Exploring the Environmental Causes of Autism and Learning Disabilities
By Cristina Farrell, MD

On December 8, 2010, the Mount Sinai Children’s Environmental Health Center (CEHC), in partnership with Autism Speaks, presented a day long workshop at the New York Academy of Medicine in New York City. The goal of the meeting was to invite research leaders from around the world to share their insights on studying autism and the environment and to seek these experts’ guidance to refine further research strategy.

As a result of the workshop, CEHC will create an action plan for discovery of the unrecognized environmental causes of autism and learning disabilities in children. Over the next months, CEHC will develop a prioritized list, outlining suspect chemicals that we believe are most likely to cause autism and learning disabilities.

The workshop allowed us to examine current knowledge and ongoing research that may contribute to our understanding of which chemicals to investigate further as potential environmental causes of autism. During the day, 14 researchers highlighted their respective research projects and recent findings. The first half of the day was devoted to a review of current studies, research collaborations, and some preliminary results.

The Need for Studies of Environmental Causation of Autism and Learning Disabilities
Philip J. Landrigan, MD, MSc

Ethel H. Wise Professor and Chairman, Department of Preventive Medicine, Professor of Pediatrics, Dean for Global Health
Mount Sinai School of Medicine

Dr. Landrigan opened the workshop by presenting the case for an environmental contribution, specifically by toxic chemicals in the environment, to autism and learning disabilities. Autism may result from a combination of genetic susceptibility and exposure – “the wrong chemical at the wrong time” – and certain environmental toxins may be harmful to fetal brains during windows of vulnerability that change with brain development.

Dr. Landrigan identified several environmental exposures that have been linked to autism:

1. **Thalidomide**: A medication taken by women in early pregnancy during the 1950s.
2. **Misoprostol**: A medication used in other parts of the world to induce abortion in the first trimester.
3. **Prenatal Rubella Infection**: Timing of the infection during pregnancy determines the severity of neurodevelopmental effects.
4. **Valproic Acid**: A medication used to control epilepsy.
5. **Organophosphate Insecticides – Chlorpyrifos**: A pesticide once widely used in the US. It is now banned and used only in agricultural settings.

While these chemicals do not account for the current rise in autism, as none are commonly used in the US, their proven link illustrates that early exposure to the wrong chemical can cause autism – establishing proof of principle for an environmental contribution. Currently, we lack safety and toxicity data on thousands of synthetic chemicals, many of which can be found in the blood and urine of most people in the industrialized world. In most cases, we do not know whether the chemicals are toxic or not. Identifying an environmental trigger of ASD could be the path to prevention.
Next, Dr. Birnbaum explained the importance of understanding “environment” as a broad concept:

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<td>• Industrial and agricultural chemicals</td>
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<td>• Physical agents (heat and radiation)</td>
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<td>• Foods and nutrients</td>
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<td>• Prescription drugs</td>
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<td>• Lifestyle choices</td>
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<td>• Socioeconomic factors</td>
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<td>• Interactions between all of these parts of the environment</td>
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Dr. Birnbaum also described the work that NIEHS is engaged in, including 14 Children’s Environmental Health and Disease Prevention Centers, funded by a partnership between NIEHS and the EPA. Six of these centers focus almost exclusively on neurodevelopmental disorders as they relate to the environment. During the remainder of the morning, we heard from principal investigators at these sites about several large epidemiologic studies that are in progress. These studies include:

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<th>CHARGE study:</th>
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<td>One of the few large case control studies looking for causes and contributing factors for autism</td>
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<th>EARLI study:</th>
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<td>A prospective, “enriched risk” model, recruiting women who are pregnant or planning to become pregnant and have at least one child with autism</td>
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Environment and Autism: State of the Science and the CHARGE Study

Irva Hertz-Picciotto, PhD
Professor & Chief, Division of Environmental and Occupational Health, Department of Public Health Sciences
University of California, Davis

Dr. Hertz-Picciotto began with a review of autism’s history, definition, diagnosis, and what is known about its epidemiology. She explained how California’s Lanerman Act of 1977 helped create an important database that allows us to generate hypotheses about ASD diagnosis. Using time and trend analysis, Dr. Hertz-Picciotto made a convincing case that not all of the 600% increase in California children receiving services for an ASD diagnosis is artefactual; at least 200% of the increase seems to be from a true increase in incidence, possibly due to an environmental factor.

She also noted that the incidence of several other childhood disorders has dramatically increased during the same time period – which could be explained by a common set of exposures. When environmental variation is small, genes will appear to explain most of the variability in disease rates. But when an environmental toxin that also happens to be a “sufficient cause” for the disease affects a large portion of the population (for example, lead), a more powerful environmental component is observed. Dr. Hertz-Picciotto also stated:

- New findings from the CHARGE study published in Environmental Health Perspectives indicate that children whose mothers lived <309m from a freeway at the time of delivery had about twice the odds of being diagnosed with autism, compared to children whose mothers lived farther from a freeway.

- Unpublished research that finds maternal antibodies to fetal brain tissue only seen in mothers of children with ASD. This suggests that the mother’s prenatal inflammatory response to fetal brain tissue could cause a derangement in fetal brain development – leading to or creating vulnerability for the development of ASD.
The EARLI Network

Craig J. Newschaffer, PhD
Professor and Chairman, Department of Epidemiology and Biostatistics, Drexel University School of Public Health

Dr. Newschaffer described the **EARLI study**, which will track 1,200 mothers of autistic children as they experience their second pregnancy. Mothers – and their homes and families – will be tested for various exposures before, during, and after birth, and the second sibling will be tracked for three years for developmental and biological outcomes measurement.

CDC’s Response to Autism

Coleen A. Boyle, PhD
Acting Director, National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention

After describing the public health principles of surveillance, epidemiology, and prevention, Dr. Boyle discussed CDC’s activities in each of these areas, including the ADDM active surveillance program from which we get the statistic that 1 of every 110 American 8 year olds have an ASD. She then described the **Study to Explore Early Development (SEED)**, a collaborative, multi-year, six-state case control study. SEED aims to better characterize the behavioral and physical characteristics (phenotype) of ASD, learn more about ASD comorbidities, and generate hypotheses regarding risk factors. It will look at immunology, occupational exposures, teratogens, lifestyle, socioeconomic status, genetics, and nutrition.

The National Children’s Study

Marion J. Balsam, MD
Research Partnerships Program Director, the National Children’s Study
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Dr. Balsam discussed **the National Children’s Study (NCS)**, a longitudinal observational study that aims to enroll 100,000 subjects and follow them from the prenatal period to age 21. Unprecedented in scope and complexity, it is the largest long term study in the US to look at environmental effects on child health and development. The NCS involves biological samples from the prenatal and postnatal periods, from the child and the parents. The rationale is that many diseases have suspected environmental contributors; there is much concern about exposures, but little evidence about their actual effects.

The Korea Autism Study

Young-Shin Kim, MD, MPH, PhD
Assistant Professor, the Child Study Center, Yale School of Medicine

International research has the potential to uncover important environmental contributions, as genetics and environmental factors differ greatly worldwide. Along these lines, Dr. Kim described the **Korean Autism Study (KAS)**, a large-scale cohort study that examines gene-environment interactions. Researchers collect biologic, phenotypic, behavioral, and environmental exposure data on children with and without autism (n=10,000).

**KAS is unique because of the Korean population’s genetic characteristics, defined by:**
- An ethnically homogenous ancestral group. No national aboriginals.
- Minimal immigration and strong social pressures against marriage to non-Koreans.
- Rare consanguinity, meaning less shared genetic material within members of the same family.
Highlighting additional international research, Ms. Roth introduced the Norwegian Mother and Child Cohort Study, which ran from 1999-2009 and is available for collaborative or independent use by other investigators. The study captured data on 107,000 pregnancies through questionnaires during and after pregnancy and is linked to national registries such as the birth registry. 80,000 of the child subjects turned 3 years old in 2010, and 20,000 turned 7. Ms. Roth also noted that biosamples from this study are part of a national biobank and invited researchers present at the meeting to consider utilization of these samples for studying gene x environment interactions in autism.

Resources at the Mount Sinai School of Medicine

Since a goal of the workshop was to utilize the knowledge of experts in the field and participants in the audience, researchers from the Mount Sinai School of Medicine also presented their work. These researchers described their projects in an effort to help understand how these efforts could be developed into studies which uncover environmental contributions to ASD. Presentations included:

- **Latha V. Soorya, PhD**, from the Seaver Autism Center, which conducts clinical, industry, and basic science (genetics, neuroimaging) research in Mount Sinai’s Department of Psychiatry.
- **Stephanie M. Engel, PhD** from Mount Sinai’s CEHC, discussing research on prenatal phthalate exposure and neurodevelopmental impairment, including a prospective birth cohort study with periodic neurodevelopmental assessments, urine, and blood collection.
- **Patrick R. Hof, MD**, a neurobiologist working to characterize regional, discrete, and cell type specific neuronal pathology in autism. He is using age- and gender-matched autopsy brain specimens from people with autism to look at neuron morphology, focusing on a type of neuron thought to control the autonomic nervous system and related to the sense of self and other emotional aspects of human function that are affected in autism. This neuron appears to be abnormally distributed in the brains of people with autism.
- **Luca Lambertini, PhD** from Mount Sinai’s CEHC, discussed the Mount Sinai pregnancy biobank, a cord blood and placental tissue repository that will be a valuable resource in studying prenatal exposures and child neurodevelopment, as well as identifying biomarkers for autism and other disorders.

The Way Forward

At the end of the meeting, Dr. Landrigan emphasized that any progress we will make in unraveling causes of ASD will be multidisciplinary and includes those who have been the core of ASD research and clinical work.

Beyond that core community, we need a range of other scientific disciplines, including toxicology/animal research, epidemiologic, biomarkers, and physiologic and neurophysiologic outcome measures – as part of the “new” epidemiology, which his more than “just counting bodies.” We finished the workshop with the following conclusions:

1. **Unanimous consensus that the possibility of an environmental contribution to autism and learning disabilities warrants serious consideration and systematic investigation.**
2. **Agreement that discovery of the environmental causes of autism and learning disabilities is going to be a multidisciplinary effort – combining epidemiological, laboratory, and basic science studies.**
3. **CEHC’s commitment to developing a prioritized list of suspect chemicals, which we believe are most likely to cause autism and learning disabilities.**
4. **Importance of the Mount Sinai Pregnancy Biobank, which will play a crucial role as a platform for discovery of the environmental causes of autism and learning disabilities.**