Children's Health Centers: Past, Present, and Future

A physician who conducted some of the first studies documenting the effect of lead poisoning on children. An epidemiologist studying the effects of exposure to diethylstilbestrol (DES). A toxicologist pointing out the many different chemical exposures associated with impulsivity. Though each of their disciplines uses a different language, all of these scientists study the links between the environment and childhood disease. They are just a few of the researchers who converged at the "Children's Environmental Health Research: Past, Present, and Future" conference held 22–23 January 2007 at the NIEHS. Sponsored in full by the NIEHS and planned jointly with the EPA, the conference aimed to get scientists talking about what types of research have been most effective. The result was recommendations to help chart the course for NIEHS children's environmental health research over the next five to ten years, including the future of the Centers for Children's Environmental Health and Disease Prevention Research.

Joseph Tart/EHP

Maintaining a Critical Mass

Phil Landrigan, a pediatrician and chairman of community and preventive medicine at the Mount Sinai School of Medicine, who chaired the workshop, says the children's research centers have created a critical mass of researchers in pediatrics, epidemiology, toxicology, human development, and other disciplines pursuing children's health issues. "By virtue of having this critical mass, we were able in ten years to gain convergent toxicological and epidemiological information on the developmental neurotoxicity of the organophosphate pesticides, [a process] that took nearly one hundred years to accomplish in the case of lead," he says. In 2000, on the basis of this emerging science, the EPA banned residential use of the pesticides chlorpyrifos and diazinon, and research in the children's centers has documented the success of community interventions to reduce children's pesticide exposures using integrated pest management. "Another great advantage of the centers," says Landrigan, "is that they are superb interdisciplinary incubators of the next generation of research leaders in children's environmental health."

Specific goals of the workshop included discussing recommendations for advancing research to home in on the contributions of the environment to disease in children, to develop better exposure and effects monitoring, to develop new strategies for intervention in and prevention of children's diseases, and to translate research findings into clinical and public health practice.

The meeting was organized into sessions focusing on four case studies. The first discussions covered two cases in which epidemiological and toxicological research has led to successful interventions—lead neurotoxicity and asthma. Then scientists discussed whether lessons learned from these case studies may provide insight into the best approaches to take in addressing two emerging syndromes that may be included in future NIEHS research efforts—attention deficit/hyperactivity disorder (ADHD) and metabolic syndrome. Metabolic syndrome is defined by a cluster of three or more conditions, including high blood glucose, high blood pressure, elevated plasma triglyceride level, a low level of high-density lipoproteins ("good cholesterol"), and abdominal obesity.

Conference participants repeatedly pointed out the need to focus more on the basic mechanisms behind disease, rather than simply identifying epidemiological associations between exposures and disease. Identifying the mechanism behind an association helps speed up acceptance of a finding, says Chris Portier, NIEHS associate director for risk assessment. Several researchers also stressed the need to more systematically design studies so that epidemiological investigations and basic mechanistic studies coincide.

"We need to start looking at exposures that are able to be studied by both epidemiology and basic science," says Theodore Slotkin, a professor of pharmacology and cancer biology at Duke University. "When those types of studies do overlap, it's great, but we need to start connecting those things in a more organized way."

Another topic that was raised repeatedly was the need for support of a major prospective epidemiological study of the effect of the environment on children's health, such as the National Children's Study. "Cohort studies are really invaluable because you're measuring the exposure prior to any kind of outcome that occurs, so you avoid biases that a lot of other epidemiological study designs are prone to," says Elizabeth Hatch, an associate professor of epidemiology at the Boston University School of Public Health.

Landrigan agrees that such a study is needed. "I see it as complementary to other more focused research programs, not replacing them," he says. "Large prospective studies with banked biological specimens, archived historical information, and high-quality genetic data are extraordinarily powerful for identifying previously unrecognized etiologic associations and for elucidating synergies among environmental exposures as well as gene–environment interactions."

In a similar vein, some workshop participants mentioned the need to increase the length of the funding cycle from the usual three to five years, to allow for more long-term, longitudinal studies. "That's something that's been under debate at NIEHS and NIH for some time," Portier says.

Complex Conditions

It has become apparent that just as asthma is a complex condition with many causes, so are metabolic syndrome and ADHD. In exploring possible causes, scientists are pinpointing not only current environmental factors such as diet but also early exposures, even before pregnancy, which may contribute to such conditions in offspring by disrupting hormones or early programming of growth and development.

As a culprit in the obesity epidemic, Robert Lustig, a professor of pediatric endocrinology at the University of California, San Francisco, pointed to high consumption of fructose, mainly in the form of man-made high-fructose corn syrup, found in a wide range of foods and drinks. Many scientists have pointed out that the rise in use of high-fructose corn syrup coincides with the obesity epidemic.

Lustig suggested some possible mechanisms. Unlike glucose, fructose doesn't stimulate insulin production, and it does not produce feelings of fullness when consumed, because it doesn't suppress ghrelin, a hormone that is thought to stimulate hunger (many of these findings are reviewed by Yuren Wei of Colorado State University and colleagues in the January 2007 *Journal of Nutritional Biochemistry*). Lustig also pointed to a study in the July 2005 issue of *Diabetes* in which David Faeh of the University of Lausanne, Switzerland, showed that normal male adults who were overfed fructose for six days developed several features of metabolic syndrome. These included increases in triglycerides and *de novo* lipogenesis—the conversion of carbohydrates into fat.

Amanda Drake, a clinician/scientist at the University of Edinburgh who studies early-life origins of disease, pointed to prenatal targets that, if perturbed at the right time, may predispose offspring to obesity and associated conditions through programming of the growth and development of tissues or of the brain. For instance, she discussed studies that have shown a strong link between low birth weight and impaired glucose tolerance, type II diabetes, dyslipidemia, and metabolic syndrome. Such studies suggest that

David Lewis/Shutterstock

Headliners | Allergies

NIEHS-Supported Research

Ragweed Subpollen Particles Reach Deep into Lungs

Bacsi A, Choudhury BK, Dharajiya N, Sur S, Boldogh I. 2006. Subpollen particles: carriers of allergenic proteins and oxidases. J Allergy Clin Immunol 118:844–850.

During the flowering season, high humidity and moisture trigger the release of pollen grains from grasses, trees, and shrubs. Allergens contained in these pollen grains can cause reactions in the skin, eyes, and upper and lower respiratory tracts. Seasonal asthma also is associated with pollen exposure.

How pollen allergens contribute to inflammation in the lower airways has puzzled researchers since few pollen grains reach the peripheral airways due to their size. In this report, NIEHS grantees Sanjiv Sur and Istvan Boldogh, with colleagues at the University of Texas Medical Branch in Galveston, present new findings suggesting that fragments of pollen grains, called subpollen particles (SPPs), are capable of reaching the lower airway regions and causing the clinical symptoms associated with seasonal asthma.

This same research team recently reported that ragweed pollen grains contain intrinsic NAD(P)H oxidases, and that exposure to them generates oxidative stress in the airway epithelium within minutes of exposure. In the current study, the investigators analyzed bronchial epithelial cells after exposure to hydrated short ragweed (*Ambrosia artemisiifolia*) and redroot pigweed (*Amaranthus retroflexus*) pollen grains. They also used an experimental mouse model of asthma to challenge sensitized mice with intranasally applied SPPs.

The researchers found that ragweed pollen grains release SPPs in the size range of 0.5–4.5 μm, small enough to reach lower airways. They determined that the SPPs contained allergenic proteins and possessed NADH or NAD(P)H oxidase activity. Exposure of cultured cells to SPPs caused significant increases in the generation of reactive oxygen species and induced airway inflammation in laboratory mice. Pretreatment of the SPPs with NADH and NAD(P)H oxidase inhibitors reduced their ability to increase reactive oxygen species in the airway epithelial cells and reduced airway inflammation.

This is the first report to demonstrate the presence of allergenic proteins and oxidase activity in SPPs of respirable size. The study provides insight into the potential role of SPPs in seasonal asthma and suggests that oxidase inhibitors may be useful therapeutic agents in reducing or preventing oxidative damage and inflammation. **–Jerry Phelps**

these conditions may be modulated by postnatal growth, Drake says. That is, during accelerated postnatal growth—a compensation for low birth weight—the body may switch on processes that incline the body toward obesity and associated conditions.

The wide-ranging perspectives of the participants became apparent as they discussed which avenues of study may most quickly determine mechanisms behind associations. Some suggested there is value in studying a single toxicant and trying to elucidate all its effects, as was done with lead. "What would have happened with lead if we hadn't focused on all the symptoms of exposure? We may be limiting what we know by focusing only on, for example, ADHD [to the exclusion of other conditions]," says Slotkin. He suggested that while funding work on a specific disease such as ADHD is a good way to stimulate research, programs should be flexible enough that their direction can be broadened based on new findings.

In the session on metabolic syndrome, with regards to obesity in particular, one candidate that emerged for study was the synthetic estrogen DES because it has been used as a model for potential effects of endocrine disruptors. For example, in the July 2005 *Birth Defects Research Part A: Clinical and Molecular Teratology*, Retha Newbold and colleagues from the NIEHS found that mice exposed to low doses of DES during pregnancy produced offspring that became overweight later in life. Although there are no human studies to date of the effect of DES on weight, findings on other effects of the compound in humans have paralleled what has been found in animals, Hatch said. She is exploring possible associations between DES exposure and obesity in humans by collecting data on body mass index and waist circumference in an ongoing National Cancer Institute–funded study of DES-exposed and unexposed women.

Other researchers pointed to the need to better understand the common pathways that may be affected by many different exposures. In the session on ADHD, Jason Richardson, an assistant professor of environmental and occupational medicine at the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, pointed to recent studies suggesting that different toxicants, perhaps acting at different key time points, are associated with one particular behavior—impulsivity. For instance, in the December 2006 issue of *EHP*, Paul Stewart and colleagues showed that children with either prenatal polychlorinated biphenyl (PCB) exposure, postnatal lead exposure, or prenatal methylmercury exposure all showed increased impulsivity.

"We're starting to see that it may be that divergent compounds converge upon common pathways and may lead to impulsivity not only in animal models but in the human population," Richardson says. "Instead of looking at one toxicant at a time, maybe we can use these common pathways to really try to pin down mechanisms by which divergent compounds produce common behavioral effects."

Such exposures may act on several systems in the brain. There is firm evidence for their action on the dopamine system; for example, in the August 2006 issue of *Toxicological Sciences*, Richardson and colleagues including Mike Caudle of Emory University showed that PCB exposure disrupts dopamine transport in mice. In addition, in the November 2002 issue of *EHP*, Richard Seegal of the New York State Department of Health showed that exposure of adult rats to low concentrations of PCBs initially increased concentrations of circulating dopamine, but significantly decreased them after three days.

"Based on the documented effects of certain developmental neurotoxicants on the dopamine system and the link between dopaminergic alterations and behavioral deficits, such as impulsive-like behaviors, this appears to be a promising avenue for investigation in order to understand both the effects of chemical exposure on the nervous system and how these effects translate into behavioral abnormalities," Richardson says.

What's Next for the Centers

Among the conference attendees was a committee of senior scientists charged with reviewing the Centers for Children's Environmental Health and Disease Prevention Research program and related investigator-initiated research on children's health. After meeting in separate evening sessions during the workshop, the committee drafted a report that was released for public comment in mid-March 2007.

The review committee has expressed broad and strong support for the children's center mechanism to continue, according to Kim Boekelheide, a professor of pathology and lab medicine at Brown University and a member of the committee. "It's an important mechanism that provides an interdisciplinary approach to what is a very important problem," he says. The committee also generally agreed on the need to strengthen the centers' basic-mechanisms research component, while keeping programs focused on actual children's health issues.

After a 30-day public comment period, the science advisory board of the NIEHS—the National Advisory Environmental Health Sciences Council—will discuss the review committee's report and comments in a public teleconference. In May, after considering the board's recommendations, NIEHS director David Schwartz will propose how the institute should move forward in funding children's environmental health research, says Portier.

The NIEHS would fund research along many different avenues as long as the proposal was highly rated scientifically, according to Portier. "We wouldn't rule anything out," he says, "because obviously we want the best science we can possibly get." **–Angela Spivey**

BEYOND THE BENCH

Healthy Home, Healthy Community

We like to think of home as a safe haven, but sometimes this shelter can harbor a wide range of health hazards. Children living in urban, low-income, and minority neighborhoods are often at greater risk of exposure to home-based health hazards than other groups, but implementing affordable, effective methods to alleviate the risk can be challenging. A new interactive museum housed in a residential property in Rochester, New York, now offers children and adults hands-on, real-world examples of hidden hazards in the home along with guidelines on simple preventive measures.

For more than two years, the Environmental Health Sciences Center (EHSC) of the University of Rochester and its community partners, the Southwest Area Neighborhood Association (SWAN) and the Rochester Fatherhood Resource Initiative (RFRI), worked together to develop an easily accessible, community-based program that would promote environmental health in the home. In June 2006 they launched the Rochester Healthy Home museum.

Musings on a healthy environment. The Healthy Home interactive museum teaches community members how to identify and mitigate health hazards in residences. (Above) SWAN high school interns Scott Blue and Isiah Johnson teach Rochester mayor Robert Duffy about healthy housekeeping in the "Asthma Safe Bedroom."

Left to right: Danielle Ruppert; Kate Kuholski

Eleanor Coleman, SWAN's community asset manager, explains, "We have found that community residents respond better to hands-on education than to printed materials." Katrina Korfmacher, the center's Community Outreach and Education Core coordinator, adds, "Our role was to bring together the existing resources within the community, develop the technical information for displays, and support the initial setup of the Healthy Home."

Korfmacher says the center and its community partners spent several months locating a residential building that was large enough to accommodate groups of visitors, solving commercial zoning issues, and finding a landlord who was amenable to such a unique project. The Healthy Home is located adjacent to the historic Susan B. Anthony neighborhood in a community with high poverty, a low number of owner-occupants, and one of the highest lead poisoning rates in the city.

The neighborhood location is important to SWAN outreach coordinator Shehrina Tabassum, who says, "We wanted it to be accessible to low-income residents who might not be able to travel across town to visit a Healthy Home." According to a 2002 report by the Center for Governmental Research, 34% of the children living in the SouthWest neighborhood represented by SWAN have blood lead concentrations above the CDC "threshold of concern" of 10 µg/dL. James Richardson, president of a residents' group called the Lennox Street Block Club, notes that many of the century-old homes in this area have environmental hazards and that nearby residents will benefit from the interactive displays at the Healthy Home. "When it is hands-on, people seem to believe it a little more," he says.

The partners focused on some of the major risks present in many homes—asthma triggers, lead hazards, household chemicals such as pesticides and cleaners, and indoor air quality hazards—to create topical posters and hands-on displays. For example, the "Lead Room" has three display windows that demonstrate different methods for treating painted window frames for lead hazards, including instructions and cost information for lead-safe work practices to minimize the disturbance of lead-based paint. The "Asthma Safe Bedroom" displays pillowcase covers and other asthma trigger reduction tools, and offers tips for avoiding mold growth along with other appropriate housekeeping guidelines. In the kitchen, visitors find displays explaining the risks of exposure to certain common household chemicals as well as tips for safe handling and storage. The Healthy Home also educates visitors about potential causes of injuries such as electrical shock and choking hazards, as well as possible carbon monoxide poisoning risks such as defective furnaces.

With emphasis on the idea that creating a healthy home environment is a shared responsibility, the partnership encourages visits from all community stakeholders. In its first six months of operation, the Healthy Home has welcomed more than 400 visitors, including residents, students of all ages, teachers, contractors, property owners, and elected officials, all of whom can apply the lessons learned in the museum to their respective community roles. The Healthy Home hosts outreach activities such as support group meetings (for example, for families of asthmatic children), neighborhood block group meetings, and free safe practices training courses (by the end of 2006, 67 people had received training in a series of lead safety courses). The partnership also conducts community presentations and distributes information at health fairs on the topics covered in the Healthy Home.

Admission to the Healthy Home is free, and guided tours are available. In the near future, the partners plan to increase outreach efforts through youth programs, home health visiting nurses, and others. Meanwhile, center staff are evaluating the impact of the Healthy Home on visitors' knowledge and behaviors, and are writing a guide to help other communities develop similar facilities.
–Tanya Tillett

For More Information
http://www2.envmed.rochester.edu/envmed/ehsc/outreach/CommunityPartners/CommunityPartnersHH.html