

New Thinking on Neurodevelopment

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The notion that some substances in the environment can damage the nervous system has an ancient history. The neurotoxicity of lead was recognized more than 2,000 years ago by the Greek physician Dioscorides, who wrote, "Lead makes the mind give way." In the intervening millennia many other substances have been added to the list of known or suspected neurotoxicants. Despite this accumulation of knowledge, there is still much that isn't understood about how neurotoxicants affect the developing brain, especially the effects of low-dose exposures. Today researchers are taking a hard look at low-dose exposures *in utero* and during childhood to unravel some of the mysteries of impaired neurodevelopment.

About 17% of school-age children in the United States suffer from a disability that affects their behavior, memory, or ability to learn, according to a study published in the March 1994 issue of *Pediatrics* by a team from the Centers for Disease Control and Prevention (CDC). The list of maladies includes attention deficit/hyperactivity disorder (ADHD), autistic spectrum disorders, epilepsy, Tourette syndrome, and less specific conditions such as mental retardation and cerebral palsy. All are believed to be the outcome of some abnormal process that unfolded as the brain was developing *in utero* or in the young child.

These disorders have an enormous impact on families and society. According to the 1996 book *Learning Disabilities: Lifelong Issues*, children with these disorders have higher rates of mental illness and suicide, and are more likely to engage in substance abuse and to commit crimes as adults. The overall economic cost of neurodevelopmental disorders in the United States is estimated to be \$81.5-167 billion per year, according to a report published in the **December 2001 issue of *EHP Supplements***.

Potentially even more disturbing is that a number of epidemiologic studies suggest that the incidence of certain disorders is on the rise. In the United States, the diagnosis of autistic spectrum disorders increased from 4-5 per 10,000 children in the 1980s to 30-60 per 10,000 children in the 1990s, according to a report in the August 2003 *Journal of Autism and Developmental Disorders*. Similarly, notes a report in the February 2002 issue of *CNS Drugs*, the diagnosis of ADHD grew 250% between 1990 and 1998. The number of children in special education programs classified with learning disabilities increased 191% between 1977 and 1994, according to an article in *Advances in Learning and Behavioral Disabilities, Volume 12*, published in 1998.

So what is going on? The short answer is that no one really knows. There's not even consensus on what the soaring rates actually mean. Heightened public awareness could account for the surge in the numbers, or it may be that physicians are getting better at diagnosing the conditions. Some autism researchers believe the rise in that condition's prevalence simply reflects changes in diagnostic criteria over the last 25 years. On the other hand, some scientists believe that the rates of neurodevelopmental disease are truly increasing, and that the growing burden of chemicals in the environment may play a role.

With that in mind, investigators are considering the effects of gene-environment interactions. A child with a mild genetic tendency toward a neurodevelopmental disorder might develop without clinically measurable abnormalities in the absence of environmental "hits." However, children in industrialized nations develop and grow up in a veritable sea of xenobiotic chemicals, says Isaac Pessah, director of the University of California, Davis, Center for Children's Environmental Health and

Disease Prevention. “Fortunately,” he says, “most of us have a host of defense mechanisms that protect us from adverse outcomes. However, genetic polymorphisms, complex epistasis, and cytogenetic abnormalities could weaken these defenses and amplify chemical damage, initiating a freefall into a clinical syndrome.”

Pessah cites the example of autism. He says susceptibility for autism is likely conferred by several defective genes, no one of which can account for all the core symptoms of social disinterest, repetitive and overly focused behaviors, and problems in communication. Could multiple genetic liabilities and exposure to a chemically complex environment act in concert to increase the incidence and severity of the condition?

Despite the uncertainties, many scientists believe it would be wise to err on the side of caution when it comes to a research agenda. As Martha Herbert, a pediatric neurologist at Harvard Medical School, puts it, “Even though we may have neither consensus nor certainty about an autism epidemic, there are enough studies coming in with higher numbers that we should take it seriously. Environmental hypotheses ought to be central to research now. The physiological systems that have been harmed by environmental factors may also point to treatment targets, and this might be a great way to help the children.”

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