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Exploring the Environmental Causes of Autism and Other Learning Disabilities
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National Institute of Environmental Health Sciences

- One of the National Institutes of Health, but located in Research Triangle Park, North Carolina
- Wide variety of programs supporting our mission of environmental health
  - Extramural Research and Training
  - Superfund Research Program
  - In-house laboratories
  - National Toxicology Program
“Environment” includes:

- Industrial chemicals
- Agricultural chemicals
- Physical agents (heat, radiation)
- By-products of combustion and industrial processes (dioxin)
- Foods and nutrients
- Prescription drugs
- Lifestyle choices and substance abuse
- Social and economic factors
Principles Guiding Investments

- Autism and neurodevelopmental disorders research are integral components of a larger NIEHS program that supports children’s environmental health research
- A mix of research approaches are needed—from population-based studies to laboratory investigations of relevant cellular and molecular mechanisms
- Strong partnerships, with other federal entities and public stakeholders are essential to speed discovery and ensure rapid translation to public health
- Fundamental investments in exposure science and toxicology will benefit autism research
FY10 NIEHS Extramural Research Investments in Neurodevelopment

- $30 million in FY10 funding
- > 60 projects
- Mix of human and non human studies; small/exploratory, single project and multi-project grants
Children’s Environmental Health and Disease Prevention Centers (NIEHS/EPA Partnership)

Program Description:

- Enhance communication, innovation and research excellence in Children’s Environmental Health
- Promote multidisciplinary interactions among basic scientists, clinicians, behavioral & social scientists
- Accelerate translation of basic research findings into clinical or intervention strategies
 UC Berkeley
1. Salinas Valley
2. ALL consortium
3. BD registry

UC Davis

UC SF

University, WA

National Jewish Medical Center

U. Michigan

U. Illinois

Dartmouth

Brown

Columbia

Hopkins

Duke

Michigan Study Population, Mexico City

Illinois Urbana-Champaign Study Population, New Bedford, MA
UC Davis Children’s Environmental Health and Disease Prevention Center

- Focused on autism etiology and supports research projects and service and facility Cores
  - Epidemiology of autism risk (Project 1)
  - Clinical and cellular immunology (Project 2)
  - Mouse Models (Project 3)
  - Analytical Chemistry, Molecular Genomics, Statistics Cores (Service Cores)
  - Community Outreach and Translation
**CHARGE Epidemiology Study Design**

- *Childhood Autism Risks from Genetics and the Environment*

- Case control study with 3 groups: ASD; Developmental Delay (DD); children with Typical Development (TD), ages 24-60 months

- Goal: To identify causes and contributing risk & protective factors for childhood autism, understand etiologic heterogeneity

- Population based recruitment: 1300 families

- Clinical confirmation of diagnosis

- Extensive collection of environmental, medical, lifestyle, sociodemographic, & phenotypic information

- Linkage to state-of the art laboratories through Center Core resources
Recent study results from CHARGE implicate immune alterations in autism

- Child’s T cell responses are altered (Ashwood et al., Brain, Behav, Immun. 2010)
- Elevated child cytokines are associated with impaired behavior (Ashwood et al., Brain, Behav, Immun, 2010)
- Child’s total IgG levels are reduced (Heuer et al. Autism Res 2008)
- Child’s IgG4 levels are increased (Enstrom et al. Brain Behav Immun 2009)
- Child’s TGF-beta levels are reduced (Ashwood et al. J Neuroimmunol 2008)
Conclusion In this exploratory study, children with autism were more likely to have mitochondrial dysfunction, mtDNA overreplication, and mtDNA deletions than typically developing children.

JAMA. 2010;304(21):2389-2396 www.jama.com
Columbia Center for Children’s Environmental Health and Disease Prevention

- Current Center focused on childhood obesity and neurodevelopment
- Follow up of NY inner-city birth cohort study, with extensive pre- and postnatal exposure data available
  - Endocrine disrupters and obesity among inner-city children (*Project 1*)
  - Endocrine disrupters, epigenetic mechanisms and neurodevelopment (*Project 2*)
  - Molecular consequences of prenatal BPA, PAH exposure across generations (*Project 3*)
- Data Management, Statistics and Community modeling (*Cores*)
- Community Outreach and Translation
Recent findings from Columbia Children’s Center

- PAH or PAH-DNA adducts are associated with
  - Reduction in birth weight and head circumference
  - Developmental delays at age 3
  - Reduced IQ scores at age 5
  - Attention/behavioral problems through age 7

Sources: Perera et al., 2006, 2009; Wang et al., in prep.; Edwards et al., 2009., Tang et al., 2008
Adverse Effects of Prenatal PAHs on Children’s IQ

Differences in Full-Scale, Verbal IQ and Performance IQ associated with high prenatal PAH exposure

Mean IQ score

(n = 249). Mean IQ levels are adjusted for ETS exposure during pregnancy, gender of child, ethnicity, mother’s intelligence (TONI), mother’s education, and the quality of the home caretaking environment (HOME).

EARLI: Early Autism Risk Longitudinal Investigation

- NIH Autism Centers of Excellence (ACE) Network R01
- Lead institute: NIEHS, cofunding by NIMH, NICHD, NINDS
- Four site study enrolling mothers with at least one child with autism who are planning to become pregnant or in the early stages of a subsequent pregnancy
- Enriched risk cohort design offers advantages for detecting autism risk and g x e interplay
- Prospective, real time data collection during critical periods of early development avoids disadvantages of retrospective methods of exposure assessment
- Enrollment began Spring 2009; enrollment target is 1200 mothers
Organophosphate exposure linked to risk of ADHD

Adjusted for gender, age, race/ethnicity, PIR, fasting duration, and logarithmically transformed urinary creatinine concentration.

* p<0.05
Prenatal BPA exposure is associated with childhood behavior

- Prenatal exposure to BPA is associated with externalizing behaviors in 2 year-old children, especially female children.
Examples of NIEHS investigator-initiated mechanistic research in neurodevelopment

- Modeling developmental neurotoxicity in zebrafish, Elwood Linney, Duke University
- NMDA receptor function in lead neurotoxicity, Tomas Guilarte, Columbia University
- Developmental pesticide exposure and ADHD, Jason Richardson, UMDNJ-Robert Woods Johnson Medical School
- Effects of methylmercury on neuronal cell migration, Hitoshi Komuro, Cleveland Clinic, Lerner College of Medicine
- PCBs, PBDEs, hearing loss and attention/impulsivity: mechanistic studies in animals, Susan Schantz, University of Illinois, Champaign
Increased autism prevalence among Somali immigrants in Minneapolis?

- Mn Department of Health confirmed increased administrative prevalence of Somalis in preschool autism classes
- NIEHS is working with sister NIH institutes, CDC and Autism Speaks to support a study to determine whether there is a true increase in prevalence
- Answering the prevalence question is needed before research to understand causes can be considered
Environmental Epigenetics Program: To examine the impact of gene-environment interactions on diseases by studying alterations in gene expression as influenced by environmental exposures

- Epigenetic Interaction of MECP2 and Organic Pollutants in Neurodevelopment
  Janine LaSalle, UC-Davis

Epigenetics Roadmap Program: NIEHS co-leads trans-NIH Roadmap efforts in epigenomics to understand the importance of epigenetic marks and how environmental exposures may alter them

- Environment, the Perinatal Epigenome and Risk for Autism and Related Disorders
  Danielle Fallin/Andy Feinberg, Johns Hopkins University
NIEHS Intramural Research in Neurodevelopment

- The Laboratory of Neurobiology (LN) investigates
  - Mechanism of thyroid hormone signaling and its disruption by environmental toxicants
  - Development of functional populations of noradrenergic and cholinergic neurons in the CNS
  - Developmental regulation of synaptic plasticity
  - Mechanism of rapid gene regulation by neuronal signaling
  - Role of DNA methylation in epigenetic regulation
  - Effects of ethanol and nicotine on neuronal excitability

- The Pediatric Epidemiology Group, studies the effects of environmental chemicals on childhood growth/development (e.g., child nutrition)

- The Biomarker-based Epidemiology Group, is focused on health effects of early exposure to background levels of environmental contaminants (e.g., developmental effects of endocrine disruptors)
After birth, brain development primarily involves refinement of the connections between neurons at synapses, where chemical neuro-transmission occurs.

Patterns of neuronal electrical activity strengthen some synapses but weaken others, some to the point of complete withdrawal.
Toxicity testing has relied traditionally on cancer endpoints

Increased interest in neurodevelopmental outcomes

NTP is currently exploring an Integrated Testing Protocol for Examining the Effects of Developmental Exposure on the Nervous, Reproductive, and Immune Systems which includes:

- Expansion of Nervous System Endpoints to assess Sensory, Motor, and Cognitive Endpoints
Summary

- NIEHS research investment in the area of neurodevelopment in fiscal year 2010 was approximately 30 million dollars.

- NIEHS supported studies span from human epidemiology to mechanistic laboratory investigations and from small exploratory projects to single investigator-initiated project to coordinated multi-component programs.

- NIEHS support for basic research in neurotoxicology and exposure science will be essential for understanding and informing human studies in autism.

**Future NIEHS activities in neurodevelopment will emphasize:**
- Priorities identified through strategic planning
- Coordination with other federal agencies
- Meaningful involvement of affected communities
- Translation of findings to public health & prevention
Thank you!