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Neurotoxicology: What Can Context Teach Us?

Neurodevelopment and cognitive function are among the most important outcomes of interest in public health, particularly with the rise of developed countries dominated by knowledge-based economies. In developing countries and poor communities in the United States, the simultaneous presence of several adverse childhood exposures can alter both the development and organization of the central nervous system.[1]

Perhaps the most common factors that predispose children to adverse neurodevelopmental outcomes are malnutrition, environmental toxicants, and sociocultural conditions that act as psychosocial stressors. Because these factors tend to cluster in the poorest populations, studies typically statistically adjust for the potential confounding effects of joint exposure to eliminate bias in the estimate of the main effect. This paradigm has been the standard in neuroepidemiologic research for many years and has done much to identify neurotoxicants and better establish the basic principles and methodology of neurotoxicology research. However, all paradigms merit periodic reevaluation, and the idea that we must consider multiple toxic exposures primarily as confounders may not be the optimal approach to understanding how environment molds the developing brain.

In this issue of *The Journal*, Solon et al[2] report a 2% to 3% decrease in cognitive test scores for every 1-ug/dL increase in blood lead level. This is a remarkable finding; previously, the generally accepted dose-response relationship between blood lead level and child neurodevelopment test score (as measured by the Bayley Scale Mental Developmental Index or by IQ test) was a $< 1\%$ decrease for every 1-μg/dL increase in blood lead level. As the authors point out, however, most of the previous studies were conducted in more developed countries. Their findings may be more representative of the effects of lead in developing countries, which have different social, toxicologic, and nutritional factors jointly influencing neurodevelopment compared with developed countries.

But if we adjust for these factors, why does the main effect of lead still differ so greatly between developing and developed countries? The initial response might be to suggest that the findings of Solon et al are due to unmeasured confounding (eg, unmeasured genetic, nutritional, or social factors), which both track with increased risk of lead poisoning and are independently neurotoxic. The differences in the effect estimate of Solon et al versus those of previous studies are related to residual confounding, and the true dose-response relationship between lead level and neurodevelopmental outcomes is actually similar in developing and developed countries. If these confounders had been measured more precisely, so the argument goes, then we would have found exactly that. Indeed, most studies of lead poisoning adjust for the effects of socioeconomic factors, nutrition (eg, iron deficiency), and, to a lesser extent, genetics.

For years now, in both population-based and animal research, the goal has been to narrow in on the main effect of a specific neurotoxicant. Animal

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studies are typically tightly controlled experiments in which the only factor differing between groups is the dose of the neurotoxicant. Although epidemiologic studies may measure concurrent effects of social and other physical/chemical risk factors, the potential for synergistic joint effects of such factors when combined with lead poisoning are seldom considered. Instead, each factor is treated as an independent risk factor for neurodevelopmental toxicity, and its variance and covariance are adjusted for statistically. Although observational in nature, this is still fundamentally a reductionist approach, like an experimental study.

But what do we lose by reducing a toxicant simply to its main effect? Should we expect main effects to remain relatively constant across populations? Main effects are more likely to be relative across populations, that is, they are dependent on context. Life does not occur in a cage; people are inherently different, and societies are inherently different. Thus, toxicants may plausibly act differently in different people (host susceptibility) or even in different societies. Even though it is certainly plausible that nutrition, genetics, or social environment are true confounders of chemical toxicant effects, it is equally biologically plausible that they may be modifiers of chemical toxicant effects, an assumption that calls for a different statistical approach than modeling effects as confounders. Not doing this represents a missed opportunity, and perhaps studying the interactions of social, nutritional, and genetic factors with neurotoxicants chemicals can provide insight into strategies for preventing and even treating the effects of chemical toxicants.

I do not mean to imply that no work has been done to address context as a factor in neurotoxicogy. To illustrate, we need only look to animal research on enriched environments. An enriched environment itself alters neurodevelopment, but the effect may not end there. Recent animal studies have demonstrated modification of lead toxicity in rats by a socially enriched environment. For example, Schneider et al[3] found that animals raised in social isolation were more sensitive to the neurotoxic effects of lead compared with animals raised in an enriched environment. Perhaps even more striking, Guilarte et al[4] found that in rats, an enriched environment provided after lead exposure was associated with reversal of lead-induced learning impairment, increased gene expression of hippocampal N-methyl-D-aspartate receptors, and increased induction of brain-derived neurotrophic factor mRNA. The former study suggests that social factors modify the toxicity of lead; the latter study suggests that modifying the social environment may be an effective treatment after lead exposure. This is a promising and immensely important finding. Although chelation has not been associated with improved developmental outcomes after lead exposure, this line of study suggests that social and perhaps behavioral interventions might be an effective strategy for treating lead-poisoned children.

Even though observational research studies in humans are not optimal for determining treatment effect, they nonetheless can point us toward potential treatments. In epidemiology, studying the joint effects of 2 risk factors on an outcome is termed "effect modification." One factor modifies the effect of the other. Addressing effect modification addresses the effect of context in studies of neurotoxicity and provides insight into the underlying biology of that toxicity. Solon et al found that serum folate modified the association between lead level and cognitive outcomes. This finding has 2 potential meanings. One of these is that the nutritional context in which lead poisoning occurs in the Philippines may differ from that in more developed countries and may help explain the steeper dose-response curve between blood lead level and cognitive outcomes in the Philippines. The second is that folate supplementation might be an effective treatment or preventive intervention in children at high risk for lead poisoning. Although the relationship between lead and folate is not well understood, and further research is needed to determine the underlying biology of this interaction, studying folate as an effect modifier of lead rather than as a confounder of lead poisoning can open up new biological pathways of study and, most importantly, identify potential interventions.

Had Solon et al merely modeled serum folate as a confounder of lead poisoning, they would have missed this opening. Effect modification (and the more familiar concept of "biological synergism") means that joint exposure is multiplicatively more (or less) toxic compared with effects that occur when the modifying factor is absent. Studies of effect modification are difficult to conduct, because they require larger sample sizes and more measurements, increasing costs. But such costs come with exceptional potential benefits. Clearly, more investigation is needed into the role of folate in lead poisoning and potential mechanisms, such as changes in DNA methylation, a process involving folate metabolism[5] and known to be influenced by metals.[6,7] Whether the findings of such investigations will lead to the development of new treatment approaches for lead poisoning is speculative at this stage, but what is clear is that toxicologic research needs to consider the possibility that joint exposures act synergistically and not independently. Doing so will improve our understanding of how environment shapes health and what interventions can either help prevent or treat toxic exposures.

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