

Children's Environmental Health: Today's Pediatric Frontier

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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

FACTORS	INFANTS	CHILDREN	ADULTS
Surface Area: Body Mass Ratio (m^2/kg)	0.067	0.047	0.025
Respiratory Ventilation Rate ($ml/kg/m^2$ lung surf. area/min)	133		2
Drinking Water Intake ($ml/kg/day$)	43.5	35.5	19.9
Rate of Lead Absorption	42-53%	30-40%	7-15%

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





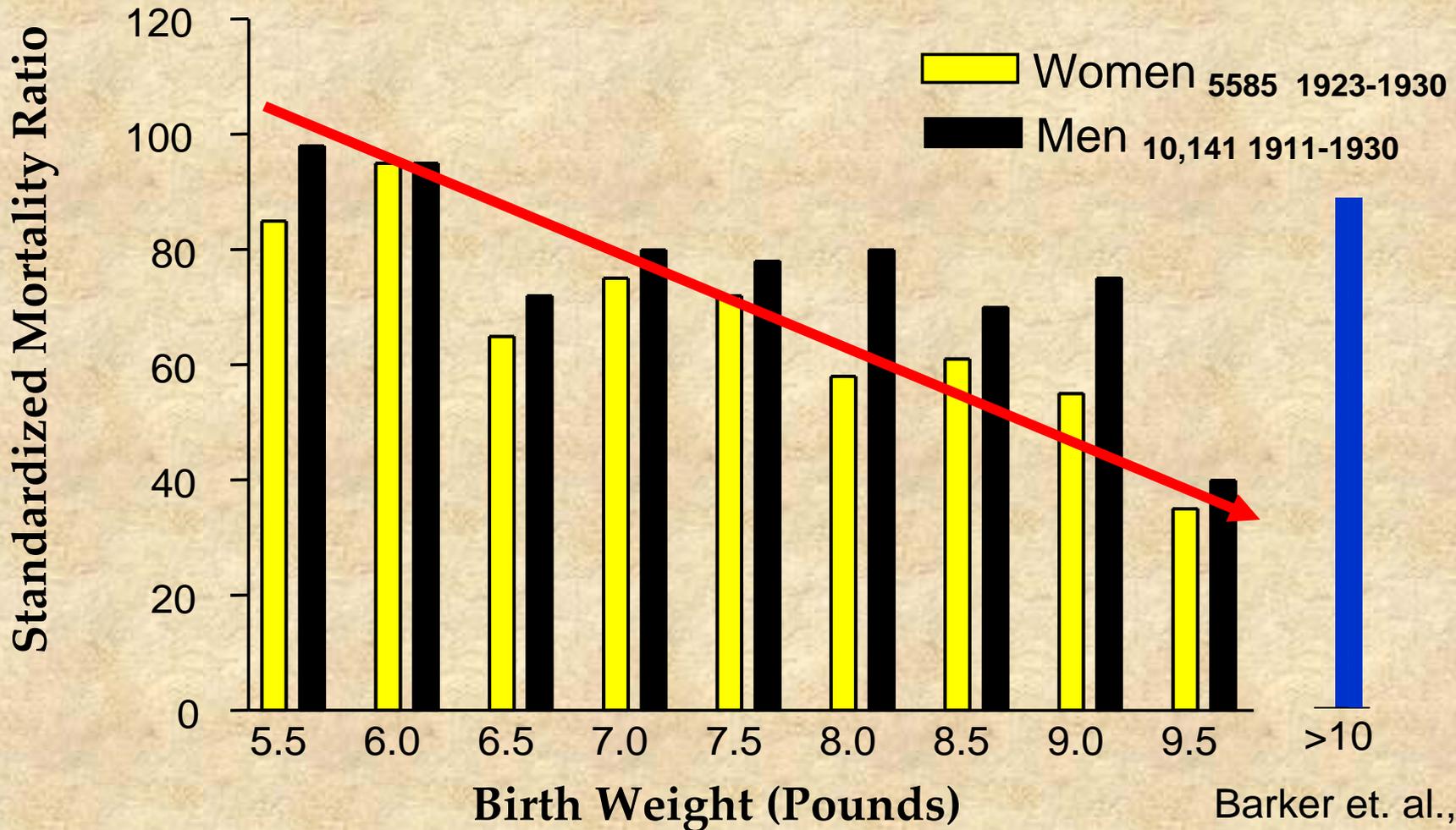
Crossing the Frontier

- **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

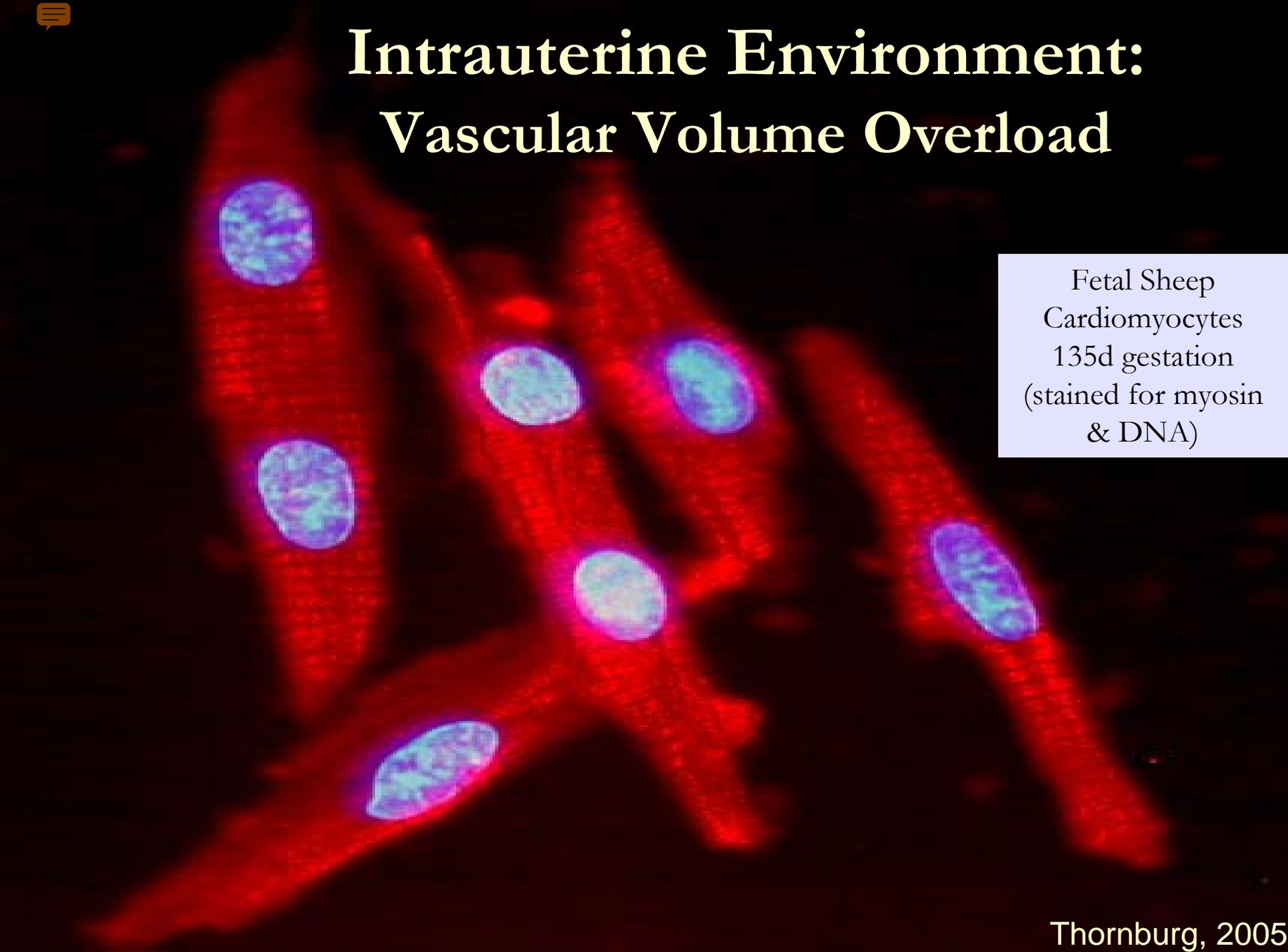
Effect of Birth Weight on Cardiovascular Mortality



Barker et. al., 1989

Intrauterine Environment: Cardiac Development

“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”

A fluorescence micrograph showing several fetal sheep cardiomyocytes. The cells are stained for myosin (red) and DNA (blue). The myosin staining highlights the striated structure of the muscle cells, while the DNA staining shows the nuclei. The cells are arranged in a somewhat parallel fashion, with some showing clear striations.

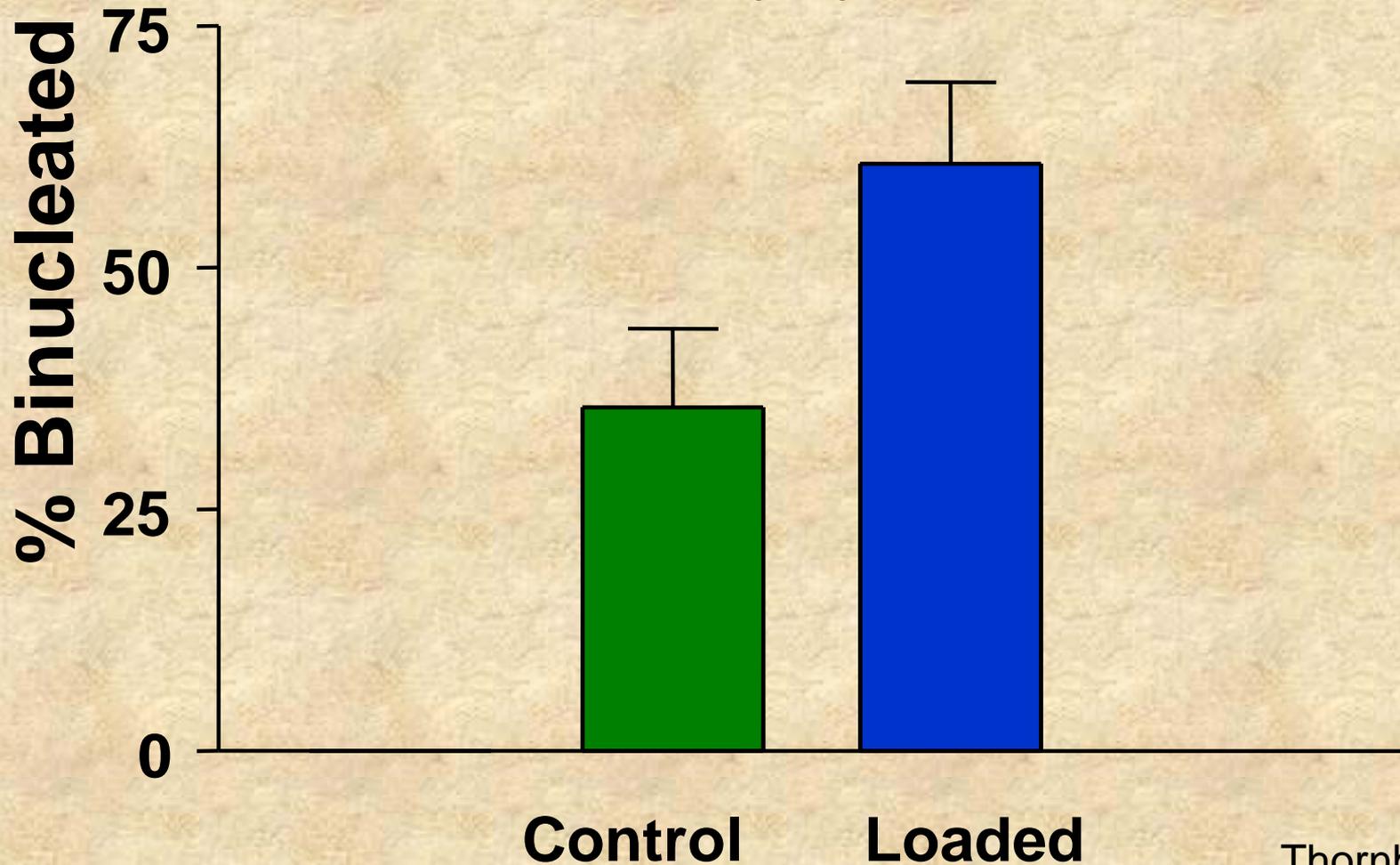
Intrauterine Environment: Vascular Volume Overload

Fetal Sheep
Cardiomyocytes
135d gestation
(stained for myosin
& DNA)



Intrauterine Environment: Cardiac Development

Effect of Volume Load on
Cardiomyocyte Binucleation





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



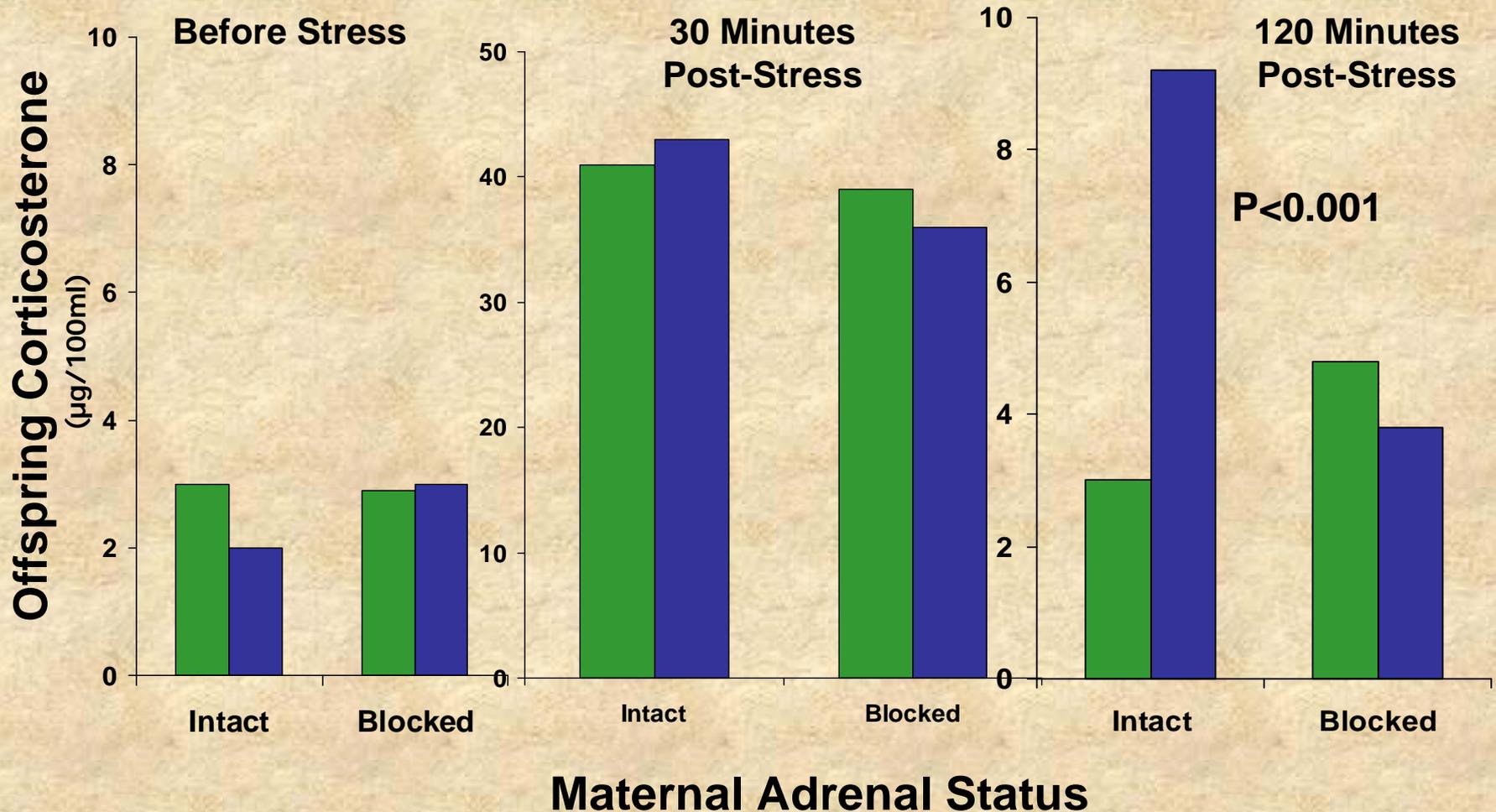
Intrauterine Environment:

Stress in Pregnancy—Offspring Response



Control

Prenatal Stress

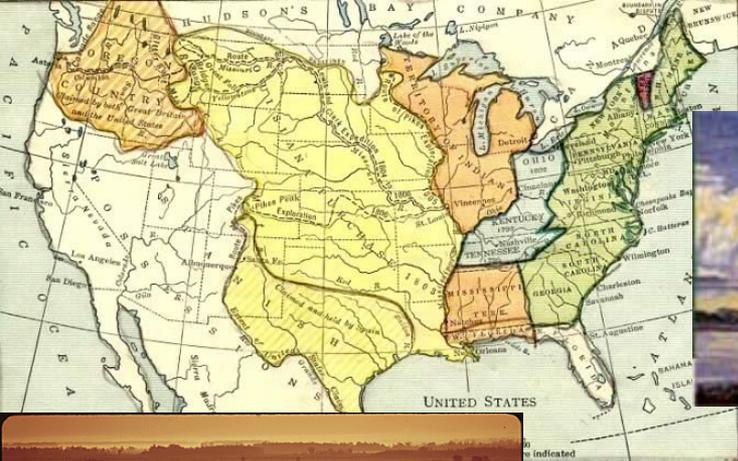


Intrauterine Environment: Stress in Pregnancy



- 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?



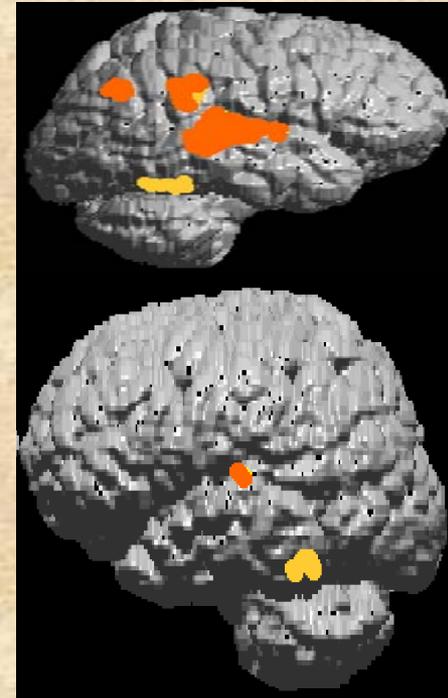


Prenatal and Postnatal Environments

Neurodevelopmental and Learning Disabilities

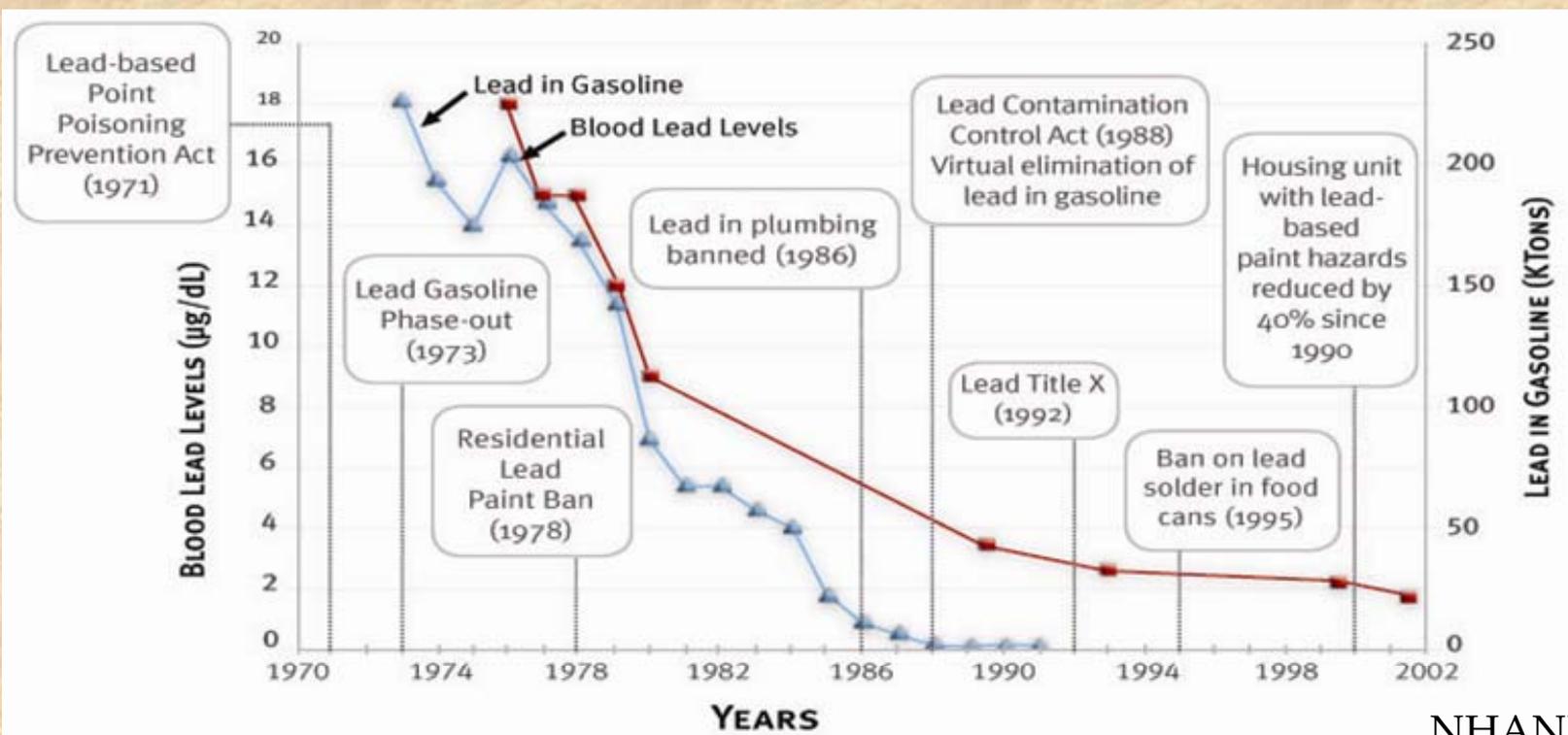


- Affect 8 percent to 17% of children ages 3-17 in U.S.
- Etiology unknown for >75%
- Many environmental associations postulated, studied
- Exposure may be prenatal, infancy (breast milk), childhood
- Examples: lead, PCBs and dioxins



Neurodevelopmental Disabilities: Lead

- Risk level lowered from 60 $\mu\text{g}/\text{dl}$ to 10 $\mu\text{g}/\text{dl}$
- Removed from paint and gasoline 1970s
- Marked decline in mean blood lead level





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



Significant Negative Effect in Infancy Only



No Association with Motor Development



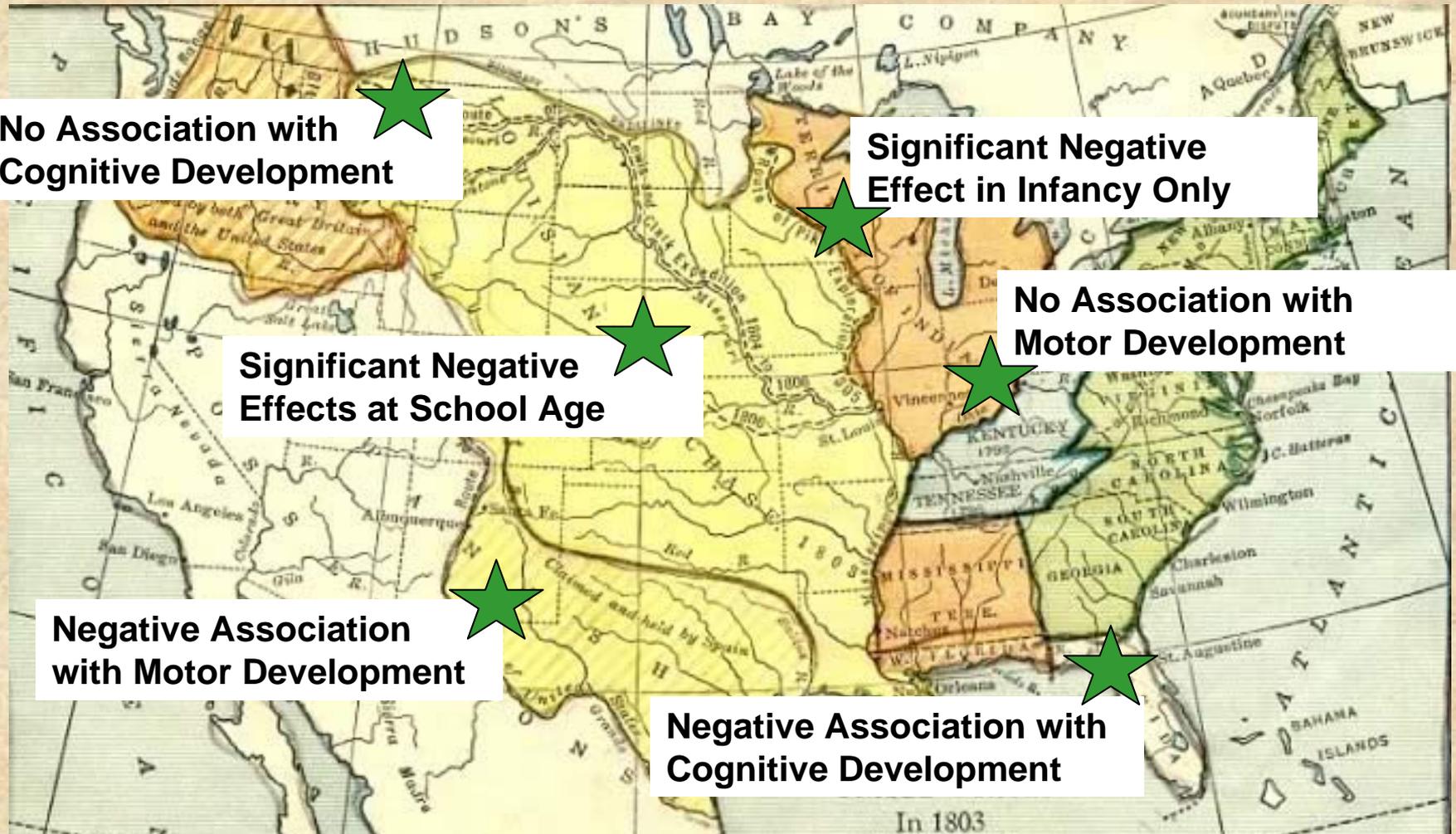
Significant Negative Effects at School Age



Negative Association with Motor Development



Negative Association with Cognitive Development



In 1803

Autism and Autism Spectrum Disorders (ASDs)

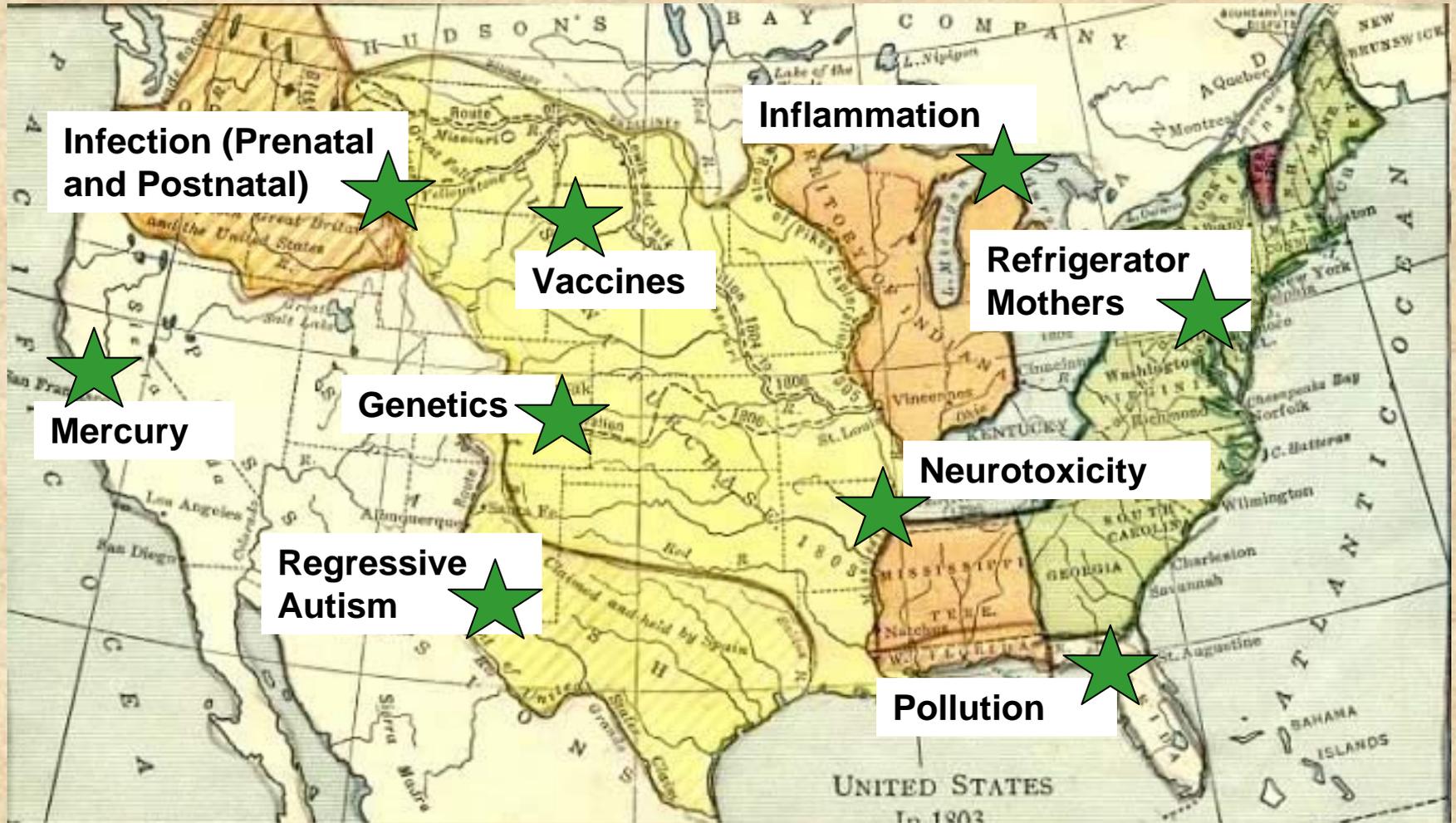


- One of the most common serious neurodevelopmental disorders
- Great public health concern—nearly 10-fold prevalence increase (up to 6/1,000)
- Great economic burden
- Reasons for increase in prevalence unclear
- Heritability of autism well established
- Chromosomal aberrations or genetic mechanism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





Autism and ASDs: Exposure-Outcome Relationship



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



PL 106-310: Children's Health Act of 2000



- (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)



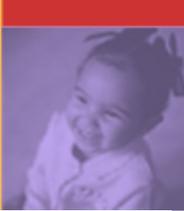
Study Concepts (cont.)

- 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'...

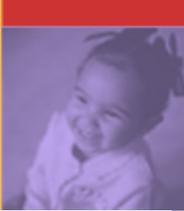


Measures Anticipated: Exposures

- 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



HEALTH GROWTH ENVIRONMENT

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

