for age, sex, the APOE-ε4 allele, and testing technician (six domains $P \leq 0.01$, one domain $P \leq 0.05$)[Shih et al., 2006]. Blood lead was not associated with any cognitive domain. Associations with tibia lead were attenuated after adjustment for years of education, wealth, and race/ethnicity. We concluded that independent of recent lead dose, retained cumulative dose resulting from previous environmental exposures may have persistent effects on cognitive function. Furthermore, a portion of age-related decrements in cognitive function in this population may be due to earlier life lead exposure.

There are several other important observations from the BMS (unpublished). First, in the longitudinal analysis, there was a weak signal in the association of tibia lead with declines in cognitive domain scores over time. The contrast in findings between the cross-sectional and longitudinal analysis may suggest that the effect of cumulative lead dose in this population may be persistent, but perhaps not progressive. We view this finding as preliminary, especially given the point, we previously made about cross-sectional studies. As before, outcome assessment in the cross-sectional analysis represents the cumulative change over many decades attributable to aging, exposure to neurotoxicants, and other factors. In contrast, the longitudinal analysis only evaluated continued change over 28 months. Second, to evaluate whether the social environment may interact with cumulative lead dose to influence cognitive function, we created a neighborhood-based metric of psychosocial hazards, termed the Neighborhood Psychosocial Hazards (NPH) scale, measured at the neighborhood (not person) level, consisting of indicators of social disorganization, public safety, physical disorder, and economic deprivation [Glass et al., 2006]. A growing literature in animals documents that ''environmental stress'' may interact with lead to cause worse cognitive and behavioral outcomes [Virgolini et al., 2004, 2005, 2006]. Across four quartiles of NPH, the association of tibia lead with cognitive domain scores got progressively stronger; for three domains the *P*-value for the trend in tibia lead slopes across the four quartiles of NPH was <0.05 and for a fourth the $P < 0.10$, even after adjustment for a number of potential confounding variables including race/ethnicity and socioeconomic status. This indicates that cumulative lead dose was worse for cognitive function among persons in ''bad'' neighborhoods, an interaction of the social environment and a neurotoxicant. This novel and interesting finding may offer new targets for interventions to prevent the long-term consequences of cumulative lead dose.

Thus, the findings in the BMS generally support the findings of our previous studies. The influence of cumulative lead dose on cognitive function is at least persistent, and may be progressive.

DISCUSSION

The notion that past exposure to lead during adulthood can cause persistent or progressive changes in the brain is a relatively new concept that has emerged from our work over the past 15 years. Evidence indicates that lead causes cognitive decline that is at least persistent, and in at least one study [Schwartz et al., 2000; Links et al., 2001], after mixed exposure to organic and inorganic lead, appears to be persistent and possibly progressive. Evaluation of brain structure in relation to past lead exposure is limited to just one study [Stewart et al., 2006]. Our own work over the past 15 years suggests that the effect of lead exposure is on par with the effect of aging, and the two effects are approximately additive. To some degree, our work raises a broader question about the extent to which progressive changes in the brain typically ascribed to aging are more likely to be explained by the cumulative effect of exposure to neurotoxicants.

To advance our understanding of the structural changes associated with lead in our former organolead workers, we are obtaining a second MRI on study participants. In the current phase of data collection, we are using newer technologies—diffusion tensor and FLAIR imaging—that will enhance visualization of WM tracts and improve understanding of the WM lesions. The second MRIs will also provide the means to evaluate longitudinal change in volume as a function of cumulative lead dose, and evaluate whether change in structural volumes is associated with change in cognitive function.

We believe that more extensive use of imaging technology (structural, functional, CT, MRI, SPECT, PET, MRS) is likely to advance understanding of how lead and

other neurotoxicants affect the brain. While measures of cognitive function have been the dominant outcome in studies of lead, such measures may be too non-specific and imprecise to both identify when and how persistent brain effects emerge and to specifically identify the locus of change. This is because detection of a progressive neurodegenerative condition based on functional measures is likely to be the latent outcome of sub-clinical premature neuronal loss for which there are numerous examples (e.g., motor neuron disease following sub-clinical polio infection, ALS/Parkinsonism dementia, dementia pugilistica). But, neuronal changes may occur well in advance of detectable functional changes.

For lead, there are several possible mechanisms of action that could result in structural change to the brain and that support biological plausibility of the relation. Lead could increase apoptosis [Fox et al., 1997; Sharifi et al., 2002], change cellular architecture, increase oxidative stress, or enhance vascular or inflammatory mechanisms. Lead could also moderate age-related structural changes in the CNS. Regan described lead-induced inhibition of post-natal structuring of the rat cerebellum [Regan and Fox, 1995], due to desialylation of N-CAM proteins (cell adhesion molecules), mechanisms described by Davey [Davey and Breen, 1998b], who has also reported interactions between lead and β-amyloid precursor protein [Davey and Breen, 1998a]. We believe that more incisive measures offered by imaging technology will be required to decipher the role of these and other potential mechanisms [Atamna et al., 2002] in understanding the locus of change in the brain [Kempermann and Gage, 2000; Kempermann et al., 2004].

Implications of These Findings

Since the review of Balbus-Kornfeld et al. [1995], our research in combination with others [Stewart et al., 1999, 2006; Schwartz et al., 2000, 2001, 2005; Wright et al., 2003; Weisskopf et al., 2004; Bleecker et al., 2005; Winker et al., 2005, 2006; Shih et al., 2006], lend strong support to the notion that ubiquitous exposures like lead alter the ''normal'' trajectory of cognitive function (Fig. 4). Age-related changes in brain function may be a surrogate, in part or whole, for the cumulative effects of exogenous insults. The latent effects of lead evidenced by studies over the past decade indicate that the lead standards of the U.S. Occupational Safety and Health Administration are woefully inadequate to protect lead workers. Current standards are based on a health construct (i.e., acute toxicity of lead) that is outdated. Our studies and others have demonstrated that cognitive function declines over time as a function of cumulative lead dose; if future cognitive decline is to be prevented, lead workers must be protected from acquiring pre-determined cumulative lead doses, not just specified blood lead levels during employment. We believe this body of work suggests that blood lead

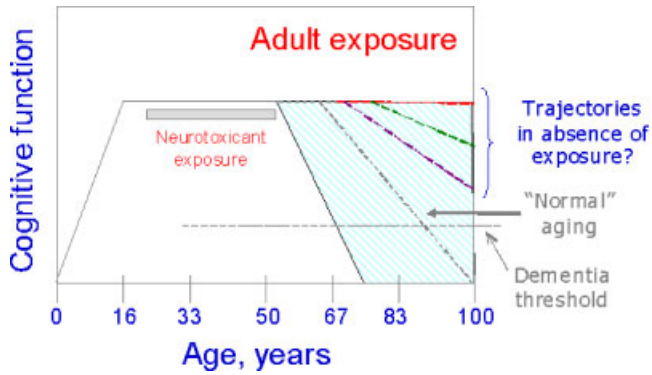

FIGURE 4. One implication of our two decades of results is that perhaps the conception of panel D in Figure 1 was incorrect. It is possible that in the absence of neurotoxicants and other insults, the "normal trajectory" would be much less steep with age. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

levels should be kept below 20 μg/dl to prevent the acute effects of recent dose and tibia lead levels should be kept below 15 μg/g to prevent the chronic effects of cumulative dose. A tibia lead of 15 μg/g would likely result from a cumulative blood lead index (CBLI, the area under the curve of blood lead vs. time) of 150 to 300 μg-years per dl [Somervaille et al., 1988; Armstrong et al., 1992; Roels et al., 1995; Cake et al., 1996], which would result, for example, from an average blood lead level of 15 to 30 μg/dl; for 10 years or 5 to 10 μg/dl for 30 years.

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