NIEHS Investigates Links between Children, the Environment, and Neurotoxicity

Autism, attention deficit/hyperactivity disorder (ADHD), and other neurodevelopmental, learning, and behavioral disorders may by some estimates affect as many as 1 in 6 U.S. children—or some 12 million children—according to a U.S. Census Bureau report published in the journal *Pediatrics* in 1993. The consequences of these disorders can be tragic, their familial, societal, and economic costs immense, and the resulting disabilities lifelong. While exposure to certain environmental chemicals is recognized or suspected of causing neurodevelopmental deficits, the origins of most of these disorders are still unknown. Today scientists are focused on investigating the possibility that at least some of the brain disorders that affect many children are produced when environmental triggers interact with genes in susceptible individuals.

Kenneth Olden, director of the NIEHS, was a keynote speaker at the 2001 annual conference of the Learning Disabilities Association of America (LDA), held 7–9 February 2001 in New York City. The LDA is a volunteer, parent-led organization dedicated to pursuing advocacy initiatives that focus on preventing learning disabilities and supporting education and research on these conditions. In his address, Olden referred to a quote by Judith Stern of the University of California at Davis—"genetics loads the gun, but environment pulls the trigger"—that eloquently illustrates the current scientific thinking that genetic susceptibility and exposure to environmental toxicants interact in the individual to produce disease. Said Olden, "Current gaps in our knowledge keep us from preventing the loaded gun from going off again and again." Understanding these gene–environment interactions may be the key to finding the cause of many illnesses with no known etiology, including some neurodevelopmental disabilities.

Many observers believe that reducing the burden that environmental threats cause in children's health will take a major concerted effort involving strongly committed collaborations, perhaps between groups such as the LDA and the NIEHS. In such a scenario, advocacy leaders such as the LDA could inform the research agenda by bringing forward the concerns and priorities of the children and parents who are directly affected by neurodevelopmental disorders. In turn, the NIEHS could support and provide the sound scientific research data that make the advocacy efforts more compelling and effective. As LDA member Audrey McMahon points out, "This marriage between brain sciences research with advances in environmental neurotoxicology and community participation is the only model that can guide us to a new appreciation of needs and solutions."

Presentations at the LDA annual conference illustrated the need for increased efforts in research on the effects of environmental toxicants on brain development and behavior. Annette Kirshner, a program administrator in the Organs and Systems Toxicology Branch of the NIEHS Division of Extramural Research and Training, pointed out that the NIEHS dedicated over 10% of its 2000 extramural research budget to supporting research in children's environmental health.

According to Kirshner, one series of NIEHS-supported studies showed that exposure to an environmental toxicant early in development may result in behavioral and cognitive effects later in life. Kirshner noted that Herbert Needleman and colleagues at Pennsylvania's University of Pittsburgh School of Medicine found that lead exposure early in life is associated with increased risk for antisocial and delinquent behavior, high school failure, and reading deficits in young adults. In a paper published in the 7 February 1996 issue of the *Journal of the American Medical Association*, Needleman and colleagues estimated that 15% of delinquency is attributable to lead exposure. Some scientists dispute this conclusion, because lead exposure is also correlated with other factors, such as poverty, that are associated with delinquency. More research is needed before it is known whether lead and other environmental toxicants are involved in producing changes in children's behavior, temperament, and ability to learn.

ADHD: On the Rise?

ADHD is a developmental disability characterized by inattention, impulsivity, and hyperactivity. It is one of the most commonly diagnosed behavioral conditions of childhood. The NIH consensus statement on the diagnosis and treatment of ADHD, published in 1998, estimated that at least 3–5% of U.S. children have the disorder. Moreover, the incidence of ADHD may be on the rise.

A survey of office-based physicians published in the December 1999 issue of the *Archives of Pediatrics and Adolescent Medicine* by researcher Julie Magno Zito and colleagues at the University of Maryland in Baltimore found that all ADHD-related visits between 1989 and 1996 increased by 90% in children, from 1.9% of total physician visits to 3.6%. The use of stimulants such as Ritalin to treat ADHD in children rose 14% during this same period, according to the same study. Such increases in office visits and stimulant treatment may be explained by several factors, including a greater awareness of the disorder, a greater acceptance of medication to treat behavioral disorders, and a broadening of the definition of ADHD. But it is also possible that such increases may be explained by growth in the actual incidence rate.

The causes of ADHD are largely unknown. Some studies have shown that genetic factors may play a role, while others suggest that substances in the environment may have an effect. A paper by Deborah C. Rice of the U.S. Environmental Protection Agency, published in the June 2000 issue of *EHP Supplements*, suggests that lead and polychlorinated biphenyls might play a role. To investigate further, the NIEHS is supporting a large, comprehensive study of children with ADHD, led by Andrew Rowland, a research fellow in the Epidemiology Branch of the NIEHS Division of Intramural Research.

The study uses ADHD diagnostic and epidemiologic criteria to screen all children attending elementary schools in Johnston County, North Carolina. About 83% of all parents of elementary schoolchildren agreed to their child's teacher completing a form about their child's attention and behavior. The researchers then interviewed mothers of children who appeared to have symptoms of ADHD along with a randomly selected group of controls. Children who met the diagnostic criteria for ADHD by showing symptoms and impairment at school and home were considered cases. In all, about 550 cases and 550 controls were interviewed, making this one of the largest population-based studies of ADHD to date.

Schools are required to conduct learning disability evaluations and design classroom accommodations for children who are diagnosed with ADHD. At the time the study was first proposed, Johnston County school officials were worried that they would not have the financial or staff resources to do the additional testing or required classroom accommodations if the study uncovered

Reuther/EHP

many new cases of ADHD. But the team was able to devise a way to measure ADHD incidence in a way that was scientifically sound while addressing the school system's concerns.

The researchers worked with the schools to form a coalition of local organizations including the county health and mental health departments, the state mental health department, the county office of juvenile justice, the county department of social services, and the University of North Carolina at Chapel Hill Department of Psychiatry to work with children identified by the study. A grant by the Kate B. Reynolds Charitable Trust allowed the coalition to hire a health educator to show parents, teachers, and medical professionals how to work more effectively with children with ADHD and to help coordinate a mobile clinic of university doctors who were available to treat and refer children identified by the study. The study involved collaboration between the many interested groups. As Rowland describes it, "We were only able to do the study by working closely with the schools and the community. Without the close cooperation of the schools and the community partners, we would not have been able to do the study, and the study would have failed scientifically." A preliminary description of the study was published in the September–October 2000 issue of *Neurotoxicology and Teratology*.

An important preliminary finding of the Johnston County study is that many children being treated with stimulant medications continue to meet the full diagnostic criteria for ADHD despite being treated, says Rowland. This may indicate deficiencies in clinical followup and a lack of coordination between health care providers, parents, and schools. The second phase of the study aims to assess whether preterm delivery is related to the risk of ADHD and whether *in utero* exposures to cigarette smoke, alcohol, and other environmental agents are risk factors for ADHD.

Seeking an Understanding of Autism

The NIEHS is also interested in exploring the potential role of environmental factors in autism. Autism refers to a group of developmental disorders (also referred to as autism spectrum disorders) that includes autistic disorder, atypical autism, and Asperger syndrome. Children with these disorders display deficits in social interaction and communication and the presence of repetitive and/or restrictive behaviors or interests. It is not known how many children in the United States have autistic disorders, and estimates vary widely. Recent research from the Centers for Disease Control and Prevention (CDC) indicates that as many as 2 out of every 1,000 children may be affected by some form of these disorders; a different analysis of data from the 1992–1994 National Health Interview Surveys, part of a CDC study to find the prevalence of many different diseases, showed that 4 out of every 10,000 U.S. children were reported by their parents to have been diagnosed with autism. Whatever the numbers, they do not adequately convey the emotional, financial, and societal toll that autism can take on families and communities.

The NIEHS is supporting several research efforts to investigate the role that environmental factors may have in causing autism in children. Cindy Lawler is the extramural program staff representative to the NIH Autism Coordinating Committee, a group of NIH directors and institute representatives charged with enhancing the quality, pace, and coordination of efforts across the NIH to prevent and find a cure for autism. Eventually this committee will be replaced with an expanded committee that includes all the relevant NIH institutes, other agencies such as the CDC, and parent representatives.

The NIEHS has welcomed input from autism advocacy and parent organizations. Parent representatives meet once per year with the committee to discuss upcoming NIH autism initiatives, to

highlight important findings in autism, and to seek parents' input into the research agenda. This yearly conference is sponsored by all member institutes on the committee, including the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, and the National Institute of Child Health and Human Development. In the summer of 2001 the NIEHS and the National Institute of Child Health and Human Development will take the lead as primary sponsors of a meeting focusing on cellular and molecular mechanisms in autism and related neurodevelopmental disorders.

A meeting held on 23 October 2000 at the NIEHS illustrates how exchanges between parents/advocates and researchers can result in increased understanding of the needs of the people affected by autism and fruitful collaboration on shaping research priorities. Representatives from the NIEHS and several advocacy groups met to discuss ways to increase research efforts, improve clinical testing, and reduce or eliminate the environmental toxic exposures that may cause or aggravate neurodevelopmental conditions. Various research avenues were discussed, including the possibility that ethylmercury, a component of thimerosal, which is used in childhood vaccines as a preservative, may be a trigger of autism in susceptible individuals. Says Sallie Bernard, executive director of Sensible Action For Ending Mercury-Induced Neurological Disorders, a parent group advocating for the elimination of mercury from vaccines and other products, "The appearance of signs of autism occurs in a significant number of children who develop and behave normally until being immunized." The NIEHS is supporting studies to investigate the pharmacokinetics of ethylmercury in vaccines. (Ethylmercury is already being phased out of childhood vaccines in response to concerns about its potential toxicity, particularly whether it can enter the brain to the same extent as the related compound methylmercury.)

To further expand its research portfolio on children's neurodevelopmental disorders, the NIEHS is jointly sponsoring a new initiative in autism research. Along with other relevant institutes of the NIH, the NIEHS has issued a program announcement titled "Research on Autism and Autism Spectrum Disorders" (PA-01-051). In addition, the existing NIEHS and Environmental Protection Agency–sponsored network of Centers for Children's Environmental Health and Disease Prevention Research will be expanded from the 8 currently funded to 10 or 11. These new centers will focus on

NTP Center Reports on Phthalate Concerns

An expert panel convened by the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) has announced that after intensive evaluation of seven phthalates, only one presents a serious concern to human reproduction or development. Di(2-ethylhexyl) phthalate, or DEHP, is considered of serious concern for the possibility of adverse effects on the developing reproductive tract of male infants exposed to high concentrations of the phthalate through medical procedures using phthalate-containing equipment such as intravenous bags and tubing.

The center is currently preparing the *NTP Center Report on Phthalates*, due for release late this summer. Michael Shelby, director of the CERHR, says, "The report will provide an independent, scientifically rigorous document for use by all stakeholders in any further discussions that might ensue on the reproductive effects of these seven phthalates."

Created in 1998 by the NTP and the NIEHS to assess the human reproductive health risks associated with exposures to environmental chemicals, the CERHR announced in April 1999 that it was turning its attention to the risks posed by seven phthalates, which are used as plasticizers in a spectrum of polyvinyl chloride–based products ranging from flexible tubing to plastic toys. The phthalates selected for evaluation included DEHP, butyl benzyl phthalate (BBP), di-*n*-butyl phthalate (DBP), di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP), di-*n*-hexyl phthalate (DnHP), and di-*n*-octyl phthalate (DnOP). The chemicals were selected based on their high production volume, the number of people potentially exposed to them, their use in products especially intended for children (such as toys), and evidence of reproductive or developmental toxicity. To evaluate the seven phthalates, the center brought together a panel of 16 experts in toxicology, epidemiology, and other relevant fields from government, research, and academic institutions from across the United States.

Over a period of 15 months, the panel evaluated the published data for each phthalate to determine whether or not it is likely to present a risk to human reproduction or development. The panel considered the amount and quality of data available in two primary areas: human exposures to the phthalate in question and experimental evidence for its reproductive and developmental toxicity.

The panel assigned minimal concern to DINP for adverse developmental outcomes in children exposed *in utero* and for adverse effects on the reproductive system of exposed adults. There was, however, low concern for potential developmental and reproductive health effects in children who might be exposed through mouthing toys or other DINP-containing objects. For BBP, DnOP, DBP, and DIDP, there was minimal or

addressing developmental disorders including those of neurologic origin.

Building a Data Framework

One reason why it is not known whether ADHD, autism, and other neurodevelopmental disabilities are related to environmental factors is because so little is known about the toxicity of many chemicals present in the environment. Evidence of the need for testing chemical effects on brain development was presented in the report *Polluting Our Future: Chemical Pollution in the U.S. That Affects Child Development and Learning*, published jointly by the LDA, the National Environmental Trust, and Physicians for Social Responsibility. The report presents data from federal sources such as the Toxics Release Inventory and other national databases available through the Emergency Planning and Community Right-to-Know Act of 1986.

The data show that 1.2 billion pounds of chemicals were reported by industries to be released into air and water in 1998. Of these, an estimated 53% are known or suspected agents in affecting neurologic or developmental function. These figures may actually be much higher because, says the report, it has been estimated that only 5% of chemicals released into the environment are reported to the national databases. Because most of these chemicals are not tested for their effect on the developing brain, it is possible that many neurodevelopmental and learning disabilities are due to children's exposure to these potential neurotoxicants. The LDA is calling for regulatory agencies to support testing of the effects of food additives, pesticides, drugs, and other industrial chemicals on the developing brain. In the meantime, as Olden describes it, "We live in a state of toxic ignorance."

The NIEHS is positioned to play a central role in investigating the relationship between learning disabilities of unknown cause and environmental exposures during brain development. One promising area of research is new technology using DNA microarrays, which offers the opportunity to examine the interaction between toxicants and genetic susceptibility at the molecular level. This technology will yield a database of toxicity fingerprints of known toxicants against which chemicals of unknown toxicity can be compared. This line of research has been established at the NIEHS as the National Center for Toxicogenomics and is described on their Web site at http://www.niehs.nih.gov/nct/home.htm. The eventual compilation of such a database will be welcome news for both the advocacy and research communities who are concerned with children's environmental health. **–Luz Claudio**

negligible concern for adverse effects on the reproductive system of exposed adults or for potential developmental and reproductive health effects of exposed children. For one chemical, DnHP, there were insufficient data for the panel to reach any conclusions. The panel had only minimal concern that current estimated exposures to DEHP would adversely affect the reproductive system of adults.

Following initial publication of the panel's findings in October 2000, the NTP and the CERHR have gathered public comments that will be incorporated into the *NTP Center Report on Phthalates*, along with newly available data published since the panel's last meeting. The final report will also include critical data needs and a list of planned or ongoing studies that address those needs.

Two studies released since the panel completed its reports have provided interesting postscripts to their findings. First is a report by scientists from the NTP and the Centers for Disease Control and Prevention, published in the October 2000 issue of *EHP*, which found that the highest DBP metabolite concentrations in a large study sampling were found in women of reproductive age. (This study also provides the first measure of phthalate metabolites in the body; other studies, including those reviewed by the panel, were calculations of doses based on exposure data.) Second is an article published in the December 2000 issue of the *Journal of Pediatric Surgery* by scientists at the University of Heidelberg medical complex in Mannheim, Germany, which firmly bolsters the panel's concern that premature infants are exposed to high doses of DEHP through the use of medical equipment made of phthalate-containing polyvinyl chloride plastic. The German authors are now investigating whether the high DEHP doses they observed are related to the hepatobiliary dysfunction common with tube-feeding.

The final report will be available to federal and state regulatory and health agencies, nongovernmental organizations, industry groups, and the public, and will be posted on the CERHR Web site at http://cerhr.niehs.nih.gov/. **–Susan M. Booker**

Seven Phthalate Esters Tested and Their Uses

Chemical	Uses
di(2-ethylhexyl) phthalate (DEHP)	Building products, food packaging, children's products, medical equipment
butyl benzyl phthalate (BBP)	Vinyl tile, food conveyor belts, artificial leather, traffic cones
di-*n*-butyl phthalate (DBP)	Latex adhesives, cellulose plastics, dyes
di-isononyl phthalate (DINP)	Garden hoses, shoes/shoe soles, toys, construction materials
di-isodecyl phthalate (DIDP)	Automobile undercoating, wires and cables, shoes, carpet backing, pool liners
di-*n*-hexyl phthalate (DnHP)	Automobile parts, tool handles, dishwasher baskets, flooring, tarps, flea collars
di-*n*-octyl phthalate (DnOP)	Flooring and carpet tile, canvas tarps, notebook covers