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The Impact of Toxins on the Developing Brain

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Abstract

The impact of toxins on the developing brain is usually subtle for an individual child, but the damage can be substantial at the population level. Numerous challenges must be addressed to definitively test the impact of toxins on brain development in children: We must quantify exposure using a biologic marker or pollutant; account for an ever-expanding set of potential confounders; identify critical windows of vulnerability; and repeatedly examine the association of biologic markers of toxins with intellectual abilities, behaviors, and brain function in distinct cohorts. Despite these challenges, numerous toxins have been implicated in the development of intellectual deficits and mental disorders in children. Yet, too little has been done to protect children from these ubiquitous but insidious toxins. The objective of this review is to provide an overview on the population impact of toxins on the developing brain and describe implications for public health.

ENVIRONMENTAL DISASTERS

The impact of toxins on the developing brain was first recognized in the aftermath of environmental disasters (103). In the early 1900s, in an epidemic of lead poisoning from paint in Queensland, Australia, children presented with frank anemia, paralysis of the lower limbs, and blindness; many died (125). In the 1950s, in a Japanese fishing village on the shores of Minamata Bay, mothers who ingested mercury-contaminated fish gave birth to children with severe motor dysfunction and mental retardation (51). The epidemic of congenital mercury poisoning in Minamata—as well as the thalidomide-induced epidemic of phocomelia (seal-limb) in the 1950s—made it clear that, contrary to prevailing beliefs, the placenta is not a barrier against toxins (70). In 1955, in Japan, ingestion of arsenic-contaminated powdered milk by children resulted in more than 12,000 cases of arsenic poisoning. Children who had been exposed to arsenic-contaminated milk were 10 times more likely to be mentally retarded as compared with national rates (87). In 1968 in Japan and in 1979 in Taiwan, the ingestion of polychlorinated biphenyl (PCB)-contaminated rice bran oil by pregnant women led to fetal wasting and cola-colored, "dull" children (26, 103). These epidemics served as warnings that environmental toxins can adversely impact or retard brain development.

These disasters seem remote, but evidence has accumulated over the past century that implicates ubiquitous, low-level exposures to an ever-growing litany of environmental toxins in the development of diminished birth weight, shortened gestation, intellectual deficits, and mental disorders in children. The consequences of low-level exposures are usually subtle for an individual child, but the population impact on brain function can be substantial (10, 43, 47). Not surprisingly, the impact of environmental toxins on brain-based disorders is often overlooked, underestimated, or ignored.

NEW MORBIDITIES

The causes of death and disability in children have shifted over the past century. Concerted public health efforts to control tuberculosis, cholera, typhoid, and other infectious agents in the early twentieth century led to a dramatic reduction in child mortality, followed by a rise in life expectancy. By the end of the twentieth century, the "new morbidities of childhood"—attention deficit hyperactivity disorder (ADHD), autism, asthma, obesity, and preterm birth—had emerged. Learning disabilities and mental disorders are now two of the most prevalent morbidities in children. About 7.6% of US children are estimated to have a parent-reported learning disability, and 13% are estimated to have a mental disorder, including anxiety, autism, conduct disorder, depression, or ADHD (14, 20, 21, 44, 76) (**Figure 1**).

The prevalence of developmental disabilities has increased in US children. From 1997–1999 to 2006–2008, Boyle et al. (14) noted a 17% increase in the prevalence of parent-reported

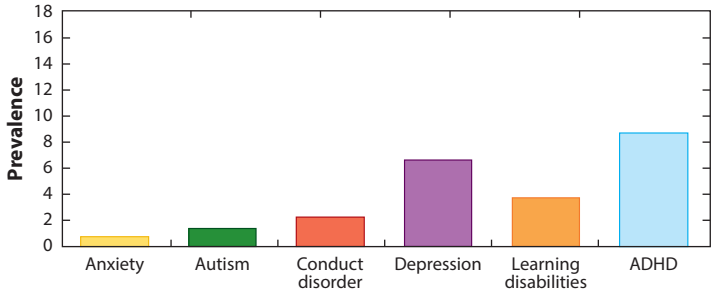


Figure 1

Prevalence of learning disabilities and mental disorders in US children. Data from 14, 21, 76.

developmental disabilities, representing an additional 1.8 million US children having a developmental disability. The prevalence of autism has increased dramatically, even after accounting for severity of symptoms, access, age at diagnosis, and immigration (53). The Centers for Disease Control and Prevention (CDC) (21) reported a 123% increase from 2002 to 2010 in the prevalence of autism spectrum disorder (ASD) among 8-year-old children, the age of peak prevalence, in a regional network. Using the National Survey of Children's Health, the CDC (20) also reported that the percent of children who had parent-reported ADHD increased by 22%, from 7.8% in 2003 to 9.5% in 2007. Quantifying trends in mental disorders is often limited by our reliance on parent-reported diagnosis and surveillance. Still, these data indicate that we are in the midst of an epidemic of brain-based disorders.

VULNERABILITY OF THE DEVELOPING BRAIN

The developing brain is particularly vulnerable to environmental toxins. The blood–brain barrier of the developing brain is not fully formed, and it is more permeable to toxins than is the mature brain (104). The rapid growth of the brain during the second trimester of fetal development is followed by neuronal migration, differentiation, proliferation, and pruning throughout early childhood (104). Growing cells are more vulnerable to toxins, and the brain forms over a longer period than do other organs (101, 104). Finally, the brain is composed of many different types of neurons, each type having a distinct growth phase and potentially a different toxicity profile (104).

Environmental toxins can impact the developing brain through various mechanisms. Some toxins, such as mercury, cause cell death and alter cell migration and cell proliferation (101, 104). Lead disrupts neurotransmission, synaptogenesis, and synaptic trimming (101, 104, 110). Dichlorodiphenyl trichloroethane (DDT), PCBs, polybrominated diphenyl ethers (PBDEs), phthalates, and bisphenol A appear to act—at least in part—by disrupting estrogenic or thyroid hormones (17, 28, 27, 74). Another potential mechanism by which toxins may impact brain development is through epigenomic alterations—heritable alterations in gene expression that do not entail changes in the DNA sequence (5). Many environmental toxins, including airborne pollutants, arsenic, lead, diethylstilbestrol (DES), tobacco, and bisphenol A, alter the methylation pattern of the epigenome, one of the more well-understood types of epigenetic modifications (5, 42, 90, 94). Still, epigenetic alterations have yet to be directly linked with neurobehavioral effects in children. Understanding the mechanism of toxicity is important, but it is not essential to regulate a chemical or pollutant.

PBDE = flame retardants

During fetal development, the brain is particularly vulnerable to some toxins, such as methyl mercury and PCBs (39, 56, 61, 107–109). Methyl mercury affects proliferation and migration of neurons; methyl mercury and PCBs both affect synaptogenesis (101). These processes occur predominately during fetal development. In contrast, the brain is particularly vulnerable to lead exposure during early childhood (55, 110). Lead exposure interferes with synaptogenesis, the trimming of synaptic connections, and myelination; the latter two processes occur predominantly during childhood (101, 104). For most toxins, there is insufficient evidence to draw any firm conclusions about specific windows of vulnerability. For example, exposure to PBDEs has been studied in five prospective birth cohort studies (24, 36, 46, 52, 106), but only two tested whether prenatal or postnatal PBDE exposure was more strongly associated with neurobehavioral end points (36, 46). Eskenazi and her colleagues found that certain end points were more strongly associated with prenatal PBDE exposures, whereas other end points were more strongly associated with childhood exposures (36). Gascon and coworkers found that childhood but not prenatal exposures elevated attention deficit symptoms (46). Thus, although we know the developing brain is especially vulnerable to the impact of toxins, the specific windows of vulnerability are not well

characterized for many toxins. Moreover, different regions of the brain may have distinct windows of vulnerability for the same toxin.

Other factors can contribute to the heightened sensitivity of the developing brain to toxins. In some cases, such as with mercury, the concentrations in the fetus are higher than those found in the mother (96). The fetus or newborn may also lack critical enzymes to metabolize environmental toxicants, such as lower concentrations of PON1, an enzyme that has been shown to metabolize organophosphate pesticides (25). Young children are often more heavily exposed to toxins, such as lead, cotinine (a metabolite of nicotine and biomarker of tobacco exposure), and bisphenol A than are older children and adults owing to differences in metabolism, mouthing behaviors, dietary intake, and respiratory rates (16, 66).

MEASURING EXPOSURE TO TOXINS

Biologic markers, or biomarkers, of exposure, which can enhance our ability to quantify an individual's internal dose of a contaminant, are revolutionizing the study of environmental toxins in the same way genetic tests are revolutionizing the study of heritability (65). Early studies of environmental toxins relied on questionnaires about diet, proximity to an industry, or age of housing to estimate exposure, but we can now use biomarkers to measure the internal dose of many environmental chemicals in human tissues and link these exposures with a disability or disease (112). Still, identifying the critical windows of vulnerability and determining how well a particular tissue reflects the target organ for a specific toxin can be challenging. Moreover, in the absence of innovative tools to measure biomarkers of exposure retrospectively (4), we will require large prospective birth cohorts to identify critical windows during fetal development for uncommon conditions such as autism.

The vast majority of people in the United States, including pregnant women and children, are routinely exposed to many confirmed or suspected toxins (134). The litany of toxins or suspected toxins that can be routinely detected in the blood or urine of pregnant women and children is extensive: metals (mercury, lead, cadmium, and arsenic), persistent pollutants (PBDEs, PCBs, and DDT), and nonpersistent chemicals (triclosan, pyrethroids, organophosphate insecticides, bisphenol A, and phthalates) to name only a few (134). Some of the contaminants are established neurotoxins or endocrine-disrupting chemicals, but most of them have not been tested for neurotoxicity (48). Nor has there been any systematic attempt to examine the impact of additive or synergistic effects of chemical mixtures.

Some critics have argued that the concentrations of environmental contaminants routinely found in pregnant women and children are too low to alter behavior. But, as described below, the concentrations of environmental contaminants shown to be toxic—that is, to alter brain function or behavior—are comparable with the therapeutic window for methylphenidate (5 to 30 ppb), the most commonly prescribed drug used to control or reduce ADHD symptoms in children (120).

THE IMPACT OF TOXINS ON COGNITION

Lead, PCBs, and mercury are established risk factors for cognitive deficits (49, 56, 61, 68, 82, 109, 113, 127). In a pooled analysis of 7 cohorts involving over 1,300 children, Lanphear and colleagues found that an increase in low-level, concurrent blood lead concentrations, from <1 to 10 μg/dL (<10 ppb to 100 ppb), was associated with a 6.9 IQ point decrement (68). Research on the relationship of prenatal exposure to PCBs—which consists of 209 related chemicals or congeners—is complicated by the degree of chlorination of the various congeners and types of tissue used to measure PCBs (113). Collectively, however, the epidemiologic and toxicologic evidence implicate prenatal PCB exposure in the development of intellectual deficits in children

(56, 114, 113, 127). In a systematic review, Karagas and coworkers found consistent evidence of adverse effects of prenatal mercury exposure on cognitive abilities in preschool children; the effects were less consistent for younger children and for studies that did not adjust for fish intake (61).

Other toxins have been consistently, but not definitively, associated with cognitive deficits in children. In three birth cohort studies, prenatal exposure to organophosphate pesticides was consistently associated with cognitive deficits in children (12, 35, 97). DiFranza and colleagues conducted a systematic review and concluded that prenatal tobacco exposure is likely associated with cognitive deficits in children, but the effects of exposure were attenuated with adjustment for other confounders (34). Airborne pollutants, using either polycyclic aromatic hydrocarbons or black soot as measures of exposure, have been linked with cognitive deficits in four prospectively followed birth cohorts (91–93, 115, 119). In one of these birth cohorts, the investigators showed an improvement in cognitive outcomes among children who were born after closure of a power plant (119). Five prospective birth cohort studies have examined the effects of exposure to PBDEs (24, 36, 46, 52, 106). PBDEs were inversely associated with cognition in four of the five studies; the results were statistically significant in three studies (24, 36, 52).

Still other toxins have been tentatively associated with cognitive deficits in children. Prenatal exposure to DDT has been associated with cognitive deficits in two of four prospective birth cohort studies (38, 37, 58, 77, 100, 123). Arsenic and manganese have been inversely associated with cognition in cross-sectional studies (75, 128, 129).

When does a suspected toxin become an established one? It is not entirely clear how much evidence is necessary to implicate an environmental contaminant or pollutant as a neurotoxin. In contrast with carcinogens, which are regularly and systematically evaluated by the International Agency for Cancer Research (IARC), there is no systematic process or criteria by which to evaluate emerging neurotoxins. This lack of formal procedure is unfortunate because it delays both the recognition of a toxin as well as any prevention efforts. Carcinogens have historically been singled out as being of paramount importance, but do toxins that impact the developing brain deserve any less attention?

QUANTIFYING THE IMPACT OF TOXINS ON BRAIN DEVELOPMENT

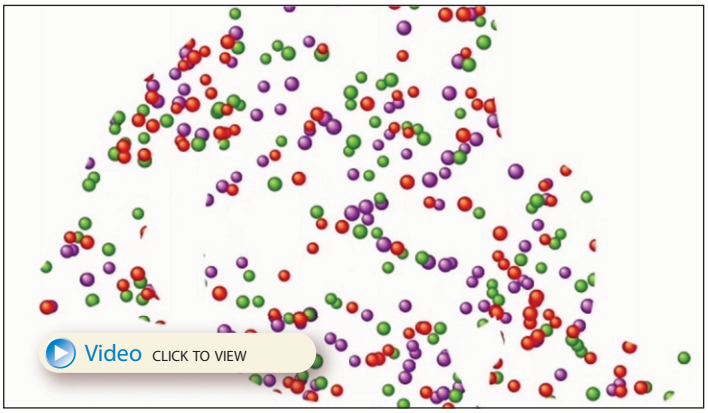
Quantifying the impacts of low-level toxin exposure on brain development is difficult. Many of these challenges result from our reliance on observational studies to investigate the effects of toxins in humans; it is notoriously difficult to infer causal associations from nonexperimental study designs. First, to quantify the independent contribution of a toxin, one must account for a variety of other factors that can impact brain development, including nutrition, maltreatment, and poverty (33). Second, there is substantial interindividual variability in the uptake and metabolism of toxins by a fetus or child owing to mouthing behaviors, genetic variability, and nutritional status. Third, toxins elevate the risk for prevalent but often nonspecific conditions or disorders, such as IQ deficits and ADHD, which makes it difficult to infer causality. Finally, it is difficult to distinguish the adverse effects of toxins from those of other social influences because impoverished children are often more heavily exposed to toxins than are affluent children. Given these obstacles—and a strict adherence to a high but arbitrary threshold for categorizing an association as statistically significant (81)—it is remarkable that the evidence linking numerous toxins with neurobehavioral insults is so robust and consistent. Still, because of the inherent challenges of observational studies, we often must rely on toxicologic studies to provide definitive evidence that environmental contaminants are toxic (69).

Once a toxin is identified, it is important to examine the shape of the dose–response relationship and ascertain whether the evidence supports a threshold. Toxins that impact brain development

are regulated as though there is a threshold, as though there is a safe level of exposure. For lead, the prototypical toxin, there is no evidence of a threshold; indeed, decrements in intellectual abilities are proportionately greater at the lowest levels (19, 68). Previous studies estimated that a 2–2.5 IQ point decrement has been linked with an increase in whole blood lead levels from 10 μg/dL (100 ppb) to 20 μg/dL (200 ppb) (68). In a pooled analysis, an increase in concurrent blood lead levels from <1 μg/dL (<10 ppb) to 10 μg/dL (100 ppb) was associated with a 6.9 IQ point deficit (68). Since then, more than a dozen articles have confirmed that blood lead concentrations are associated with IQ deficits or diminished academic abilities at levels <10 μg/dL (<100 ppb); when the investigators carefully examined the shape of the dose–response relationship, they confirmed that there were proportionately greater decrements at the lower levels of exposure (69, 80). In 2012, the CDC concluded that there is "no safe level of lead exposure"—a simple declaration with profound policy implications (22). Toxins have been regulated with the assumption that there is a threshold or a safe level of exposure. But what if there isn't one?

The shape of the dose–response relationship is not well established for many toxins. Yolton and coworkers found proportionately steeper decrements in reading abilities at the lowest levels of secondhand smoke exposure among US children, but this finding has not been replicated (137). For other established or emerging toxins, such as PCBs, organophosphate pesticides, and PBDEs, the lowest level at which adverse effects occur is less clear, but the linear relationship does not suggest a threshold (12, 24, 36, 52, 97, 113, 114). In contrast, some evidence supports a threshold for some mercury-induced deficits (108).

The impacts of toxins on the developing brain are often dismissed because the effects are subtle. Yet, subtle shifts in intellectual abilities or behaviors in a population can have a substantial impact on intellectual abilities (**Video 1**). It is not easy to discern a 5-point IQ difference between two children, but a 5-point downward shift in the population mean IQ, from 100 to 95 points, would result in a 57% increase in the number of children who have an IQ <70 points and a corresponding decrease in the number of children who have an IQ >130 points (**Figure 2**) (47). Bellinger calculated the population-wide impact of environmental toxins and other medical problems on IQ deficits in a contemporary six-year birth cohort of US children (10). The impacts of low-level exposures to lead, mercury, and organophosphate pesticides on decrements in IQ scores in U.S. children were surprisingly large, even in comparison with clinical conditions, such as ADHD and preterm birth (10). See **Figure 3**.



Video 1

Subtle shifts in the intellectual abilities of individual children from widespread exposures to toxins can have a big impact on the number of children in a population who are intellectually challenged or gifted.

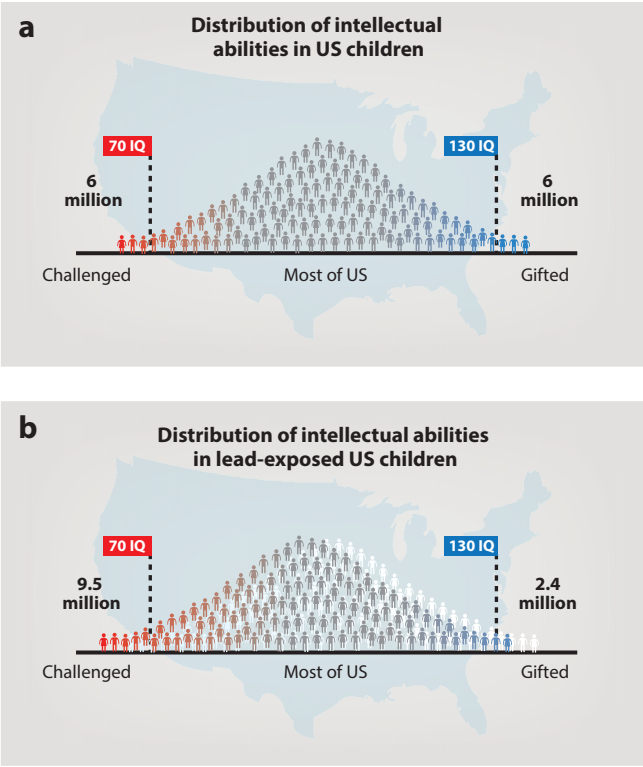


Figure 2

Little shifts matter. It is difficult to discern a 5-point IQ difference between two children, but a downward shift in the population mean IQ, from 100 to 95 points, results in a 57% increase in the number of children who have an IQ <70 points, from 6 million to 9.4 million, and a corresponding decrease in the number of children who have an IQ >130 points (panels *a* and *b*). Adapted from Reference 47.

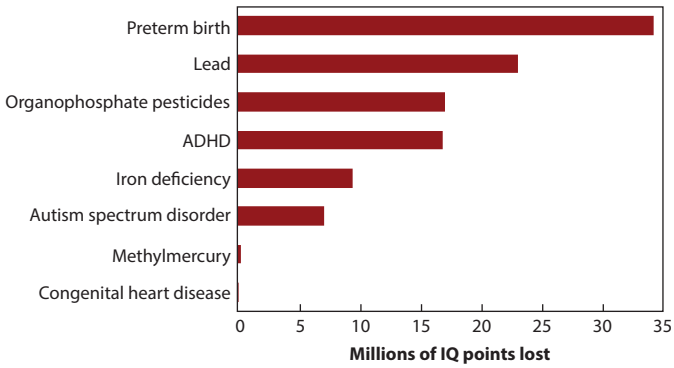


Figure 3

Estimated reduction in IQ points in a six-year cohort of US children for various risk factors. Adapted from Reference 10. Abbreviation: ADHD, attention deficit hyperactivity disorder.

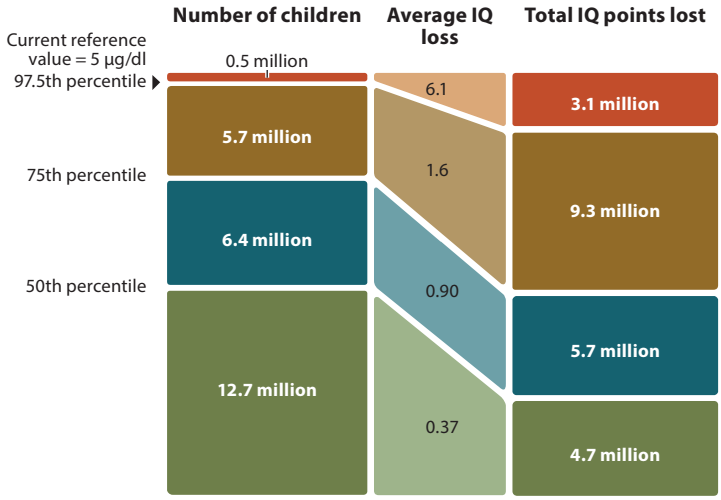


Figure 4

Prevention paradox. The majority of IQ points lost to lead exposure occur in children who have low-to-moderate exposure to lead. Adapted from Reference 10.

THE PREVENTION PARADOX

The cumulative impact of exposures to various subtle environmental influences or toxins that only modestly impact intellectual abilities can be substantial (130). Although the evidence for many of the emerging toxins—such as PBDEs, manganese, DDT, arsenic, and airborne pollutants—is not as conclusive as that for lead, PCBs, or mercury, the emerging evidence clearly shows that the cumulative impact of environmental toxins on children's intellectual abilities has been underestimated (79).

Once researchers identify a toxin, the typical strategy is to target high-risk children. This strategy, which is based on the medical model, is efficient; children who are at high risk typically exhibit more severe or overt effects than do less-exposed children. Still, unless a threshold exists, the high-risk approach will inevitably fail to protect the majority of individuals who experience deficits. The failure of the high-risk approach to protect most cases—cases that occur in low-to-moderate risk groups—is called the prevention paradox (105).

Lead-associated IQ deficits offer a compelling example of the prevention paradox. The CDC recently concluded that there is no safe level of lead exposure in children but, owing to inadequate resources, recommended using a reference value of 5 μg/dL (50 ppb) (representing the 97.5th percentile for blood lead levels in US children) for case management (22). Targeting children who have a blood lead concentration >5 μg/dL (50 ppb) is efficient; the average lead-associated IQ loss for these children is considerably larger (or greater) (6.1 IQ points) than is the loss in those who have lower blood lead concentrations (**Figure 4**). Yet children who have a blood lead concentration >5 μg/dL account for fewer than 3 million (~18%) of the 23 million IQ points lost due to lead toxicity. Thus, by focusing on high-risk children, we will ultimately fail to protect the majority of children who are adversely affected by lead and other toxins.

Toxins can have a lifelong impact on brain function (83, 132, 135). Children who have higher blood lead concentrations may never meet the same peak cognitive ability in adulthood as that in less exposed children (**Figure 5**). At the other end of the age spectrum, cognitive decline is accelerated in adults who have higher bone lead concentrations (111, 131). If this trajectory

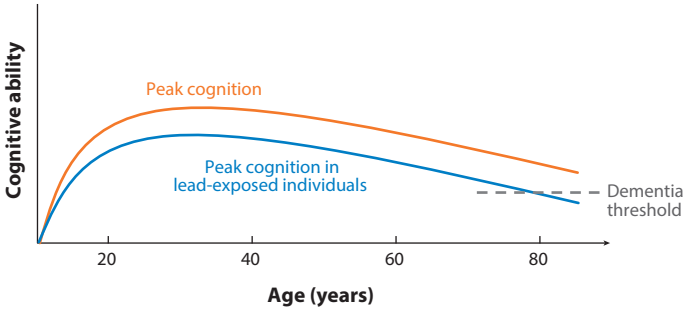


Figure 5

Lifetime impact of low-level lead exposure on cognitive function.

continues, lead-exposed adults would reach the diagnostic threshold for dementia sooner than those who have lower bone lead concentrations. Indeed, some evidence has shown that early-life lead exposure is a risk factor for the development of late-onset Alzheimer's disease (6, 7, 136). With the exception of those for lead, few birth cohorts have been studied into adulthood; however, it would be surprising if the effects of other toxins observed in school-aged children do not persist into adulthood.

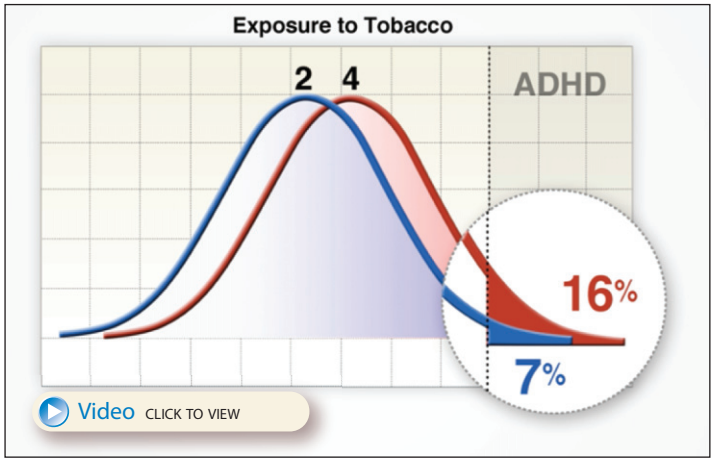
ADHD

ADHD, the most common brain disorder of childhood, affects about 1 in 10 children in the United States; boys are 2.5 times more likely to meet criteria for ADHD than are girls (44). ADHD is not a specific disorder, but a medley of maladaptive deficits and behaviors, the most prominent of which are hyperactivity, impulsivity, and inattention (3, 65). Children who have ADHD often have other comorbid conditions; about one in two children who have ADHD also have a learning disorder (3).

Exposures to some environmental toxins—especially lead and tobacco—are recognized risk factors for ADHD (39, 43, 59, 64, 65, 80, 86). Using brain imaging, researchers have shown that childhood lead exposure as well as prenatal exposures to tobacco and organophosphate pesticides are associated with alterations in brain structure that are consistent with ADHD (18, 23, 72, 98, 117). The data are sparser for other toxins, but a flurry of new studies suggests that organophosphate pesticides, mercury, PBDEs, PCBs, perfluorinated compounds (PFCs), phthalates, bisphenol A, and airborne pollutants may be risk factors for ADHD or ADHD-related behaviors (11, 13, 16, 36, 54, 62, 85, 92, 93, 97, 107, 108). Many toxins, such as lead, PCBs, bisphenol A, manganese, and mercury, disrupt dopamine or dopaminergic neurons in the prefrontal cortex (1, 57, 110). This disruption is consistent with the hypothesis that ADHD is due to a deficiency or imbalance of dopamine in the prefrontal cortex (117).

It should not be surprising that various toxins can increase the risk for ADHD; ADHD is a syndrome of behaviors and deficits that exist on a continuum (65). Environmental lead exposure increases certain ADHD-related behaviors, such as impulsivity, attention, and aggression (29, 39, 73, 82, 122). Bisphenol A exposure has been associated with anxiety and hyperactivity (16, 89). Exposure to various toxins—each of which may increase the frequency of one or more ADHD-related behaviors or deficits by a modest amount—can result in a substantial increase in the overall prevalence of ADHD.

Using National Health and Nutrition Examination Survey (NHANES) data, we found that, among 8- to 15-year-old US children, those who had blood lead concentrations in the lowest tertile (<0.7 μg/dL) (<7 ppb) exhibited, on average, only one ADHD symptom, whereas children in the highest tertile of blood lead levels (>1.3 μg/dL) (>13 ppb) exhibited three symptoms (43). This



Video 2

Using a nationally representative study of US children, this video illustrates how subtle shifts in ADHD symptoms from childhood lead exposure and prenatal tobacco exposure result in a large increase in the percent of U.S. children who have ADHD.

subtle shift in the population distribution of ADHD symptoms led to a twofold increase in the percent of children who met criteria for ADHD, from 5% to 13% (**Video 2**). Similarly, children who were unexposed to tobacco during fetal development exhibited two ADHD symptoms, whereas tobacco-exposed children exhibited four symptoms. The subtle shift in symptoms led to a twofold increase in the percent of children who met criteria for ADHD, from 7% to 16%. Children who were exposed to high childhood blood lead concentrations and prenatal tobacco smoke were eight times more likely to meet criteria for ADHD than were children who had neither exposure. We estimated that about one in three cases of ADHD in US children—equivalent to about 1 million children—are attributable to childhood lead exposure and/or prenatal tobacco exposure.

AUTISM

Autism, or ASD, is a brain-based disorder characterized by impaired social communication and repetitive or stereotypic behaviors with onset before three years of age (3). The prevalence of autism in the United States is estimated to be ~1 in 68 children, but it is higher in males (21). Until recently, the search for potential environmental factors in the development of autism was overshadowed by the search for genetic factors. It is now increasingly recognized, if not fully acknowledged, that environmental factors play an equally important role in the development of autism (50, 118).

A few environmental risk factors for autism have been tentatively identified, including folate status (45, 95, 116), environmental chemicals or drugs (17, 31, 63), and airborne pollutants (8, 60, 102, 126, 133). Folate status appears to be a key risk factor for autism and ASD. Folate supplementation has been associated with a lower risk for the development of autism (116). Folate receptor blocking antibody is significantly higher among parents of autistic children than among parents of nonautistic children (45, 95). Valproic acid, an inhibitor of folate, is also a risk factor for the development of autism (31). It is not clear whether folate is a modifier or an independent risk factor for autism, but its role in the development of autism deserves closer scrutiny.

Five studies have examined the association of airborne pollutants, including metals, diesel, and particles <2.5 microns in diameter ($PM_{2.5}$), with autism or ASD (8, 60, 102, 126, 133). Although all

these studies found significant associations with one or more components of airborne pollutants, they did not consistently identify the same pollutant. Perhaps this result is to be expected; autism, like ADHD, is a medley of maladaptive behaviors and deficits, each of which might be affected by one or more toxins. Still, replication is essential for determining whether specific components of air pollution are risk factors for autism or ASD.

These studies only cast a dim light on various potential risk factors for the development of ASD, but they are beginning to identify clues to the autism epidemic. Studies that can measure exposures that occur during critical developmental windows, especially during early pregnancy, are critical for exploring risk factors for autism and ASD.

ANTISOCIAL BEHAVIORS

Can ubiquitous exposure to a toxin result in widespread social dysfunction? (73). Lead exposure is a potent predictor of behaviors linked with delinquency and criminality, such as impulsivity, hyperactivity, and aggressive behaviors (29, 41, 73, 122). In experiments with rodents and nonhuman primates, early lead exposure caused abnormal mother–infant interactions, higher rates of antagonistic interactions, and reduced social play (32, 71). In a meta-analysis of 16 studies, Marcus concluded that lead exposure, measured using blood lead or bone lead concentrations, was a risk factor for conduct disorder (73). In a nationally representative sample, Braun and colleagues found that 8- to 15-year-old children who had blood lead concentrations in the highest quintile (>1.5 μg/dL) were 8 times more likely to meet diagnostic criteria for conduct disorder than were those in the lowest quintile (15). Only two prospective birth cohort studies have examined the impact of childhood lead exposure on antisocial behaviors; both reported that lead was a risk factor for higher rates of criminal arrest in young adults (40, 135). In two separate analyses, Nevin (84) and Reyes (99) both concluded that the downward trend in crime, especially violent crime, was due largely to the decline in blood lead concentrations. Collectively, these studies provide compelling evidence that childhood lead exposure played a central role in the epidemic of violent crime over the past century and illustrates how widespread exposure to a prevalent toxin can alter the social landscape.

THE COST OF TOXINS

The cost of toxins that impact brain development is substantial. Trasande & Liu estimated that the cost of exposures to lead, mercury, and other toxins that affect intellectual abilities exceeds $70 billion annually in the United States (124). This figure is obviously an underestimate because it does not account for the effects of other suspected toxins, such as organophosphate pesticides, PBDEs, or air pollutants. Moreover, it does not account for the cost of research to explicate the toxicity of environmental chemicals or to clean up contaminated communities. Finally, and perhaps most important, it does not account for the cost of human suffering: the impact these toxins have on children's ability to function in their daily lives and the accommodations that parents and society must make for them.

LIMITATIONS AND CONFOUNDING

Observational studies that are designed to investigate the impacts of toxins on the developing brain are limited in their ability to infer causal associations (69). First, because the exposures are not randomly assigned, there will always be a potential for unmeasured confounding. Second, some studies failed to collect or adjust for potentially important confounders, such as nurturing behaviors in the home environment (e.g., the HOME Inventory) or breastfeeding (33). Other studies did not account for exposure to secondhand smoke or other environmental toxicants or for

iron status. Most studies did not account for parental psychopathology. Indeed, there is an endless litany of potential confounders to consider, a limitation of observational studies that is often used to thwart efforts to regulate environmental toxins despite compelling evidence from both human and laboratory studies (69).

We usually worry about unmeasured confounders that may erroneously inflate the estimated association of a toxin with a deficit or disorder, but confounders can also diminish a true association (9, 30, 65). Low-level mercury exposure in fish-eating populations has been linked with deficits in cognition in some studies but not others (49, 61, 78). Ultimately, some of the conflicting results were shown to result from confounding; the beneficial effects of fish intake repressed the toxic effects of mercury exposure (30, 88). This result raises important questions about how the effects of other suspected toxicants, such as organophosphate pesticides, which are higher in pregnant women and children who ingest large quantities of fruits and vegetables, may be difficult to disentangle from beneficial nutrients.

Despite these limitations, the pattern of toxicity that has emerged over the past century is clear; low-level exposure to insidious toxins during critical windows of brain development can have lifelong impacts on an individual's ability to function and on social dysfunction. The impacts are more profound at the population level. It is not clear why more has not been done to protect children from toxins that impact brain development, but clearly we urgently need to expand our focus on prevention.

PREVENTION

The optimal strategy to prevent the development of brain-based disorders is to identify and restrict or ban the use of potential toxins before they are marketed or discharged into the environment. Unfortunately, industries are allowed to market a product until it is repeatedly shown to be toxic in both human and laboratory studies. Once a toxin is disseminated in the environment, it requires a Herculean effort to disentangle its effects from other prevalent and modifiable risk factors for brain-based disorders. There are likely to be many risk factors because brain-based disorders represent an array of behaviors or deficits that exist on a continuum. This fact should be obvious, but it is surprising how frequently we pit one risk factor against another in our ongoing search for the ever-elusive cause of disabilities in children.

Intellectual deficits or brain-based disorders in children are still often thought to result predominately from poor parenting or genes; it is not unusual, for example, to read that genes account for 70% of autism or ADHD (118, 121). But it is now widely accepted that most complex diseases and disorders, including ADHD and autism, are due to the interplay of genes and environment. Thus both genetic and environmental risk factors are necessary for most cases of brain-based disorders to develop.

Despite considerable evidence implicating toxins in the development of intellectual deficits and mental disorders in children, our efforts to control or eliminate exposure to toxins have been inadequate. Most of the contaminants and toxins readily found in human tissues—such as lead, flame retardants, bisphenol A, and phthalates—did not undergo premarket testing (70). Instead, we haphazardly conduct studies after pregnant women and children are routinely exposed to toxins or suspected toxins to untangle the toxic effects of a particular contaminant from a multitude of other risk factors.

Our initial efforts to prevent exposures to toxins typically focus on education. We pass out pamphlets, advise parents to wash their child's hands and to avoid fish that is heavily contaminated with mercury or PCBs, and admonish them not to smoke tobacco products around children or pregnant women. Education offers some small, short-term benefits, but we will inevitably fail

to protect children until we reduce or eliminate the source of toxins. The dramatic reduction in childhood lead poisoning had little or nothing to do with passing out mop buckets or admonishing mothers to wash their child's hands; blood lead concentrations plummeted because lead was phased out of gasoline and banned for use in paints, solder, and other consumer products (67). There is some potential benefit when companies, such as Walmart, phase out products that contain phthalates or other suspected toxins owing to consumer pressure, but these voluntary actions will inevitably fail to protect children because of the large number of chemicals in the marketplace and the tendency to replace confirmed or suspected toxins with other, largely untested chemicals. The only comprehensive preventive strategy is to revise the regulatory framework for environmental chemicals and industrial pollutants and ensure they are not toxic before they are marketed or discharged into the environment (2, 70).

How much evidence is necessary to ban, control, or restrict the use of a suspected or confirmed toxin? Using the principle, "first, do no harm," we have appropriately required evidence from randomized controlled trials before health care providers prescribe a drug. In contrast, we have placed the burden on parents, scientists, pediatricians, and policy makers to prove that suspected toxins are hazardous after they have been used in consumer products or widely disseminated in the environment. There is now sufficient evidence to shift the burden of proof and require industry to prove that the chemicals used in consumer products and the pollutants emitted from their plants are not toxic.

Several steps are necessary to protect children from toxins that impact the developing brain. First, we need to revise the regulatory framework to require industries to provide evidence that chemicals used in consumer products are not toxic before products are marketed (2, 70). Second, we need to enhance the US Environmental Protection Agency's ability to set standards to evaluate the impact of environmental chemicals, industrial pollutants, and airborne toxics on the developing brain. Third, we need to devise and fund a national surveillance system to quantify the prevalence of and trends in learning problems and mental disorders. One way to enhance surveillance is to augment the NHANES (76) and the National Health Interview Survey (14) with validated instruments conducted at regular intervals to measure the prevalence of learning disabilities and mental disorders. Fourth, we need to establish independent, scientific panels to systematically evaluate the evidence linking toxins or suspected toxins with brain-based disorders and intellectual deficits. These panels, like those established for suspected carcinogens, would provide a scientific forum to draw conclusions about the evidence implicating particular toxins or types of toxins that affect brain development. The panels should also be mandated to recommend standards that provide a margin of safety. Finally, we need to convene a national task force to develop a strategy to prevent the development of intellectual deficits and mental disorders in children that encompasses all aspects of brain development, including universal access to early childhood education and the elimination of exposures to toxins.

Over the past 50 years, it has become clear that low-level exposures to environmental toxins can result in substantial disease and disability. Emerging evidence indicates that other ubiquitous chemicals are toxic. We can no longer deny the substantial if insidious impact that environmental toxins have on the developing brain. It is time to develop a comprehensive strategy to protect children from the impact of environmental toxins on the developing brain.

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The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. Dr. Lanphear has served as an expert witness in California for the plaintiffs in a public nuisance case of childhood lead poisoning, a Proposition

65 case on behalf of the California Attorney General's Office, and a Canadian tribunal on trade dispute about using lead-free galvanized wire in stucco lathing, but he received no personal compensation for these services. Dr. Lanphear has served as a paid consultant on a US Environmental Protection Agency research study related to childhood lead poisoning and the California Department of Toxic Substance Control. Dr. Lanphear has received federal research awards from the National Institute of Environmental Health, the US Environmental Protection Agency, the Centers for Disease Control, and the US Department of Housing and Urban Development. He is also the recipient of federal research awards from the Canada Institutes for Health Research and Health Canada.

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