New Centers to Focus on Autism and Other Developmental Disorders

Researchers have long suspected the involvement of complex genetic factors in children's developmental disabilities, but more and more parents and health professionals believe the exposure of fetuses and newborn infants to environmental toxicants such as metals and chemicals may play a role in susceptibility. No associations have been confirmed, however. To help fill that gap in understanding, the NIEHS and the U.S. Environmental Protection Agency (EPA) have created four new children's environmental health research centers in the past year.

"We want to see what . . . environmental substances might trigger developmental problems so that we can reduce the exposures and prevent the damage," says NIEHS director Kenneth Olden. Indeed, most potential developmental toxicants remain unexamined.

"These new centers—and the eight already in existence across the country—will continue to perform and apply research that can help shed light on the links between the environment and the health of our children," says EPA administrator Christie Whitman. "They can help us take children's health protection to a new level." The centers, which have already started their research projects, will each receive $1 million per year for five years, the same funding level of the existing centers, which opened in 1998.

"The creation of the centers is an incredibly important step forward in protecting children," asserts Daniel Swartz, executive director of the Children's Environmental Health Network. Swartz also lauded the multidisciplinary structure of the centers, which each have strong community participation and outreach components built into their research forums. "Involving the community will enable the centers to move quickly from research questions to policy making," he says.

Reining In the Soaring Rate of Autism

Two new centers at the University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical School in Piscataway and at the University of California at Davis will study environmental factors that may be related to autism. At its most severe, autism is a withdrawn state in which children do not interact with their surroundings and other people. Nationally, the prevalence of autism is soaring.

In some areas in New Jersey and California, 1 in every 150 children is diagnosed with mild to severe forms of the disorder. Though its frequency has not been studied on a large scale, autism may occur that frequently nationwide, some experts estimate. Meanwhile, a general lack of knowledge about the causes of autism has stymied policy and prevention efforts. The same holds true for other behavioral problems such as attention deficit/hyperactivity disorder (ADHD).

Researchers estimate that 2–10 yet-to-be-identified susceptibility genes are involved in autism. But because the disorder's frequency has been increasing, they suspect that exposure during pregnancy and infancy to mercury-containing compounds, halogenated aromatics, pesticides, pharmaceuticals such as the seizure medication valproic acid, and even vaccine additives may alter the degree to which genetic factors are expressed. "There's more to it than genes alone," says George Lambert, a pediatrician and toxicologist who heads the New Jersey center. "There's clearly a gene–environment interaction at play."

Three basic science projects at the New Jersey center are examining facets of brain development, beginning with nerve development and proceeding to behavior in the fully developed adult animal. The studies are looking at critical windows for brain development in the forebrain and hindbrain and will attempt to link exposures or disturbances at these times to later behavioral dysfunction. In the past five years, the importance of signaling activity from the immune system during critical periods of neurodevelopment and subsequent normal brain development has been established.

Two clinical projects interact with community groups representing children with autism and their families. These projects explore the link between environmental neurotoxicants and the clinical course of autism and growth of various brain regions, as well as a relationship between any possible gene–environment interactions and autism. Researchers will also look at variability in children's genetic susceptibility to environmental toxicants. Magnetic resonance imaging will be used to see if children with higher exposures to environmental toxicants have different patterns of brain growth and development. A third clinical project will assess exposures of children enrolled in the clinical studies, determine the need for interventions to reduce exposure to brain toxicants, and assess the impact of such interventions.

At the Davis center, researchers seek to understand how exposure to environmental chemicals may increase the risk and severity of autism, and to identify which combinations of chemical exposures confer the greatest threat. The center's team of eight principal investigators is probing common patterns of dysfunction in autism and mechanisms by which known nervous and immune system toxicants contribute to abnormal development of social behavior in children. Three interdisciplinary research projects are in the works, according to center director Isaac Pessah, a professor of molecular biosciences at the Davis School of Veterinary Medicine.

The first project will be the first comprehensive case–control epidemiologic study of environmental factors in the etiology of autism. Tissue samples and exhaustive information will be collected from about 2,000 children from geographically distinct areas of

The mind of a child. Four new federal research centers will focus on understanding the link between exposure to environmental agents and effects on childhood brain development.

PhotoDisc

California. Approximately one-third will have autism, one-third will have mental retardation, and one-third will be developing typically. The second project will use animal models to identify, also for the first time, how known nervous system toxicants of concern to children's health influence the development of social behavior and mediating brain regions such as the amygdala. The third project will integrate elements of projects one and two in order to examine molecular mechanisms underlying brain dysfunction associated with human autism in animal models of autism.

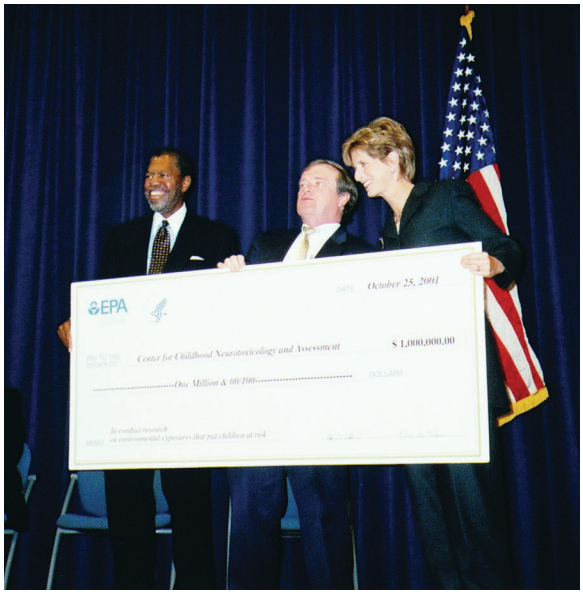
All three projects will be run out of the Davis Medical Investigation of Neurodevelopmental Disorders Institute, which has a strong relationship with the autism advocacy community. The center has capitalized on this relationship by partnering with parents of children with autism in the design of studies at the center and plans to directly share results with the community.

Analyzing the Link between Lead, IQ, and Antisocial Behavior

The third center, headed by pediatrics professor Bruce Lanphear at Children's Hospital Medical Center in Cincinnati, Ohio, is working to reduce disease and disability in children caused by environmental hazards such as lead exposure, environmental tobacco smoke, and pesticides used in the inner city.

Although children's blood lead concentrations have dropped nationally since lead was removed from paint and gasoline, work remains to further reduce exposures and to find what levels are safe and how the metal works. For example, new evidence reveals that lower lead concentrations than previously thought may affect IQ. A community-based program out of the Cincinnati center is testing the idea that keeping children's lead levels very low—at concentrations of 2.7 micrograms per deciliter or lower—will permit them to score higher on IQ and other tests and will result in less hearing loss and fewer behavioral problems at age three. The center will also examine in a cohort that has been followed for 20 years the relationship between lead and antisocial behavior, including delinquency, criminality, and incarceration in adulthood, as well as conduct disorders and features consistent with ADHD in early adulthood.

A second team will determine whether samples of meconium (a newborn's first bowel movement) can be used for analysis of various environmental chemicals and neurotoxicants to which the embryo and fetus are exposed through maternal consumption. Meconium may be a more direct and cumulative measure or biomarker of fetal exposure to environmental toxicants including lead, alcohol, tobacco smoke, polychlorinated biphenyls (PCBs), mercury, and pesticides than conventional methods, some studies reveal. Currently, researchers use markers from maternal blood, urine, and hair, which measure exposure indirectly and have a shorter half-life.



Big money for little kids. NIEHS director Kenneth Olden (left) and EPA administrator Christie Whitman (right) award a check for $1 million to George Lambert (middle), director of the Center for Childhood Neurotoxicology and Assessment, one of four new Children's Environmental Health Centers.

Another research program will test whether children's developmental problems can be linked to their exposure to pesticides, environmental tobacco smoke, and lead before and after birth. In a novel use of magnetic resonance imaging, the center will evaluate in 240 young adults brain metabolism and function in specific areas of the brain that may have been damaged by documented childhood exposures to lead. The study will relate environmental lead exposure with changes in brain neurochemistry, structure, and function.

The work will come full circle by testing the safety and efficacy of interventions such as home test kits and videos to reduce exposures to prevalent environmental toxicants. Researchers will also set up a healthy homes resource center in collaboration with the Better Housing League of Greater Cincinnati.

"Brain Food" Toxicants and the Brain

Scientists led by toxicologist Susan Schantz at the University of Illinois at Urbana-Champaign, home of the fourth center, will study the impact of exposure to PCBs and methylmercury on cognitive, sensory, and motor development of children from nearby Hmong and other Laotian communities. After emigrating from Laos to the United States after the Vietnam War, these people settled in Wisconsin's Great Lakes region in communities along the Fox River near Green Bay. Due to a traditional diet heavy in fish and their proximity to waters polluted by Wisconsin's paper mills, they have consumed lake fish laden with PCBs and mercury.

"We're depending heavily on the community viewpoint to design the study," Schantz says. The assessments of the children will focus on specific aspects of behavioral and sensory function that have not been adequately addressed in previous human studies. Although earlier studies revealed developmental delays associated with exposure, the team hopes to develop effective end points in human models for the first time.

Researchers at the center will also study in laboratory rodents the mechanisms by which these pollutants induce neurologic deficits in children. The effects of exposure to PCBs alone, methylmercury alone, and the two in combination will be examined. The findings may have broader ramifications, as the general U.S. population has low-level exposures to these chemicals, Schantz explains.

The work will expand a long-standing research partnership with the Laotian and Hmong communities to provide families with practical information that will help them to reduce their exposures. In total, the team, which includes researchers at the University of Texas at Houston and the State University of New York at Buffalo, hopes to enroll more than 280 mothers and babies in the final study.

By all accounts, including those from industry, the centers are a much-needed boost for the field of children's environmental health, itself still in infancy. "There are still huge, important questions to be answered," Swartz says. "We're only beginning to understand the possible differences in mechanisms of action of carcinogens in children and in effects of cumulative exposures." **–Julie Wakefield**

William Grigg/NIEHS Office of Communications