Children’s Environmental Health: Today’s Pediatric Frontier

Duane Alexander, M.D.
Director, NICHD
Yesterday’s Pediatric Frontiers

• Infection
• Nutrition
• Surgery
• Endocrine Disorders
• Low Birth Weight
Today’s Pediatric Frontier: Environmental Health

**Known Agents:**
- Lead, mercury, alcohol
- Rubella, CMV
- Radiation
- Thalidomide, Dilantin, Accutane, DES

**Suspect Agents:**
- Chemical products
- Pesticides
- Food additives
- Violence and stress
- Neighborhoods

**Suspect Conditions:**
- Cardiovascular Disease
- Birth defects
- Learning disabilities
- Autism
- Cancer
- Asthma
- Obesity
- Preterm labor
- Diabetes
Why Study Children?

- Increased vulnerability to environmental exposures
- Windows of vulnerability (from fetal to adult)
- Immature detoxification & protection mechanisms
- Differences in metabolism & behavior
## Children Are Different

Physiological and Behavioral Factors Increase Exposure in Children

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>INFANTS</th>
<th>CHILDREN</th>
<th>ADULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface Area: Body Mass Ratio (m²/kg)</td>
<td>0.067</td>
<td>0.047</td>
<td>0.025</td>
</tr>
<tr>
<td>Respiratory Ventilation Rate (ml/kg/m² lung surf. area/min)</td>
<td>133</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Drinking Water Intake (ml/kg/day)</td>
<td>43.5</td>
<td>35.5</td>
<td>19.9</td>
</tr>
<tr>
<td>Rate of Lead Absorption</td>
<td>42-53%</td>
<td>30-40%</td>
<td>7-15%</td>
</tr>
</tbody>
</table>

Selevan et. al., 2000
Why a Frontier?

- Many disorders without known cause
- Wide variety of association claims, but no evidence
- Postulated, but not proven
  - N too small
  - Start too late
  - Follow-up too short (often only once)
  - 1 exposure/1 outcome/1 time
Crossing each geographic or medical frontier required its own unique approaches
  • Infection—sanitation, vaccines
  • Surgery—techniques and skills
  • Low birth weight—substitute life-support system

Environmental health also requires unique approach
  • Begin before birth
  • Organized planned studies
  • Large population
  • Multiple simultaneous measures of multiple exposures and outcomes
  • Relate to genetic constitution
  • Long-term follow-up

Harder in many ways than earlier frontiers
Intrauterine Environment: Barker Hypothesis

Effect of Birth Weight on Cardiovascular Mortality

- Women (5585, 1923-1930)
- Men (10,141, 1911-1930)

Barker et. al., 1989
“A dramatic change in cardiomyocyte cell cycle regulation occurs in the transition from the prenatal to postnatal period. During this time myocardial growth shifts from a hyperplastic to a hypertrophic phenotype. The changes in terminally differentiated myocytes are characterized by…the formation of binucleated cells”

Boehm & Nabel, 2003
Fetal Sheep Cardiomyocytes 135d gestation (stained for myosin & DNA)

Intrauterine Environment: Vascular Volume Overload

Thornburg, 2005
Intrauterine Environment: Cardiac Development

Effect of Volume Load on Cardiomyocyte Binucleation

% Binucleated

Control     Loaded

0 25 50 75

Thornburg, 2005
Intrauterine Environment: Stress in Pregnancy

- “Pregnant Rat in a Tube” Study
- Hypothesis: Stressing the pregnant rat raises her glucocorticoid level and affects the fetus with long-term consequences
Intrauterine Environment:
Stress in Pregnancy—Offspring Response

Maternal Adrenal Status

- Intact
- Blocked

Before Stress

30 Minutes Post-Stress

120 Minutes Post-Stress

Offspring Corticosterone (µg/100ml)

- Control
- Prenatal Stress

P<0.001

Barbazanges et al., 1996
Intrauterine Environment: Stress in Pregnancy

- Are there other adverse effects of maternal stress in pregnancy?
  - On birth weight?
  - On premature delivery?
  - On the fetus, manifesting in childhood or adulthood?

- What are the mechanisms?
Prenatal and Postnatal Environments
Neurodevelopmental and Learning Disabilities

- Affect 8 percent to 17% of children ages 3-17 in U.S.
- Etiology unknown for >75%
- Many environmental associations postulated, studied
- Exposure may be prenatal, infancy (breast milk), childhood
- Examples: lead, PCBs and dioxins
Neurodevelopmental Disabilities: Lead

- Risk level lowered from 60 µg/dl to 10 µg/dl
- Removed from paint and gasoline 1970s
- Marked decline in mean blood lead level

NHANES, 2002
Neurodevelopmental Disabilities: PCBs and Dioxins

- Two of the most frequently cited environmental concerns
- Inconsistent results of studies
Neurodevelopmental Disabilities: PCBs and Dioxins

- No Association with Cognitive Development
- Negative Association with Motor Development
- Significant Negative Effect in Infancy Only
- No Association with Motor Development
- Negative Association with Cognitive Development
- Significant Negative Effects at School Age
Autism and Autism Spectrum Disorders (ASDs)

- One of the most common serious neurodevelopmental disorders
- Great public health concern—nearly 10-fold prevalence increase (up to 6/1,000)
- Great economic burden
- Reasons for increase in prevalence unclear
- Heritability of autism well established
- Chromosomal aberrations or genetic mechanism elusive; environmental (non-genetic) factors assumed to play important role in etiology
Autism and ASDs: Exposure-Outcome Relationship

- Infection (Prenatal and Postnatal)
- Inflammation
- Vaccines
- Refrigerator Mothers
- Mercury
- Genetics
- Neurotoxicity
- Regressive Autism
- Pollution
Childhood Cancers

- Great public concern and priority
- Relative rarity makes difficult to study (242/100,000 age 0-14)
- Multiple types and subtypes
- Clusters and lack of heritability suggest environmental role
- Case control studies for etiological factors problematic
  - Exposure measures limited and often biased
  - Controls difficult to obtain
Asthma

- Most common chronic disease of childhood
- Prevalence has doubled in the past 20 years
- One million U.S. children younger than age 18 have asthma
- Pediatric asthma costs $14 billion annually
- Clear relationship to air pollution
Facing the Frontier

- Environmental health frontier requires its own unique approach:
  - Organized planned studies
  - Large population
  - Begin before birth
  - Multiple simultaneous measures of multiple exposures and outcomes
  - Relate to genetic constitution
  - Long-term follow-up
The National Children’s Study

- Largest long-term study of children’s health and development ever to be conducted in the U.S.

- Longitudinal study of children, their families, and their environment (over 21 years or longer, from before birth)

- Environment defined broadly (chemical, physical, behavioral, social, cultural)

- Approximately 100,000 children included to study important but less common outcomes
(a) PURPOSE - … to authorize NICHD to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development.

(b) IN GENERAL - The Director of NICHD shall establish a consortium of representatives from appropriate Federal agencies (including the CDC and EPA) to:

- (1) plan, develop, and implement a prospective cohort study, from birth to adulthood, to evaluate the effects of both chronic and intermittent exposures on child health and human development; and
- (2) investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes…

(e) AUTHORIZATION OF APPROPRIATIONS - There are authorized to be appropriated to carry out this section $18,000,000 for fiscal year 2001, and such sums as may be necessary for each the fiscal years 2002 through 2005.
Study Concepts

- Longitudinal study of children, their families and their environment
- National in scope
- Hypothesis driven
- Environment defined broadly (chemical, physical, behavioral, social, cultural)
- Study common range of “environmental” exposures and less common outcomes (n~100,000)
Study Concepts (cont.)

- Exposure period begins in pregnancy or before
- Environment & genetic expression
- State-of-the-art technology
  - Tracking
  - Measurement
  - Data management
- Consortium of multiple agencies
- Extensive public-private partnerships
- National resource for future studies
Priority
Environmental Exposures

- **Physical** environment: housing, neighborhoods and communities, climate, radiation…

- **Chemical** exposures: air, water, soil, food, dust, industrial products, pharmaceuticals…

  complex ubiquitous low-level exposures

  unique exposures (special sub-studies)

- **Biological** environment: intrauterine, infection, nutrition; inflammatory and metabolic response…

- **Genetics**: genetic components of disease; effects of environmental exposures on gene expression…

- **Psychosocial** milieu: influence of family, school, socio-economics, community, stress…
Priority Outcomes

- **Pregnancy outcome**: preterm birth, birth defects, fetal influences on adult health. EARLY results!

- **Neurodevelopment and Behavior**: cognitive development (IQ), autism, learning disabilities, schizophrenia, depression, adjustment, normal variation, resilience…

- **Injury**: intentional and unintentional; violence…

- **Asthma**: environmental/genetic/infectious/immune factors..

- **Obesity and Physical Development**: diabetes, pubertal/reproductive development, growth, obesity ‘epidemic’…
Measures Anticipated: Exposures

- DNA
- Environmental samples: air, water, dust
- Bio-markers for chemicals: blood, breast milk, hair, tissue, etc.
- Interview and history
- Serology and medical data
- Housing and living characteristics
- Family and social experiences
- Neighborhood and community characteristics
Measures Anticipated: Outcomes

- Fetal growth and outcome of pregnancy
- Birth defects and newborn exam
- Growth, nutrition, and physical development
- Medical condition and history: illness (e.g. asthma, obesity), conditions, and injuries
- Cognitive and emotional development
- Mental, developmental and behavioral conditions
- Development of maternal pelvic floor disorders
Study Sample: Specifics

- National probability sample drawn by NCHS
- 105 locations roughly corresponding to counties, or clusters of adjoining counties; 79 metropolitan, 26 rural
- 13 self-representing counties; remaining counties placed into strata based on:
  - Metropolitan status
  - Geography
  - Average number of births per year
  - Race, ethnicity, percent low birth weight
National Children’s Study Locations
Vanguard locations: Study Centers awarded (bold)

- Lincoln, Pipestone, and Yellow Medicine Counties, Minnesota
- and Brookings County, South Dakota
- Salt Lake County, Utah
- Waukesha County, Wisconsin
- New York City (Queens), New York
- Montgomery County, Pennsylvania
- Orange County, California
- Duplin County, North Carolina
So, The NCS Will Provide…

- The answer to concerns about known exposures during pregnancy and childhood to potential toxicants
- The power to determine absence of effects or benefit of exposures to various products important for our economy
- Causal factors for a number of diseases and conditions of children with suspected environmental causes
- How multiple causes interact to result in multiple outcomes
- Large sample size required to apply knowledge of the human genome to understand multi-factorial genetic conditions and gene-environment interactions
- Identification of early life factors that contribute to many adult conditions
- A national resource to answer future questions by using stored biological and environmental samples and the extensive data for decades to come
Today’s Pediatric Frontier