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Neurotoxicity and Outcomes from Developmental Lead Exposure: Persistent or Permanent?

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Background: Childhood lead poisoning remains an important public health issue in the United States, as well as elsewhere in the world. Although primary prevention is a major goal and it is critically important to keep children from getting poisoned, it is also important to explore ways to reduce the neurotoxic effects of lead in those children already poisoned. Whether lead-induced neurotoxicity and its related adverse outcomes are viewed as "permanent" or "persistent" may influence the way in which potential remediation efforts are considered for improving outcomes from childhood lead poisoning.

Objectives: The objective of this commentary was to discuss the ideas of permanence and persistence in relation to the direct neurotoxic effects of lead on the brain and the resulting adverse outcomes from these effects. Recent new insights regarding potential mitigation of lead-induced neurotoxic effects on brain and behavior are considered along with clinical information on neurorehabilitation to suggest potential strategies for improving cognitive/behavioral outcomes in lead-poisoned children.

Discussion: The distinction between permanent and persistent in regard to lead-induced neurotoxicity and its resulting outcomes may have broad implications for public health policies in response to the problem of childhood lead exposure. The term permanent implies that the damage is irreversible with little chance of improvement. However, there is evidence that at least some of the adverse cognitive/behavioral outcomes from lead exposure are persistent rather than permanent and potentially amenable, under the appropriate circumstances, to some level of mitigation. This author recommends that clinical, interventional research efforts be devoted to exploring optimal neurorehabilitative and enrichment conditions to stimulate plasticity and enhance functioning to determine the extent to which promising results from preclinical studies of lead-induced brain damage and the mitigation of these effects can be successfully translated to humans. https://doi.org/10.1289/EHP12371

Over the last several decades, regulations designed to reduce or remove lead from the environment have resulted in decreases in children's blood lead levels, at least at a population level.[1] However, millions of children still live in lead-contaminated communities and lead-contaminated housing, where exposure to deteriorating lead paint and toxic dust, as well as contaminated water from lead-containing supply lines and old plumbing fixtures, continue to cause children to have elevated blood lead levels.[2,3] Although the U.S. Centers for Disease Control recently reduced the blood lead reference level [i.e., "based on the 97.5th percentile of the blood lead values among U.S. children 1–5 years from 2015–2016 and 2017–2018 National Health and Nutrition Examination Survey (NHANES) cycles"] to 3.5 μg/dL,[4] it is uniformly recognized that there is no threshold for the toxic effects of lead on a child's brain[5] and thus, developmental lead exposure continues to be a significant public health concern. Considering that no level of lead in a child's blood is considered safe, in this commentary, the terms lead poisoning and lead exposure are used interchangeably.

Historically, lead-induced neurotoxicity and its related adverse outcomes have been considered to be permanent. Even as recently as 2016, a Policy Statement on Prevention of Childhood Lead Toxicity from the American Academy of Pediatrics[2] stated, "No effective treatments ameliorate the permanent developmental effects of lead toxicity." But, is lead-induced neurotoxicity and the adverse cognitive and behavioral outcomes that stem from it "permanent" or "persistent"? This is not simply a semantic issue and there is no simple answer to this question. It is this author's opinion that the distinction between permanent and persistent in regard to lead-induced neurotoxicity and its resulting outcomes may have broad implications for public health policies in response to the problem of childhood lead exposure. When thinking about this complicated issue, it is perhaps useful to separately consider direct neurotoxic effects of lead from the adverse outcomes from those effects.

Direct neurotoxic effects of developmental lead exposure include apoptosis, excitotoxicity, mitochondrial damage, effects on neurotransmitter synthesis and release and second messenger systems, abnormal myelin formation, and abnormal dendritic branching patterns, among other effects.[6] Cell loss, defects in neurogenesis, and structural defects in neural architecture that are induced by lead exposure prenatally or postnatally can be reasonably assumed to be permanent, and this would be true centrally and peripherally. An animal study has suggested that lead (at very high doses) can cause ototoxicity and sensory hearing loss through lead-induced loss or dysfunction of outer hair cells and degeneration of spiral ganglion neurons in the cochlea.[7] Such damage, resulting in cell loss, would be expected to be permanent. However, much of the work on lead exposure and hearing loss, at least in humans, suggests that lead-induced damage occurs primarily in central auditory processing networks.[8] In one study, blood lead levels were inversely associated with measures of central auditory processing in 5-y-old children, and when deficits were seen, they appeared on a test with a strong central processing component.[9] If lead-induced auditory deficits are indeed primarily due to central processing deficits, these deficits may not necessarily be permanent, as one would expect from a primary sensory hearing loss, but instead may be persistent and potentially modifiable. In rats, lead exposure also caused a cortical central auditory processing deficit, and this deficit was shown to be modifiable by specific auditory training.[10] Persisting lead-induced deficits in cortical neuronal processing of spatial information of sound were remediated by behavioral training. Appropriate forms of behavioral training were shown in animal models to be able to remodel response dynamics in the auditory cortex[11–14] and restore changes in cortical spatial processing[10] induced by lead. Such studies raise the possibility that

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mitigation of lead-induced neurotoxicity can be achieved in humans under the right circumstances.

The term permanent implies that the damage is irreversible with little chance of improvement. Even if many of the direct toxic effects of lead on the brain result in permanent damage, if adverse cognitive/behavioral outcomes from lead exposure are persistent rather than permanent and therefore potentially amenable to some level of mitigation, under the appropriate circumstances, there may be hope to at least reduce the severity of some of the adverse outcomes from toxic effects of lead on the young brain. Persistent in this context means that the consequences of early life lead exposure are lasting but, if treated, have the potential to not become permanent. The problem is, however, treatments are not currently available. An important question is whether brain damage induced by lead is amenable to rehabilitation efforts aimed at stimulating structural and functional reorganization similar to, for example, what is attempted to stimulate neuroplasticity following a stroke.[15]

In 2007, our group published a paper in which we showed that lead exposure impaired the ability of the rat brain to spontaneously respond to injury, and we hypothesized that this was due to a lead-induced "alteration in the brain's capacity for structural and/or functional plasticity."[16] In that paper, we stated, "Further work is now needed in order to examine a wider variety of behaviors and study animals for longer periods of time post-lesion to examine whether lead exposure merely delays functional recovery or if lead-exposed animals permanently have worse outcomes than non–lead-exposed animals."[16] In 2012, our group published a paper describing the effects of developmental lead exposure on the hippocampal transcriptome in the rat[17] in which we stated, "the picture that emerges is that developmental lead poisoning may result in a generalized disorder of plasticity, with sequelae ranging from learning and memory deficits to an impaired ability of the brain to respond to stress or injury." It appears that the propensity for central nervous system plasticity may be impaired after early life lead exposure and that this effect is rooted at least in part in widespread alterations in transcriptional profiles in the brain. This author hypothesizes that though such effects on plasticity are persistent, they can become permanent if not addressed.

In a recent publication from our group, we described relationships between early life lead exposure and living in an enriched vs. a nonenriched postnatal environment on adult genome-wide transcription profiles in the CA1 region of the hippocampus of rats.[18] In this RNA-sequencing study, we found that expression of >3,500 genes was differentially affected by early postnatal lead exposure and that environmental enrichment further modified the lead-altered transcriptome. "Minimal significant differential gene expression changes were observed as a consequence of living in the enriched environment in normal control animals and the transcriptome of lead-exposed enriched animals was indistinguishable from that of non–lead-exposed control enriched animals." Remarkably, we also found that living in the enriched environment largely reversed the vast majority of lead-induced alterations to the hippocampal transcriptome.[18] Animals raised in the enriched environment also had no memory deficit, whereas animals raised in a nonenriched environment had a lead-induced memory deficit. Further, "the biological, cellular, or molecular processes that were downregulated due to lead exposure were upregulated by environmental enrichment and vice versa."[18] The expression of a large number of genes involved in synaptic transmission, plasticity, cytoskeletal regulation, and transcriptional regulation, as well as epigenetic regulators and long noncoding RNAs, were altered by lead exposure, and environmental enrichment, for the most part, reversed these lead exposure-induced alterations in expression.[18] Thus, at least in animal studies, there is evidence for a biological mechanism through which some adverse outcomes from the effects of lead on the brain may be reversible under appropriately stimulating, enriched conditions.

There are multiple factors that contribute to enrichment or nonenrichment in humans. Socioeconomic status (SES) is a complex societal construct that encompasses factors including income, "educational attainment, financial security, subjective perceptions of social status and social class," as well as a variety of other factors.[19] Low SES is characterized by poverty and multiple physical and psychosocial stressors on parents and children.[19] As previously described, children from low-SES families are less likely to have experiences that support the development of fundamental skills needed for academic success, including such skills as vocabulary, oral language, and reading.[20] Low-SES households also typically have less access to books, computers, and stimulating toys, and there are often less-enriching parent–child interactions.[21,22] It has been known for decades that children born to low-SES households routinely sustain the highest blood lead levels and that for similar levels of exposure, have more severe outcomes from exposure to lead than children born to high-SES households[23–27] Rutter[24] hypothesized that "economically disadvantaged children, because of a neuropsychological status rendered fragile by environmental influences, might be more vulnerable to the neurotoxic effects of lead." Bellinger et al.[28] reported that social class was a modifier of the association between development and lead exposure, with a child's age at exposure, level of exposure, and socioeconomic status combining to modify neurodevelopmental outcomes. Bellinger et al.[29] went on to suggest that in studies of the effects of lead on neurodevelopment, variables, such as sex and social class, should be viewed as effect modifiers rather than as confounders. Forty years later, these ideas are supported by a variety of findings (*vide infra*). For example, Marshall et al.[30] recently reported that with increasing risk of lead exposure, "children from lower versus higher income families exhibited lower cognitive test scores, smaller cortical volumes, and smaller cortical surface area" compared with children from higher-SES families. These authors suggested that reducing lead exposure risk might preferentially benefit children from low-SES families, and that a greater understanding of the interacting factors of SES and lead exposure will be important for improving outcomes in lead-exposed children.

Yet, not all children who grow up in an impoverished environment experience similar adverse neurobehavioral consequences. Recent research suggests that children who receive supportive interventions can develop resilience to the consequences of poverty and low-SES environments.[31] Childhood hippocampus, amygdala, and cortical gray matter volumes can vary as a function of SES and family poverty, with children from poorer families having smaller hippocampal, amygdala, and cortical volumes,[32–34] as well as effects on other brain structures.[35,36] In addition to associations between SES and brain structure, there is also a relation between SES and brain activation patterns, with decreased task-related brain activation patterns in children from low-SES families.[37] Recently, effects of poverty on hippocampal, amygdala, and white matter volumes in healthy children were shown to be mediated in large part by the level of caregiving support,[38] leading the investigators to suggest that "attempts to enhance early caregiving should be a focused public health target for prevention and early intervention." A randomized, controlled study of children whose parents received a supportive parenting intervention (training on family management, problem solving, and support for academic activities) or a control intervention showed that children of parents who received the supportive parenting intervention did not display a previously noted association between number of years living in poverty and hippocampal/amygdala gray matter volume measured at 25 years of age.[31] There is also evidence that supportive

parenting interventions protected against poverty-related alterations in resting state connectivity in central executive and emotional regulation networks.[39] Such studies support the idea that psychosocial interventions may play an important role in mitigating persistent negative effects of poverty on brain structure and function in children, preventing them from becoming permanent effects. In their analysis of data from the Adolescent Brain Cognitive Development (ABCD) Study, Tomasi and Volkow[40] suggested that quality of child care and "lack of supportive/educational stimulation in children from low-income homes might drive the reduced cortical volume and cortical thickness" found in these children.

Although there are at least a few studies that have systematically examined potential protective factors and interventions to mitigate the effects of poverty, including quality of child caregiving, on children's brain development and function[37] this author is not aware of any that have examined this in relation to outcomes from poverty and childhood lead exposure and suggests that these types of studies are now necessary. Just as studies of the association between childhood poverty and brain development and function suggest that this relationship is persistent but not immutable,[37] it is possible that the same may true for the association between lead-induced effects on brain development and function (with or without the association with poverty). However, owing to the nature of lead's effects on the brain, lead-induced changes in brain development, structure, and function may be more severe and more pervasive than changes associated with poverty alone. This author suggests that well-designed clinical interventional research studies, based on those previously conducted with presumed non–lead-exposed populations, are needed to determine the extent to which the young lead-exposed brain can respond to rehabilitation efforts and achieve functional and structural reorganization to the extent necessary to have functional relevance.

A further suggestion of this author is that in addition to using community-based efforts to enhance the quality of the environment and early caregiving, the application of cognitive training, provided in the home or in preschool, child care, or the school setting, might also be a way to potentially stimulate plasticity and improve cognitive and educational outcomes in lead-exposed children and prevent persistent cognitive/educational impairments from becoming permanent. Cognitive training has been successful in improving function in adult and young brains damaged by certain diseases (e.g., schizophrenia,[41] cancer,[42,43] physical trauma[44,45]). Cognitive training also improved cognition in patients with mild cognitive impairment and stimulated plasticity, as demonstrated by normalized brain activation patterns.[46] Cognitive improvements and functional plasticity have also been reported in children from low-SES families following cognitive training.[47–50] Although this is still an emerging field and more work needs to be done to validate transference beyond trained cognitive domains and the persistence of training-related improvements, it appears to offer another potential avenue to stimulate plasticity and enhance recruitment of brain circuits involved in critical cognitive functions. The extent to which cognitive training might improve cognitive functioning and stimulate brain plasticity in lead-exposed children has not been systematically studied, but this author suggests that this needs to be investigated, using successful studies with low-SES families and presumed non–lead-exposed pediatric populations as a guide.

Molecular and cellular data from animal studies suggest a potential blunting of the capacity for structural and functional plasticity as a consequence of early life lead exposure that is persistent and potentially permanent, with far-reaching negative effects on cognition, behavior, and educational outcomes. However, data on animal models of lead toxicity from this author's group[18,51,52] and others[53,54] have shown that environmental enrichment can mitigate negative effects of lead exposure on at least some cognitive functions and alter molecular processes in the brain to effectively reverse many lead-induced changes in gene expression. In our study published in 2001,[51] the first to apply environmental enrichment to lead-exposed animals, we found that rearing in nonenriched or enriched environments had no significant effect on learning curves but that being reared in an enriched environment did have a significant effect on spatial memory in the Morris water maze (MWM) in lead-exposed animals.[51] Environmental enrichment of lead-exposed animals also resulted in higher levels of trophic factor mRNA expression in the hippocampus, compared with nonenriched lead-exposed animals.[51] This important first study demonstrated that lead-induced neurotoxicity and memory deficits were potentially modifiable by environmental conditions, but it had several shortcomings in the use of only males, only post-weaning lead exposures (concurrent with enrichment), relatively high lead exposure (1,500 ppm) and high blood lead levels (>20 μg/dL), and use of behavioral extremes [enrichment (8 rats in a large enclosure with stimulus objects that were changed three times a week) vs. isolation (single cage housing)]. A subsequent study by Guilarte et al. in 2003[53] also examined effects of environmental enrichment on learning and memory in the MWM but in adult rats exposed to lead during gestation and lactation up until weaning. Because this study assessed animals as adults after early life lead exposure, it demonstrated that environmental enrichment could reverse spatial learning and memory deficits resulting from early life developmental exposure to lead. However, the shortcomings in this study included the study of only males, the nonenriched condition being isolation (i.e., single cage housing), and a high level of lead exposure (1,500 ppm). A study by Cao et al. in 2008[54] also used only male rats exposed to a high level of lead (1,500 ppm) from gestation through weaning and housed in large, enriched environments (8 per large cage with enrichment items) or nonenriched environments (2 animals per cage with no enrichment items) and confirmed results from the Guilarte et al. study that enrichment could reverse lead-induced spatial learning and memory deficits. They also extended these findings to show that enrichment also reversed lead-induced deficits in synaptic plasticity mechanisms (i.e., long-term potentiation in the hippocampus). Given that the studies mentioned thus far examined interactive effects of lead and enrichment only in males, our group studied the effects of different levels of lead exposure (250, 750, and 1,500 ppm; gestation through weaning) in male and female rats raised in a nonenriched (3 animals/cage, no toys) or an enriched environment (6 animals/large cage with a variety of toys changed twice weekly) on learning and memory in the MWM.[52] This study showed complex interactions between sex and level of lead exposure on the expression of learning and memory deficits and as well as complex interactive effects of sex, level of lead exposure and environmental enrichment on the reversal of lead-induced learning and memory impairments. Importantly, this study not only showed sex-dependent effects of lead on learning and memory (i.e., sex as an effect modifier and not simply a confounder to be controlled for) but also that enrichment could exert positive effects on lead-induced cognitive deficits in females as well as in males.

There is no question that primary prevention of lead poisoning is important for the health and well-being of the population. An important study by Billings and Schnepel[55] showed that a number of adverse outcomes previously associated with early life lead exposure, such as poor school performance and behavioral problems (including antisocial behaviors), can be substantially improved or reversed through interventions triggered by the detection of elevated blood lead levels. As described by the authors, these interventions included nutritional assessments, educating caregivers on improving nutrition and reducing exposure to lead in the home, a

home environment investigation, medical evaluations, developmental assessments, and referrals for lead remediation services. Interventions that reduced a child's lead exposure and reduced blood lead levels over the observation period were shown to improve educational and behavioral outcomes.[55] These authors suggested that positive effects from their study likely resulted from a combination of influences from the public health response and the parental response to the lead exposure and that reducing continued exposure to lead and generally improving overall health of the children contributed to the beneficial effects observed.

Although preventing children from being poisoned by lead is critical and interventional strategies as proposed by Billings and Schnepel are important, more still needs to be done for the millions of children already exposed to toxic levels of lead. These children often have significant neuropsychological deficits across multiple cognitive domains[56] that affect not only their school performance[57,58] but their socialization and self-esteem.[6] It is likely that the brain of a lead-exposed child is not incapable of plasticity, but perhaps these children may require exposure to more intense plasticity-inducing stimuli than what might be expected to induce plasticity to a non–lead-exposed brain, and more than they are currently exposed to at home or at school, to affect significant functional change.

Living in poverty by itself has been associated with important persistent and potentially permanent negative effects on brain development and cognitive/behavioral outcomes. There is an increased risk of lead exposure in children from lower-income families,[30] and low income was also associated with higher blood lead levels in Phase I of NHANES.[59] A child's brain already negatively affected by the adverse effects of poverty would likely be further negatively affected by exposure to the potent neurotoxicant lead. This author suggests that research that applies what is known about brain plasticity and ways to study it and enhance it following injury needs to be conducted to try to improve life outcomes for lead-exposed children, particularly those with the added disadvantage of living in a low-SES situation. In animal studies of stroke, the combination of an enriched environment with rehabilitation training led to significant improvements in functional recovery in animals with large lesions, whereas rehabilitative training or enriched environment alone did not produce significant improvements in functional recovery.[15] As with stroke and other types of brain injury, including lead-induced brain injury, the injury does not impair the functioning of the entire brain and attention needs to be paid to the unique aspects of individual cases.[56] As we have stated previously, "Brain injuries from the majority of etiologies do not produce a diffuse dampening of neurocognitive functioning in individuals—rather, symptoms are typically focal impairments of specific neuropsychological processes observed in association with relatively normal functioning in other neuropsychological domains."[56] The same is true for brain injury induced by lead poisoning. This realization is critical to efforts aimed at potentially ameliorating the negative cognitive/behavioral effects of lead poisoning. Primary prevention is critical and even if lead poisoning could be eliminated tomorrow, something more needs to be done to try to improve outcomes for the millions of children already poisoned by lead. For example, well-designed community/family-based training studies aimed at improving brain function, cognition, and behavior, in addition to controlled clinical studies of cognitive training effects in lead-exposed children, as discussed previously in this commentary, are needed to determine optimal neurorehabilitative and enrichment conditions to stimulate plasticity and enhance functioning. Moreover, such studies can determine the extent to which the promising results obtained from animal studies of lead –induced brain damage and the mitigation of these effects can be successfully translated to humans.

What has been suggested in this commentary will require the dedication of behavioral scientists, toxicologists, clinicians, and local and national advocates, as well as support from various funding agencies to achieve the goal of modifying the adverse neurodevelopmental outcomes from lead exposure. It is not possible at this point to estimate what the cost might be to conduct interventional studies such as those suggested in this commentary. However, considering the enormous social and behavioral costs of childhood lead exposure,[60] the costs of studies suggested in this commentary will pale in comparison with the costs of not trying to improve outcomes from childhood lead exposure. There will of course be challenges and difficulties in implementing the strategies and interventions suggested in this commentary, but the futures of millions of lead-exposed children are at stake and an attempt at improving their chances for success at least needs to be made.

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