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Invited Perspective: Challenging the Dogma of Lead Neurotoxicity

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The commentary by Schneider[1] in this issue of *Environmental Health Perspectives* provides a thoughtful perspective that requires the attention of those responsible for advocating and advancing children's health and public health at large. The first tenet of the environmental health sciences is to prevent exposure to harmful chemicals, that is, primary prevention. When prevention is not possible, or it is ineffective, evidence-based interventions can change outcomes and improve quality of life. Yet this principle of public health has not been fully effective in one of the worst cases of environmentally induced neurological disease known to humanity: childhood lead intoxication.

A large body of epidemiological studies over many decades provides indisputable evidence that childhood lead exposure, at progressively lower levels, impairs cognitive domains involved in school performance.[2–4] These lead-induced effects are associated with downward economic and social mobility[5] and the emergence of psychopathologies in adolescence and in young adults.[6–12] Limited effort and resources are being dedicated for discovering interventions that can effectively improve the lives of millions of children globally who have been, and continue to be, exposed to lead. The lack of a sustained effort to find effective interventions for the millions of children who have already been exposed and exhibit learning and behavioral problems is most likely based on the dogma that the problem is insurmountable or that the toxic effects of lead on the brain are permanent or irreversible. In his commentary, Schneider posits the potential benefits of enriching experiences in stimulating brain function and provides evidence of a strategy that needs further exploration.[1]

In the 1970s, successful implementation of public health policy to remove lead from consumer products resulted in a progressive decrease in blood lead levels in the U.S. general population.[13–15] However, despite this significant achievement, childhood lead intoxication remains a major public health problem around the world owing to the millions of tons of lead deposited in the environment from anthropogenic sources. Besides the historically recognized sources of lead exposure from paint, gasoline, service pipes in water distribution systems, contaminated air, and soil polluted by decades of lead dispersion in the environment,[16] new and unexpected sources continue to be discovered, providing further evidence of the insidious problem. The most recent example in the news is the finding of old telephone cables that are degrading and leaching lead into the surrounding environment.[17] In low- and middle-income countries, increasing sources of lead exposure arise from repositories of electronic waste or used automobile and motorbike batteries, which are recycled to remove lead and other toxic, but valuable, metals.[16]

The magnitude of this silent, and often forgotten, toxic reality is best summarized in the 2020 UNICEF report "The Toxic Truth: Children's Exposure to Lead Pollution Undermines a Generation of Future Potential."[16] This report presents estimates of the number of children ≤19 years of age who have blood lead levels >5 mg/dL. In the United States, the number is estimated at 0.8–2.0 million; globally, it is at >800 million,[16] or ∼40% of this age range. The standard of care for highly lead-intoxicated children is succimer chelation, developed in the 1970s to reduce the lead body burden.[18,19] However, multicenter chelation trials with large numbers of lead-exposed children have revealed that, although succimer effectively lowers blood lead levels, it does not reverse the effects on cognitive function or neuropsychological performance.[20,21] Therefore, it is imperative that effective, safe, scalable, and low-cost approaches to mitigate the negative effects of childhood lead intoxication on brain health be developed, tested, and implemented.

Schneider also notes that studies in children of low socioeconomic status who receive supportive psychosocial interventions are largely resilient to the negative effects of poverty on brain development and function. He correctly points out that these same interventions should be tested in lead-intoxicated children. Although psychosocial and educational interventions that support brain health should be an important part of community-based programs, the current author argues that other adjunct nutritional therapies should also be considered. For example, preclinical studies on the benefits of these types of enriching interventions on reversing lead-induced learning deficits have uncovered neurobiological mechanism(s) by which they benefit the lead-exposed brain.[22,23]

A primary target of early life lead exposure on the developing brain is disruption of the *N*-methyl-D-aspartate subtype of excitatory amino acid receptor[24–27] and downstream brain-derived neurotrophic factor (BDNF) signaling.[28,29] BDNF plays a critical role in synapse formation and neuronal development and survival, regulates neuronal plasticity, and is essential for learning and memory.[30,31] Studies have shown that the exogenous addition of BDNF to hippocampal neuronal cultures exposed to lead *in vitro* during synapse formation is able to reverse lead-induced deficits in synaptic function by normalizing levels of vesicular proteins and vesicular neurotransmitter release.[28] From an *in vivo* therapeutic perspective, BDNF has limited clinical utility for brain disorders because it has a short half-life and it does not cross the blood–brain barrier.

However, intensive research efforts have discovered BDNF-mimetic molecules, such as 7,8-dihydroxyflavone (7,8-DHF), that cross the blood–brain barrier and are inexpensive and safe for human use.[32–34] 7,8-DHF is a nutrient in the flavonoid family that is abundant in fruits and vegetables in the human diet. 7,8-DHF, as a biological analog of BDNF, has been tested in an animal model of lead neurotoxicity and shown to reverse the vesicular release deficit in the hippocampus of animals that were continuously exposed to lead during brain development into adulthood.[35] Furthermore, 7,8-DHF has proven to be effective in a variety of animal models of brain disorders[36–44] and improved cognitive

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function in humans in a randomized, controlled, double-blind clinical trial.[45] The environmental enrichment and subsequent studies in animal models provide evidence that targeting the BDNF system with BDNF-mimetic nutraceuticals has the potential to substantially mitigate the toxic effects of lead on the brain. This nutritional approach—combined with community-based efforts to enhance the quality of the home environment, increase parental involvement, and provide sustained cognitive training in child care and school settings—may be a multipronged approach to mitigating the detrimental effects of early life lead exposure on children's cognitive and behavioral domains. In fact, in a 2018 study, applying a combination of these interventions to children with proven lead intoxication was associated with improvement in multiple educational and behavioral outcomes.[46]

As Schneider points out, the time has come to evaluate such approaches in children who are suffering from the devastating effects of lead intoxication using carefully designed clinical intervention trials. A small investment of resources today can have a profound effect on the future of the millions of lead-intoxicated children who otherwise may not achieve their full potential and contribute positively to society.

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