National Children's Study
Federal Advisory Committee 14th Meeting
May 31–June 1, 2006
Marriott Bethesda North Hotel and Conference Center
Bethesda, MD

This meeting was held in conjunction with the National Children's Study, which is led by a consortium of federal agency partners: the U.S. Department of Health and Human Services (DHHS) (including the National Institute of Child Health and Human Development [NICHD] and the National Institute of Environmental Health Sciences [NIEHS], two parts of the National Institutes of Health, and the Centers for Disease Control and Prevention [CDC]), and the U.S. Environmental Protection Agency (EPA).

Day One

Welcome and Introductions

Alan R. Fleischman, M.D., National Children's Study Advisory Committee Chair, Senior Advisor, New York Academy of Medicine

Dr. Fleischman welcomed the National Children's Study Federal Advisory Committee (NCSAC) members and other participants to the 14th meeting of the NCSAC. He noted that the Study is at a critical juncture in its planning and early implementation phase.

Dr. Fleischman thanked Marion J. Balsam, M.D., NCSAC Executive Secretary, and Jessica Sapienza, M.H.S., NCSAC Committee Liaison Officer, for their work organizing the meeting.

Federal Advisory Committees. Dr. Fleischman noted the following:

- The federal government may obtain advice on long-range planning and development of programs from groups of outside experts through the formation of advisory committees.
- The Federal Advisory Committee Act (Public Law 92-463; passed on October 6, 1972) creates standard and uniform procedures governing the operation of all advisory committees.
- The function of the NCSAC, as with all federal advisory committees, is to advise—to think carefully and deeply about issues and to make recommendations and give advice.
- NCSAC meetings are generally open to the public, with specific limited exceptions.
- NCSAC advice goes to the Study Director, Peter C. Scheidt, M.D., M.P.H.; to Duane Alexander, M.D., Director, NICHD; and to the Study's Interagency Coordinating Committee (ICC).

Welcome and Update of the National Children's Study

Peter C. Scheidt, M.D., M.P.H., National Children's Study Director, NICHD, NIH, DHHS

Dr. Scheidt welcomed NCSAC members. He noted that much has happened regarding the Study since the last NCSAC meeting in January 2006, including the release of the President's budget, response to the 2007 federal budget, scientific developments, community representation and engagement activities, conferences and presentations, and planning for future activities.

Funding. The Study's funding status as of May 2006 is as follows:

- For fiscal years 2000–2006, about $50 million was allocated from existing budgets of NICHD, EPA, CDC, and NIEHS. These funds have been used for:
  - Infrastructure development—Study Plan, information management system (IMS), Coordinating Center, and seven Vanguard Centers
  - Scientific development—30 workshops, 20 scientific reviews, 16 pilot studies; Study hypotheses; exposure and outcome measures; protocol development (in progress)
- In fiscal year 2007
  - $69 million is needed to implement the Study on the current timeline
- For fiscal years 2008–2034—an average of about $100 million per year for 25 years is needed to conduct the full Study.

The President's Budget. The 2007 federal budget specifies that "No funds are included in the President's budget request for FY 2007. The Study planning activities that are ongoing under contract in 2006 will be brought to close by the end of the fiscal year. There are no plans for NIH to continue to pursue the full scale study in FY 2007."

Congressional Report Language. The fiscal year 2006 House Appropriations Committee Report (H.Rpt. 109-143) stated that the Committee:

- Remains interested in NICHD efforts to launch the Study
- Is pleased with NICHD efforts to launch the Study
- Urges the Study to include an adequate sample of children to enable examination of the health and development outcomes of children conceived with the assistance of reproductive health technologies
- Further urges NICHD to coordinate the involvement of the Department and lead federal partners such that the Study is ready for the field by no later than 2007.

Media Response. The President's 2007 budget mandates for the Study generated many media responses. From February 6, 2006, to the present, there were 50 original placements and 150 total placements. The estimated total audience for these placements is 73,430,259 (about 9.6 million print coverage and about 63 million online coverage). Concerns about the importance of the Study and the impact of the 2007 budget were highlighted in a variety of national media outlets.

In the May 6, 2006, issue of the *Los Angeles Times*, Robert W. Hahn, executive director of the AEI-Brookings Joint Center for Regulatory Studies and an economist at the American Enterprise Institute, discussed the cost-benefit relationships of medical research. He noted that:

- Benefits of medical research—whether funded by government or industry—have been long established
- Benefits of Framingham Heart Study are estimated at more than $400 billion annually
- Using conservative estimates of the effects of the Study on 10 adverse health outcomes, an independent government-funded analysis determined that the return for each dollar invested could be as much as $30 by 2030.

Scientific Developments. Recent scientific developments include efforts to transform the Study plan into the protocol—the document that specifies the data collection. Protocol development has been a major focus of Program Office activity. This development began with Working Group reports, workshops, and scientific reviews. Working teams have since been integrating outcomes and recommendations of these activities into a full protocol. There will be opportunity for interim comment by the NCSAC and other national experts, including endorsement, support, advice, and suggestions.

Community Representation on Steering Committee. On January 25, 2006, the NCSAC recommended that the Steering Committee include community representatives. The ICC endorsed this recommendation and proposed two representatives, one with a community perspective and the other with a participant perspective. On March 11, 2006, the Steering Committee agreed with this concept and discussed various approaches. The recruitment and retention working team nominated a slate of candidates for interim membership, pending a plan for permanent representation. The Study Director will appoint two interim members representing the community for the July 2006 Steering Committee meeting.

Presentations and Events. The Study was involved with the following 2006 events:
- National Center for Environmental Health/Agency for Toxic Substances and Disease Registry Director's Science Seminar (February 1)
- National Academy of Sciences Workshop on Toxicogenomics and Early-Life Exposures (February 8)
- Coordinating Council on Juvenile Justice and Delinquency Prevention briefing (March 3)
- U.S. Senate Staff briefing (March 21)
- National Hispanic Medical Association briefing (March 22)
- U.S. House of Representatives briefing (April 11)
- Indian Health Service Research Conference (April 26)
- Pediatric Academic Societies (PAS) briefing (May 1)
- Workshop on Prospects and Limitations of Very Large Cohort Studies (Abbaye des Vaulx de Cernay, France, May 17).

PAS Briefing. Part of the presentation to the Pediatric Academic Societies on May 1 focused on concerns about how the Study fits into the greater research enterprise, above and beyond meeting the primary aims of the Study. The following issues were addressed during this presentation:
- Platforms for adjunct studies
- Training for clinical and epidemiological research
- Consortia for combined research
- Public use and secondary data analysis
- Expansion of investigator-initiated research (R01).

Investigator-Initiated Research. The Study is complementary, not competitive, with investigator-initiated research (R01s):
- Funds for planning and initiation of the Study come from sources that are not available for R01s (contracts line and other agencies).
- The Study seeks to expand pediatric research enterprise and does not assume a "zero sum game."

- Small investigator-initiated projects cannot study issues that require large samples, multiple measures, and long-term follow-up.
- R01 opportunities would increase with projects leveraged on the Study as adjunct studies, which would result in a net increase in investigator-initiated research—not a decrease.

Future Study Activities. The Study's future activities include:
- Completion of the protocol
- Procurements (pending fiscal year 2007 funding)
  - Awards for additional Study Centers
  - Award for the Repository
- Implementation of the North Carolina pilot study, BEfirstNC (pending Office of Management and Budget [OMB] approval)
- 2006 presentations
  - North American Congress of Epidemiology—Panel June 23
  - Teratology Society Meeting—Panel June 26
  - American Association of Clinical Chemists—July 26
  - International Conference on Child Cohort Studies—September 12
- Possible operation under an expected continuing resolution for the 2007 DHHS budget
- Termination of Study activities without funding legislation.

After Dr. Scheidt's presentation, he responded to comments and questions that addressed the following topics:
- *Relationships among various NIH studies.* Dr. Scheidt described the histories and relationships among the National Children's Study, the AGES Study, and the Genetic Association Information Network (GAIN). About 3 years ago, Frances Collins, M.D., Ph.D., Director of the National Human Genome Research Institute; Alan Guttmacher, M.D., Deputy Director of the National Human Genome Research Institute; and Duane Alexander, M.D., Director of the National Institute of Child Health and Human Development (NICHD), discussed the possibility of a large adult study to capitalize on the sequencing of the human genome. This proposed study could be built on the sample of parents and children from the National Children's Study. The study was not funded, but a large (500,000 subjects with evenly distributed ages) adult study (AGES) was subsequently proposed. AGES cannot meet the objectives of the National Children's Study because it does not include pregnant women and early exposure factors, and has a small percentage of subjects in the 0-to-10-years age range. GAIN is a series of three epidemiological genetic studies, which are separate case control studies investigating genetic factors in relation to specific targeted diseases. AGES focuses less on environment and more on genetics; environmental measures are not specified. GAIN does not have a specific relationship with AGES, and the studies are not mutually exclusive. All of these studies could be viewed as complementary.

- *Public use data sets.* The Study will establish public use data sets for each phase of the Study as quickly as possible. NIH regulations require that such data sets be established with specified timeframes. Although the Study will collect extensive data on demographic and geographic factors, there are many existing data sets that can be used and merged with the Study's data sets. These data sets provide an excellent opportunity for more intensive, more

detailed R01 studies that can be leveraged with the Study. Mechanisms and procedures for submitting proposals for adjunct studies have been established.

- *Issue of funding.* In the event of a continuing resolution, the rules of the previous year apply. Under a continuing resolution, the Study will continue current activities, planning, and work until a fiscal year 2007 budget is approved.

Children's Environmental Health: Today's Pediatric Frontier

Duane F. Alexander, M.D., Director, NICHD, NIH, DHHS

In this presentation, which was originally given at the March 23, 2006, biweekly meeting of NIH's Institute Directors and NIH Director's senior staff, Dr. Alexander discussed the important issues of children's environmental health and the future of America's children. Environmental health is among the most critical issues for children in American today.

Evolving Frontiers. Over the past several centuries, the concepts of physical and geographic frontiers have shaped American culture and tradition. Exploration of frontiers have fostered a spirit of independence, self-reliance, and physical and mental toughness—now known as the American character. The concepts of frontiers have evolved beyond the physical and geographic, and have come to be applied to science and medicine.

Pediatric Frontiers. Many of yesterday's pediatric frontiers have been conquered. Some are still being explored, and the quest to conquer these older frontiers continues. Previous frontiers included infection, nutrition, surgery, endocrine disorders, and low birth weight. Today's primary pediatric frontier is environmental health. This frontier focuses on issues such as known agents (chemicals, viruses, radiation, drugs administered during pregnancy), suspected agents (chemical products, pesticides, food additives, violence, stress, built environments), and suspected conditions (cardiovascular disease, birth defects, learning disabilities, autism, asthma, obesity, cancer).

Importance of Studying Children. Children have increased vulnerability to environmental exposures. There are critical windows of vulnerability during development (fetal to adult). Children have immature mechanisms for detoxification and protection. Children's differences in metabolism and behavior may yield higher exposure in the same environments.

Differences Among Infants, Children, and Adults. Children are different from adults and are different at different developmental stages. Physiological and behavioral factors increase exposure in children. Some of these factors are surface area : body mass ratio, respiratory ventilation rate, drinking water intake, and rate of lead absorption.

The New Frontier of Children's Environmental Health. There are many childhood disorders without a known cause. There is a wide variety of association claims but little evidence of actual causality. Many links between environmental exposures and health and developmental outcomes have been postulated, but few of these links have been proven. The lack of proof stems from insufficient numbers of subjects in children's studies, studies that start too late in childhood, follow-up periods that are generally too short (often only once), and investigations that focus on

single agents, single exposures, and single outcomes. However, this is not how nature and the environment operate.

Crossing the New Frontier. Crossing each previous scientific and medical frontier required its own unique approach (for example, infection—sanitation, vaccines; surgery—techniques and skills; low birth weight—substitute life-support system). Crossing the new frontier of children's environmental health also requires a unique approach. In many ways, crossing the pediatric frontier will be harder than crossing earlier frontiers. Pediatric studies should:

- Begin before birth
- Be organized planned studies
- Be hypothesis driven
- Use large populations
- Use multiple simultaneous measures of multiple exposures and outcomes
- Relate to genetic constitution
- Include long-term follow-up.

Intrauterine Environment. Conditions in the intrauterine environment affect the fetus and postnatal health and developmental outcomes. Determining mechanistically what happens to the fetus to permanently alter its physiology and metabolism is key to understanding these effects.

- Birth weight is an integral part of all developmental events that occur during gestation, including nutrient supply, vascular sufficiency, infection, and stress (both fetal and maternal). Lower birth weight is associated with a higher incidence of adult cardiovascular disease, with a pronounced gender effect.
- Babies born from diabetic pregnancies show increased mortality at both ends of the birth weight spectrum. There is an increasing prevalence of obese women and women with gestational diabetes mellitus delivering babies. There is a transgenerational transmission of obesity, insulin resistance, and gestational diabetes mellitus.
- Studies of sheep fetuses have shown that intrauterine stress from mercury exposure causes increased pulmonary arterial pressure or higher volume overload, which alters the cardiac maturation program. This alteration during fetal life imparts vulnerability for later onset of cardiac disease.
- Rat studies have shown that stress during pregnancy increases maternal glucocorticoid levels, which results in long-term consequences for the fetus, such as hypertension. Prenatal stress exposure affects offspring's later responses to stress, including increased corticosterone levels and greater numbers of hippocampal corticosteroid receptors.
- Other adverse effects of maternal stress during pregnancy are unknown. Maternal stress may affect birth weight and premature delivery. Maternal stress effects on the fetus may not manifest until childhood or adulthood. The mechanisms of these effects need to be determined.
- Many long-term effects of hyperglycemia have been hypothesized, including obesity and diabetes. The most clear-cut effects are birth defects and malformations. Studies have shown that improving glycemic control early in diabetic pregnancy lowers the risk of congenital malformations.

Prenatal and Postnatal Environments. A variety of prenatal and postnatal environmental exposures may be associated with several adverse health and developmental outcomes including

neurodevelopmental and learning disabilities, autism and autism spectral disorders, childhood cancers, asthma, and obesity.

- Neurodevelopmental and learning disabilities affect 8 percent to 17 percent of children ages 3–17 in the United States. The etiology is unknown for more than 75 percent of these disorders. Many environmental associations have been postulated and studied (for example, lead, PCBs, and dioxins). Exposures may occur prenatally, during infancy (breast milk), and during childhood.
- Autism and autism spectrum disorders are two of the most common serious neurodevelopmental disorders. There is a great public health concern because of the substantial increase in reported cases. The reasons for increased prevalence are unclear. Although the heritability of autism is well established, chromosomal aberrations or genetic mechanism remain elusive. Environmental (nongenetic) factors are assumed to play important role in their etiology.
- Childhood cancers are a great public concern and high priority. The relative rarity of these cancers makes them difficult to study (242 per 100,000 for ages 0–14 years), and there are multiple types and subtypes. Clustering and a lack of heritability suggest an environmental role. Case control studies for etiological factors are problematic because exposure measures are limited and often biased, and because controls are difficult to obtain. Understanding the causal factors for cancers such as leukemia will require a large longitudinal cohort(s) with multiple exposures measured prospectively.
- Asthma is the most common chronic disease of childhood. Its prevalence has doubled in the past 20 years. Today, 1 million American children younger than 18 years of age have asthma. Pediatric asthma costs $14 billion annually. Asthma has a clear relationship to air pollution. Genetics are important but cannot explain the rapid increase in asthma's prevalence. Environmental changes—alone or in combination with genes at certain times—may likely be responsible. Asthma research needs include good measurement of (1) endotoxin load in subjects and identification of endotoxin sources and (2) sensitization of subjects to house dust mite and identification of house dust mite sources before age of 2 years when relevant immune system changes occur.
- Obesity is a significant and increasing problem in United States, with major implications for quality of health and lifespan. Obesity is associated with diabetes, cardiovascular disease, metabolic syndrome, mental health disorders, school performance, and lower earning potential. Overweight tracks from childhood through adolescence and into adulthood obesity. In the 1960s, approximately 4 percent of children were overweight. From 1999 to 2002 more than 15 percent of children were overweight. Obesity is higher among African- and Mexican-American children. The factors contributing to obesity illustrate the complexity of this multifactorial condition. An ostensibly obvious cause is energy intake exceeding energy expenditure. Potential societal contributions include diet, physical inactivity, potential biological contributions, and genetic contributions. Elucidation of obesity etiologies is important to enable appropriate interventions, which requires (1) assessment of maternal anthropometric and metabolic status during pregnancy, (2) accurate dietary and nutritional assessments over time, and (3) measures of family behavior as well as child behavior.

Facing the New Frontier. Crossing each geographic or medical frontier has required its own unique approach. The new frontier of children's environmental health requires its own unique approach that includes organized planned studies with large populations. These pediatric studies

should begin before birth, investigate multiple simultaneous measures of multiple exposures and outcomes, relate exposures and outcomes to genetic constitution, and have long-term follow-up. The rewards for crossing the new frontier of children's environmental health will be great.

After Dr. Alexander's presentation, comments and questions addressed the following topics:

- *Study support.* NIH Director Elias A. Zerhouni, M.D., was an early supporter of the Study. He has expressed his support of the Study to the Domestic Policy Council, OMB, and the White House. He has argued for funding of the Study and continues to support the basic scientific purpose of the Study, even without funding in the 2007 federal budget. Before the House Appropriations Committee, Dr. Zerhouni testified that the decision to terminate the Study was strictly budgetary. There were concerns about both the Study's immediate costs and the long-term costs. By comparison, the cost of AGES is four times greater than the Study's cost, and the timeframe for AGES is shorter than the Study's timeframe. The Human Genome Project cost about $3 billion over a 12-year period. The Women's Health Initiative cost is a little less than $1 billion over a 10-year period.

- *Future presentation.* Antoinette P. Eaton, M.D., suggested that Dr. Alexander be asked to present his ideas about children's environmental health at the fall meeting of the American Academy of Pediatrics (AAP).

Panel Discussion: The National Children's Study—Big Science to Cross the Environmental Health Frontier

Dr. Fleischman, Advisory Committee Chair, introduced the panel by explaining that these national leaders in important scientific areas were asked to review documents prepared by the National Children's Study Program Office staff describing the strategies, goals, and methodologies that have been used in protocol development. (The documents were distributed to Committee members prior to the meeting). He requested that these consultants provide candid assessment of the strengths and weaknesses of the Study plans and provide recommendations to the Study.

Gene-Environment Interactions

Jeffrey C. Murray, M.D., University of Iowa, Children's Hospital of Iowa

Genetics (1) can inform investigators on what the environmental risks are to children's health, (2) can identify the specificity of those environmental risks, (3) can identify high-risk population groups, and (4) allows the targeting of environmental components in the most powerful way possible to improve and maintain children's health.

The study of simple Mendelian traits can identify single genes for traits that are inherited as dominant or recessive. Single-gene Mendelian disorders can provide good models for more complex disorders such as diabetes, hypertension, obesity, and asthma, which are unlikely to be caused by an abnormality in a single gene or by a single environmental factor. Identification of rare single-gene abnormalities causing particular clinical phenotypes such as hemoglobinopathies, sickle cell disease, and cystic fibrosis can be used to inform about the more

complex abnormalities. Confounders of simple Mendelian traits include expression, penetrance, epigenetics, mosaicism, new mutations, stochastic effects, and the environment.

The previous paradigm that a gene makes a protein—one gene, one enzyme—is no longer held true. The classical "gene" structure is now inoperative, with the exact definition of gene being constantly revised. Concepts of the postmodern gene include:

- Extended length (much longer than previously conceived)
- Regulatory elements separated by hundreds of thousands or even millions of base pairs
- Regulatory elements partitioned across chromosomes
- Posttranslational modifications (such as the addition of sugar moieties to proteins).

The Study's use of global gene expression as an important method of assaying risks in child health may be confounded by new developments. For example, understanding the expression of a particular gene in a particular tissue is dependent on how the gene is defined. Geneticists once estimated 100,000 human genes but have since revised the number to about 23,000. New discoveries that small ribonucleic acid (RNA) elements may function as "genes" may lead to further revisions of gene estimates. Other new confounders include:

- Mitochondrial deoxyribonucleic acid (DNA), including somatic changes in mitochondria
- RNA issues
- MicroRNAs
- Extensive transcription of DNA into RNA
- Transfer across generations of more than just DNA sequences
- Statistical analysis (the need for critical analytical tools to mine enormous amounts of data).

As the cost of sequencing the human genome continues to decrease, the Study could, conceivably, explicitly define the DNA component of the genome for every participant. Genotyping would no longer rely on single nucleotide polymorphisms (SNPs) and may be able to reliably determine all of a person's genetic variation. As the costs for determining SNPs continues to drop, the Study could determine a comprehensive genomewide association on all Study participants in the near future. Association approaches can identify common variants that affect large segments of a population when those common variants are responsible for disease. However, association approaches cannot identify those cases in which individual mutations arise in particular families predisposing them to disease.

Although there may be distinct genotypes for a particular enzyme, enzymatic activity within genotypes may vary broadly. Therefore, the Study needs to consider how narrowly or discretely it will define genotypes given the reality of pharmacogenetics and pharmaceutical responses that occur across a continuum.

New approaches to investigating heterogeneity in complex traits compare genetic load with environmental effects. As genetic load decreases and environmental effect increases, multifactorial components play a greater role in disease expression. The challenge for the Study is to determine the individual effects of multifactorial components (that is, "to investigate the separate and combined effects of environmental exposures…as well as gene-environment interactions on pregnancy outcomes, child health and development, and precursors of adult disease").

The Study plan is strong because it can:
- Stay open to evolving technologies as the understanding of the "gene" changes
- Measure the environment and the gene-environment interaction
- Provide high level bioinformatics and analytic capability
- Quickly provide public data sets to encourage a wide range of hypotheses testing and yet preserve subject anonymity.

From a genetics perspective, the Study has several strengths:
- Large number of subjects for investigating common diseases
- Strong case/control approach
- Strong ties to extensive environmental data
- Long-term storage of biologic samples allows for application of newly developed/unanticipated technologies and assays for as-yet unconsidered genetic components.

Concerns from a genetics perspective:
- Challenges of tissue sampling and storage (live versus inactive tissue; timing, location, processing, and storage)
- Tissue sources and the need for surrogate tissue sources
- Measures of gene effects as continuous variables
- Limited emphasis on family studies that limits the potential to measure complex traits.

Dr. Murray concluded that the Study plan is strong from the perspective of genetics and recommended that the Study consider collecting genetic information from siblings, parents and grandparents (particularly on the mother's side) to enhance the power of the Study to identify complex traits.

Social-Behavioral Determinants: Comments on Study's Neurobehavioral and Psychosocial Protocol

Deborah A. Phillips, Ph.D., Georgetown University

The Study has the potential to leave both an intellectual and practical legacy. It will be a national and international resource because it:
- Blends epidemiological, genetic, and developmental frameworks and methods
- Focuses on mechanisms as the central topic of investigation and has the direct capacity to inform policy and practice
- Gives equal weight to biologically and environmentally derived risks and protective factors, including interactive and cumulative effects, whether offsetting or exacerbating in nature
- Joins similar data sets developed, or still being developed, in other countries.

The Study will identify the modifiable influences that shift development trajectories, either positively or negatively, and will also identify the most vulnerable children, which is critical for targeting appropriate and effective resources. Fairly blunt indicators such as poverty and developmental delays are currently used to target resources. The Study's prospective, longitudinal design provides an opportunity to address critical issues of developmental timing;

unfolding of susceptibilities; exposures; intervening, moderating, and mediating factors; and positive and negative outcomes (clinical and subclinical, as well as "beating the odds").

The Study's protocol addresses almost all of the research recommendations from the Institute of Medicine's study From Neurons to Neighborhoods: The Science of Early Childhood Development, which concluded the following:

- What happens during the first months and years of life matters a lot, not because this period of development provides an indelible blueprint for adult well-being, but because it sets either a sturdy or fragile stage for what follows.
- "Zero to three" begins too late and ends too soon.
- The most important questions concern how environments influence the expression of genes and how genetic makeup, combined with children's previous experiences, affects their ongoing interactions with their environments.
- Parents and other regular caregivers in children's lives are "active ingredients" of environmental influence, and children's early development depends on the health and well-being of their parents.
- Abundant evidence from the behavioral and the neurobiological sciences has documented a wide range of environmental threats to the developing central nervous system.
- The greatest dangers arise from the combined and cumulative effects of multiple hazards.
- The growing racial, ethnic, linguistic, and cultural diversity of the early childhood population requires that all early childhood programs and medical services (and research projects) periodically reassess their appropriateness and effectiveness for the wide variety of families they are mandated to serve (study).

The Study has the potential to address the Neurons to Neighborhoods study's recommendations for future studies by examining:

- How experience is incorporated into the developing nervous system and how the boundaries are determined that differentiate deprivation from sufficiency and sufficiency from enrichment for different children who are reared in a wide variety of environments
- How biological processes, including neurochemical and neuroendocrine factors, interact with environmental influences to affect the development of complex behaviors, including self-regulatory capacities, prosocial or antisocial tendencies, planning and sustained attention, adaptive responses to stress, and working memory
- The dynamics of gene-environment interactions that underlie the development of behavior and contribute to differential susceptibility to risk and capacity for resilience, including (1) differential birth outcomes associated with exposure to prenatal hazards, (2) emergence of adverse outcomes in some children but not others in response to stressful rearing conditions, and (3) individual differences in susceptibility to diseases that manifest across development
- The mechanisms that underlie nonoptimal birth outcomes and developmental disabilities and their implications for developing specific intervention strategies to modify developmental trajectories
- The available tools for measuring important but generally neglected early developmental outcomes for use in both basic and evaluation research in an effort to improve these tools.

The strengths of the Study's neurobehavioral and psychosocial protocol include:

- Remarkably careful and systematic selection of constructs and measures that are sensitive to effects of exposures; able to capture important individual differences in age, income, racial, and ethnic groups being assessed; practical to administer in the context of the Study; and psychometrically valid both within and across developmental periods
- Tiered approach to assessment, with more detailed assessments of certain subsamples such as peer interactions in childcare/prekindergarten or children at temperament extremes and/or with special needs.

The Study needs to consider greater emphasis on addressing several critical elements:
- Capturing peer environments, particularly social hierarchies, bully/victim dynamics, neglect/isolation—which can predict both diagnostic and predictive outcomes
- Substudies of peer interactions in childcare, prekindergarten, or laboratory settings, including children at temperament extremes and/or with special needs
- Poor quality childcare as an additional "known exposure of high frequency"
- The possibility of embedded (adjunct) studies of siblings, kin, and stepparent relationships, interventions, and those conducted by isolated sites versus clusters
- Use of administrative/record data to confirm educational histories of parents and parent history of antisocial and/or high-risk behaviors (including mental health and crime).

Dr Phillips concluded that the Study design is strong from the perspective of psychological and social determinants of health outcomes as well as the interaction between genetic factors and psychosocial ones. She recommended additional measures of group and peer interactional factors on outcome.

Utility of the Study's Environmental Exposure Assessment

P. Barry Ryan, Ph.D., NCSAC Member, Emory University Rollins School of Public Health

The Study results will lead to a greater understanding of how children experience environmental exposures and how those experiences change during a child's development into adulthood. The many dimensions of a child's environmental exposures include broad levels such as community to narrower levels such as household and the individual. The Study's exposure analyses will improve the state of science in assessing relationships by characterizing the sources of pollution/contaminants, assessing levels of exposure, measuring individual doses of exposure, and determining health effects and outcomes.

The general approach to exposure assessment is through the triad of (1) environmental (chemical, physical, psychosocial) measurements; (2) biological measurements; and (3) questionnaires, diaries, and observations.
- Questionnaires can provide data such as type of residence, pesticide use in the residence, and presence of lead paint in the residence but cannot provide data on all exposures.
- Measurements of chemicals/pollutants in air, water, soil, or food can characterize environmental conditions that might be associated with exposures.
- Questionnaires and environmental conditions provide only indirect measures of exposure.
- Biomarkers such as lead in blood or pesticide metabolites in urine can provide direct evidence of exposures and are generally considered the gold standard for assessing exposures, but they do not indicate the potential health effects of environmental exposures.

- Variations in an individual's ability to metabolize or detoxify environmental contaminants such as lead and pesticides may be reflected in biomarkers.
- Biomarkers may also reflect an individual's susceptibility to environmental exposure.

Three environmental exposure domains that the Study will assess are as follows.

- **Physical.** Characterization will include information on the individual, home, neighborhood, and city or region. Information gathered by questionnaires will include demographic information, region of the country, and likely exposure sources (for example, industrial versus agricultural).
- **Chemical.** Sampling will include persistent organic compounds, nonpersistent nonvolatile organic compounds, nonpersistent semivolatile organic compounds, nonpersistent volatile organic compounds, bioaccumulative inorganic chemicals, nonbioaccumulative inorganic chemicals, and criteria air pollutants.
- **Biological.** Sampling will include biomarkers of exposure, effects (such as markers of change, early effects, and disease), and susceptibility (genetic markers such as gene polymorphisms).

The uniqueness of the Study's data collection efforts is to test hypotheses by collecting target analytes and examining the associations between analytes and related health outcomes (for example, allergens and asthma). Environmental exposure studies have historically focused on a single contaminant, single medium, and single time period. The Study is interested in more complex investigations that include simultaneous multiple contaminants, multiple media, and multiple long-term time periods.

Because of temporal variations in exposures, longitudinal studies are imperative. Children's sensitivity and susceptibility to exposures will vary over time. During its repeated household visits and examinations of children over a 21-year period, the Study's environmental assessments will:

- Supply invaluable information on trends in exposure, temporal variabilities in exposure, and the associations between such variability and health outcomes
- Be invaluable in assessing health outcomes associated with environmental exposures to children
- Reveal some measures of exposure (for example, biomarkers) that may be transient.

The strengths and benefits of the Study's approach to exposure assessment can be summarized as follows.

- The Study's model of longitudinal assessments of exposure allows for better exposure estimates for epidemiology. Strengths of the model include the ability to assess secular trends in exposure, seasonal patterns in exposure, effects of weather, pollutant/contaminant source variability, short- and long-term effects of control strategies, and effects of new exposure sources and patterns.
- The "power" of the Study's design for longitudinal assessments of exposure includes proper selection of participants, maintenance of the cohort, and accounts for changes in sample size.
- The Study offers an incredible, and perhaps unique, potential to increase scientific knowledge of the relationships among sources, exposures, doses, and effects on health and developmental outcomes.

- The combination of questionnaire, environmental, and biological measures will provide a complete understanding of "true" exposure.
- The Study's longitudinal nature affords determination of the convolution of differential exposures and susceptibilities over life stages, which is essential in understanding effects of exposure.

Dr. Ryan concluded that the Study plan for assessment of environmental exposures is strong, combining aspects of direct measurement, biomarkers, and questionnaires. He reminded the planners of the challenge of exposure assessment continually from conception to adulthood and the need to frequently measure chemicals in the environment because of the transient nature of some chemicals.

Exposure Uncertainty and Dose/Response Modeling

Louise Ryan, Ph.D., Harvard School of Public Health

The Study's concept of environmental exposure assessment involves the triad of (1) environmental (chemical, physical, psychosocial) measurements; (2) biological measurements; and (3) questionnaires, diaries, and observations. The Study cannot, however, measure everything on all subjects, at all times because of the complexity of measuring exposures as well as the high costs and subject burden. Good statistical methods can make optimal use of all available data to measure exposures as best as possible without undue costs and burden and without measuring everything on all subjects while maintaining sufficient analytical power.

Dr. Ryan has been working with Battelle to assist the Study to develop new methods to address this problem. She reported on this effort to date.

In terms of environmental epidemiology, there are two classical paradigms for approaching the complexity of exposure assessment:
- Small high-intensity studies with extremely good quality exposure measurements and very focused outcomes
- Studies with scaled-back exposure measurements, using a reliable yet practical exposure measurement and larger number of subjects to improve the power to detect dose-response relationships; a smaller, more intensive study of a subpopulation may be used to "validate" the chosen approach.

Two statistical frameworks can be used for environmental exposure assessments:
- "Gold standard" exposure measurements, which are often too expensive to measure in everyone, particularly in larger studies
- No gold standard, but multiple types of surrogates that can be used to inform about "true" exposure.

Logistic regression models can be used to estimate exposures by combining detailed information on a subsample with less detailed, slightly inaccurate information from an entire sample. For example, a full composite exposure assessment (the gold standard) of 3,000 children can be compared with a dietary assessment (the surrogate) of 100,000 children. A logistic regression analysis can be performed on the subsample of 3,000 children to correlate the gold standard to

the surrogate measure. This analysis can be formulated as a missing data problem using several approaches such as weighted estimate equations, pseudo-likelihood, and maximum likelihood. Maximum likelihood can regain much of the lost information if the poor exposure measurement (dietary assessment) has a decent correlation with the good measurement (the full assessment). The higher the correlation between the full assessment and the dietary assessment, the more information can be recaptured. Measuring a good surrogate exposure can be almost as accurate as directly measuring an exposure of interest.

Implications for analysis are as follows.

- When selection is nonrandom, naïve analysis of a subset can be biased (not just inefficient).
- As long as the chance of being selected depends on observed data, proper statistical analysis is (relatively) straightforward.

A software tool has been developed by Battelle that can determine optimal design strategy under a variety of settings.

- Assuming a maximum likelihood analysis approach, the tool can help pick the selection strategy that minimizes the variance of the estimated parameters of interest.
- There is a need to add appropriate constraints such as limits on number of subjects, total cost, and analytical power.
- The tool can distinguish costs of sampling from costs of assays.
- The user specifies types of outcomes, exposures, and surrogates.

In the conventional approach (gold standard-surrogate measure correlation), study investigators know how to analyze a subsample that has been chosen in a particular way. With the Battelle tool, the design approach can be reversed. For example, investigators may want to achieve a certain analytical power or may want to spend a certain amount of money on a study. How do the investigators decide what subsample to measure intensively and how the subsample should be measured? To determine the design strategy using the Battelle tool, investigators can specify the types of exposures to be measured, which one is considered the gold standard, the total cost for measuring exposures, as well as the individual costs for each measurement.

Complexity of complete exposure assessment precludes doing it on every subject in a study. Careful statistical analysis facilitates combining detailed exposure assessment on a subsample with a less accurate, but cheaper and practical assessment on the entire cohort, avoids bias associated with use of error-prone measure, and gains power.

Dr. Ryan concluded that many interesting directions for environmental exposure assessments and dose-response modeling remain to be explored, including modeling options, time-varying covariates, analytic approximations to speed computations, and analysis components. These creative mathematical approaches may be very useful to the Study.

NCSAC Discussion and Recommendations/General Discussion

- *Social-behavioral measures for the Study protocol.* Noting that the Neurons to Neighborhoods study described social relationships as the fundamental mediators of environmental effects, Bernice A. Pescosolido, Ph.D., suggested that the social-behavioral

determinants outlined in Dr. Phillips' presentation be incorporated into the Study's protocol. Dr. Phillips commented that relatively inexpensive approaches can capture some aspects of children's social relationships. She recommended that instead of focusing on quality of childcare, the Study could focus on peer interactions within childcare settings. Using questionnaires, childcare providers can provide observational information on social relationships and peer interactions.

- *Radiation exposure measurements.* In response to a question from Jeffrey Long, Ph.D., about measuring radiation exposure, James J. Quackenboss, M.S., explained that environmental exposure measures were selected to address specific Study hypotheses. Because of its relatively low incidence in children, cancer is not a focus of a Study hypothesis. Therefore, ionizing radiation, as well as electric and magnetic fields, at present, are not planned to be measured. However, the Study may decide to measure radiation exposure in the future or link to other available databases that have these measures.

- *Multigenerational data for genetic analyses.* Dr. Scheidt noted that the Study will collect samples and genetic data from study participants, their parents, and, to the extent possible, their siblings. In contrast, the AGES Study initially included grandparents but later determined that association studies should preclude family members. Dr. Scheidt asked whether (1) the Study might benefit from this approach, with the difference being association versus gene discovery; (2) it is possible to examine both gene association and gene discovery; or (3) AGES should reconsider its strategy. Dr. Murray explained that the Study would enroll 100,000 children and include parents and siblings. Because AGES intends to enroll 500,000 people, greater numbers of relatives that are included would result in smaller numbers of individual case families. Dr. Long commented that the inclusion of family members does not detract from association studies. If the Study is interested in studying maternal effects on the fetus, then it should specifically include maternal grandparents.

- *Adaptability and flexibility of the Study's sampling design.* Alan M. Zaslavsky, Ph.D., said that the Study needs to manage the sample in a relative complicated manner but also be adaptive and responsive to preliminary results by adjusting the sampling design as necessary.

- *Hidden costs.* David J. Schonfeld, M.D., said there may be hidden costs if the Study includes measures of exposure for individual children that are not as precise or accurate as the gold standard measures. He explained that relatively inaccurate results reported to a participant's family may trigger a subsequent more accurate but more expensive measure. The Study would have to bear the costs of the initial less expensive, less precise measure as well as the subsequent more expensive, more precise measure. The costs of the original measure and the costs of the consequence should be incorporated into Study modeling.

- *Impact of Study results on policy development.* Helen DuPlessis, M.D., M.P.H., asked whether the Study will involve translational researchers and other professionals who will interpret Study results that have implications for program and policy development of different systems and sectors—medical, civic, environmental, public health—in an effort to support optimal health and development. Dr. Fleischman replied that the NCSAC has committed itself to being accessible and available to the Study as the Study generates

important information and important evidence about outcomes and larger health policy questions. The NCSAC is committed to helping to translate Study findings into program and policy recommendations as data become available in the future.

- *Study cost estimates.* Myron Genel, M.D., asked Dr. Scheidt about the Study's total cost estimate and annual cost estimates. Dr. Scheidt answered that in 2003 the Study's total cost was estimated to be about $2.7 billion over the 25 years of the Study. Modeling of the costs of the visits and recruitment show that the annual costs will be higher during the first 8–9 years of the Study. After this period, the annual costs are estimated to be about $90 million. Dr. Scheidt explained that the Study must now be fit into what is logistically, politically, and economically feasible.

- *Central Study oversight and monitoring.* Peggy M. Shepard asked how the Study will centrally monitor ethical issues such as adverse events, interventions, and confidentiality of genetic information. Dr. Fleischman said that there will be monitoring at multiple levels. Each Study site will have responsibility for such issues with oversight by institutional review boards. The National Children's Study will have standards for confidentiality of all information; a data and safety monitoring board will review adverse events; the NCSAC's Ethics Subcommittee will be available to assist the Study with policy development; and there will be policies and procedures promulgated by the Steering Committee. In addition, the Coordinating Center is contractually required to provide specific oversight of quality assessments in all aspects of the Study. A detailed quality assessment plan is currently being developed through a pilot project.

Update on Protocol Development

Ruth A. Brenner, M.D., M.P.H., Director, Study Protocol Development

Dr. Brenner presented an update on the Study protocol and updates from the protocol development working teams.

Overview of the Study Protocol. Dr. Brenner reviewed the Study concepts, development of the protocol from 2000 to 2005, and the basic framework of the protocol. She described the approach for the Study's probability sample and the recruitment goals. The Vanguard Centers have a 5-year enrollment period, with a goal of 250 births per year and a total of 1,250 live births. The additional sites will recruit for 4 years with a goal of enrolling 1,000 live births per site. All Study sites are expected to enroll the same number of births per year (250). There will be wide variations in population density and number of births per year across the 105 Study sites. This variation is reflected across the Vanguard Center sites. As a result, some sites will enroll a larger proportion of the births, whereas other sites will enroll a smaller proportion. Variations in population density have implications for defining segment boundaries, use of stratification, and the number of segments that are selected at each Study site.

Segment Selection. The first step in defining the segments is to divide the Study sites into definable segments. The segments need not have the same number of births from one site to another. Within a site, the number of births per segment should be about equal. The segments will be geographically contiguous.

Number of Segments. The Program Office consulted outside experts to address issues related to clustering and multilevel modeling. These issues were discussed with the Sampling Working Team, which recommended between 10 and 20 segments per site (50–100 births per segment over the 4-year period). The Program Office received additional input from each of the Vanguard Centers. It was concluded that more segments provide better coverage and less clustering, with implications for cost and community involvement. The number of segments at the Vanguard Center sites range from 7 to 20. The steps for segment selection are to:

- Determine number of segments to be sampled in each site
- Determine stratification variables for segments for each site
- Define segments (Coordinating Center and Vanguard Centers)
- Evaluate definitions (Vanguard Centers)
- Select segments (Coordinating Center)
- Evaluate selection (Coordinating Center and Vanguard Centers).

Stratification. The levels of stratification are limited by number of sampled segments. If one segment is sampled per stratum within a Vanguard Center site, then the number of strata equals the number of sampled segments. Geography is the primary stratification variable for nearly all sites. Within the geographic units there may be room for one or two other classifications. For example, the Brookings, Yellow Medicine, Pipestone, and Lincoln counties (BYPL) Vanguard Center site has no strata and has 11 segments, 7 of which will be sampled. For the other sites, the number of strata defined by geography ranges from 10 to 20, which guarantees dispersion of segments across each Vanguard Center site. Other variables include income distribution, race, and ethnicity.

Comparison of Vanguard Center Sites. The Duplin County, NC, and Montgomery County, PA, sites will each select 10 segments. About 36 births are expected per segment. It is anticipated that Duplin County will have 800 births. The county's area is 819 square miles; 20 segments are defined for the county. The segments will be grouped into pairs, with one segment selected from each pair. It is anticipated that Montgomery County will have 9,400 births. The county's area is 482 square miles; 240 segments are defined. The segments are grouped into 10 strata, with one segment selected from each stratum.

Timeline for Defining the Segments. Three Vanguard Center sites (BYPL, Duplin County, and Montgomery County) have received materials related to segment definition. The remaining four sites will receive their materials by the end of June. Suggested adjustments in boundaries from the Vanguard Centers will be sent back to the Coordinating Center and the Sampling Working Team within about 2 months.

Protocol Development Working Teams. The teams formed after the award of contracts. Teams include primarily members from the Program Office, the Vanguard Centers, and the Coordinating Center as well as other experts. The teams are:

- Sampling
- Recruitment and Retention
- Neurocognitive and Social-Emotional Outcomes (suggested measures)
- Environmental Specimens (suggested measures)

- Biological Specimens (suggested measures)
- Physical Examinations (suggested measures)
- Questionnaire (suggested measures)
- Human Subjects
- IMS Development.

Recommendations from the Working Teams. The teams recommended measures based on the hypotheses and other previous work (for example, scientific literature and workshops). Criteria were established in each group. For questionnaires, the teams considered validity, reliability, and subject burden. For biological measures and samples, the teams considered reasonable volume, collection appropriate in the visit setting, and reasonable approaches to collect from a healthy population (no more than minimal risk). The Coordinating Center compiled the measures and recorded the clear rationales behind the selection of each measurement.

Results from Recommendations. The working teams developed an excellent, comprehensive set of measurements, which would allow the Study to fully address all of the proposed hypotheses. However, as expected, the recommended measurements were deemed to be too burdensome and too costly. In addition, the visits were deemed to be too long and the costs too high, particularly in the early years of the Study.

Approach to Trimming the Protocol: Length of Visits. The goal is to shorten the visit length to no more than 3–4 hours of data collections per face-to-face contact (consistent with Study Plan). The Program Office and protocol development working teams examined the time required for activities such as questionnaire, samples, specimens, and examination. The new approach assumes two data collectors per home visit, with increasing amounts of parallel data collection as participants become more familiar with the Study. Several approaches to trim questionnaires have been considered.

Approach to Trimming the Protocol: Costs. The goal is to limit the total costs to no more $2.7 billion total. Because of the particularly high costs in the Study's early years, analyses of biological and environmental samples will be deferred. The Program Office is considering awarding contracts for new Study Centers in a staggered fashion.

Projected Timeline. The projected Study timeline is:

2005–2007	Start-up phase for Vanguard Centers
2006	Completion of the Study protocol
2006–2007	Requisite reviews and approvals (OMB, per review, institutional review boards)
2006–007	Post Requests for Proposals for additional Study Centers*
2007	Award additional Study Centers (contracts)*
2008–2012	Enroll participants and begin the full Study at Vanguard Centers*
2007–2008	Start-up phase for additional Study Centers*
2009–2012	Enroll participants and begin full Study at additional centers*
2009	First Study results become available (methods, pilots, preliminary)*
2013–2033	Hypothesis-specific data analysis; publish data; public-use data sets.*

*Pending funding for fiscal year 2007

After Dr. Brenner's presentation, she responded to comments and questions that addressed the following topics:

- *Information on siblings.* The Study is currently focusing on the measurements for mother, father, and child participants. Measurements on siblings and grandparents may possibly be included, perhaps as a random subset, but these measurements are not currently being planned.

- *Home visits.* Allotting 4 hours for a home visit may not be realistic. Shorter, more frequent visits may be a better approach, which may improve retention rates. Various protocol developers and other experts have expressed differences in opinion about what constitutes reasonable burden for face-to-face session times (from 2 to 4 hours). The Study protocol is currently considering an average home visit time of 3 hours. Some of this time will be allocated to collecting environmental and biological samples. If home visits become longer than planned (for example, from 3 hours to 6 hours), the Study participants will find it necessary to take a day off of work to accommodate the visits. Bias may be introduced if participants are unable to take days off work and unable to participate in the home visits. Requiring the participants to take days off of work to remain in the Study would present both practical and ethical issues.

- *Number of data collectors.* The Study will devote two data collectors per home visit. The data collectors will conduct parallel activities during the visits, and these activities will increase as the participants become more familiar with data collection. Attempts will be made to keep the data collectors consistent from visit to visit, for as long as possible.

- *Feasibility of sampling approaches.* IMS and management of the data collectors will be challenged to handle a variety of protocols and follow varied routines as data are collected from home to home and across Study participants. Subsampling and tiered approaches to sampling will need to be carefully considered by the protocol development teams. The IMS needs to know what tests have been conducted prior to each visit, and decisions will need to be made about what measures can be collected at subsequent visits. Algorithms will need to be designed for analyses of missing data and samples.

- *Homogeneity of segments.* Because the Study is a national probability sample, densely populated urban areas—with varying degrees of socioeconomic status—were not specifically chosen. Populations within segments will not be homogeneous, and areas of poverty will be included within segments. The sampling is designed to have about the same number of births within each selected segment, although birth rates may vary from neighborhood to neighborhood within segments. Neighborhoods within segments will vary by average income and racial/ethnic composition. The sampling approach is designed to protect against overrepresentation or underrepresentation of any specific populations.

Update on Recruitment, Retention, and Community Engagement

Chris Cronk, Sc.D., Co-Principal Investigator, Waukesha Vanguard Center

Dr. Cronk described her professional background and how she became involved with the Study's recruitment, retention, and community engagement activities. The purpose of her presentation was to introduce and summarize a draft document titled Recruitment, Retention and Community Engagement in the National Children's Study. The core of this document was drafted by a small group composed of members from the Program Office, the Coordinating Center, and the Vanguard Centers. From March 2006 through May 2006, the document was evaluated and revised by representatives from all Vanguard Centers.

Purpose of the Document. The purpose of the recruitment, retention, and community engagement document is to (1) present guiding principles and a framework for partnering with communities to support the study and (2) provide guidance that will help standardize activities across sites while allowing variation responsive to individual communities.

Design. Because of the Study's complexity and length, it will be essential to have community buy-in. In addition to participant data, the Study anticipates collecting data from day care centers and occupational venues as well. The Study Plan and the request for proposals (RFPs) for the Vanguard Centers and the Coordinating Center recognize the importance of community engagement.

Diversity of Study Site Communities. The Study sites were selected to be representative of the diversity of the overall U.S. population. This diversity is reflected in the composition of the Vanguard site communities, but the Vanguard sites are not a random sample of the U.S. population.

- The Vanguard sites are 65 percent White, 12 percent Asian, 10 percent other, 8 percent African American, 4 percent two or more ethnicities, 0.6 percent American Indian, and 0.3 percent Hawaiian/Pacific Islander as compared to the overall U.S. population that is 76 percent White, 12 percent African American, 5 percent other, 4 percent Asian, 2 percent two or more ethnicities, 0.8 percent American Indian, and .01 percent Hawaiian/Pacific Islander.
- The combined Vanguard sites are 22 percent Hispanic compared with 19 percent Hispanic for the overall U.S. population.
- Median annual household income of the Vanguard sites ranges from $30,000 to $63,000 compared with the median annual household income of $42,000 for the overall U.S. population.

Community-Based Participatory Research. Although the Study has not committed to a strict community-based participatory research (CBPR) approach, there are many CBPR principles that are applicable to the Study. Three of these key principles are to (1) recognize community as a unit of identity, (2) build on strengths and resources with the community, and (3) facilitate collaborative, equitable involvement of all partners in all phases of the research.

Culture of Science and Scientists. Scientific method and practices are to some extent at odds with the tradition of participatory research. Scientists generally assume that research findings are true (at least probabilistically) and empirically verifiable. Scientists generally view scientific endeavors as occurring apart from or above social context rather than as socially/culturally constructed. This often reduces the value scientists see in the unique perspectives offered by community members.

Guiding Principles. The guiding principles of the Recruitment, Retention and Community Engagement in the National Children's Study document include:

- Collaboration that builds reciprocal relationships between Study scientists and communities is essential in order to establish and maintain true partnerships for studying the health and well-being of children.
- Mutual understanding is needed from both the Study scientists and communities. Scientists need to understand the community needs and resources while the communities need to understand the importance of maintaining the scientific integrity of the study design and data.
- Integration of knowledge and action for the mutual benefit of all parties is achieved through long-term collaborative partnerships.

Content of the Document. Dr. Cronk summarized the content of the recruitment, retention, and community engagement document. For the purposes of the Study, the document defines recruitment; retention; community; Study site; sampling segments; national, state, and regional outreach and engagement; local community outreach and engagement; and community needs assessment. The document describes the key components of recruitment, retention, and community engagement. The document also describes the approaches and activities for prerecruitment, recruitment, and retention.

Study Recruitment and Retention Activities. Study recruitment and retention activities ideally occur at multiple levels, with specific objectives and roles that reflect supporter and partner involvement and input. The goal of this process is to foster mutually beneficial partnerships that cultivate a sense of personal ownership of the Study and cultivate a sense of pride in the very important contribution of partners and participants to the health of the nation's children. Although the Study and Study sites ensure that the protocol is implemented and that information is provided to partners on an ongoing basis, these important community partners provide invaluable advice and consultation on ways to successfully implement the Study and sustain broad support throughout its course.

Closing Remarks. Dr. Cronk explained that the recruitment, retention, and community engagement document is a work in progress. The Recruitment, Retention, and Community Outreach Working Group continues to work on the document's content.

After Dr. Cronk's presentation, she responded to comments and questions and addressed the following topics:

- *Addressing local interests in a national study.* Communities need to engage with the Study in order to be responsive to local interests and needs. Responding to these needs and interests may require adjunct studies. Yet, because the Study is a national research project, the protocol will be standardized across the Study sites. Mechanisms for national oversight for adding concerns and questions about local issues or conducting local adjunct studies have been developed. The Study will have a central review and supervision process for all adjunct and add-on studies.

- *Science versus community engagement.* A challenge for the Study is to implement its scientific activities while successfully engaging communities. The recruitment, retention, and

community engagement document describes the ideal approaches for such activities. The issues of integrating science and community engagement remain to be resolved but are slowly being addressed. The NCSAC is interested in continued involvement in learning about efforts to engage local communities and conduct adjunct studies.

- *Assessment versus intervention.* Another challenge for the Study is the fine line between intervention and observation. Study participation may change participants' behaviors; that is, observation has an effect on the observed (the Hawthorne effect) and subsequently could change the outcome. It is not known whether community engagement activities and providing Study results back to communities and participants exacerbates the Hawthorne effect.

- *Variations in community engagement.* Because of the potential for variations in the definition and interpretation of community engagement and participation across Study sites, the Recruitment, Retention, and Community Outreach Working Group includes representatives from all Vanguard Centers. The group's forthright discussions have focused on this issue. There is substantial buy-in from the Steering Committee on this issue. In addition, the processes and procedures for community engagement are stipulated in the government's contracts with the Vanguard Centers. To date, the Vanguard Centers have made great strides in developing uniform and comprehensive yet flexible approaches to recruitment, retention, and community engagement.

- *Engagement of other groups and entities.* The Program Office and Steering Committee are developing strategies to engage policy makers, legislators, the media, federal agencies, national organizations, health insurers, and colleges. The NCSAC and ICC will share in activities to engage other groups and entities.

- *Study flexibility.* Study researchers need to be open to change and flexibility in engaging communities, both at a personal level and at the level of the Study. To this end, the Vanguard Centers will need assistance in refining their communication skills in order to explain and communicate the limits of the Study's flexibility.

- *Community representation and variations in engagement approaches.* Because of stratification within segments and differences in segment sizes, the extent to which segments reflect distinct communities may vary. Approaches to community engagement need to be tailored to individual Study sites and to segments within Study sites. These approaches will be determined once the segments have been selected. The Coordinating Center and Vanguard Centers will interact to tailor the engagement approaches. The iterative processes of assessing community engagement will allow flexibility to approaches, accommodate changes in community composition, and maintain meaningful engagement over the life of the Study.

- *Partnership versus engagement.* The relationship between the Study and communities should be a "win-win" situation, and communities need to express what they want to "win" from the Study. This relationship is not a true partnership because communities do not share authority, responsibility, and legal representation in decision making. To avoiding misleading communities, the Study should use the term *engagement*, not *partnership*. Implying

community partnerships may lead to false expectations from community members. A more accurate description of *recruitment, retention, and community engagement* might be *enrollment, long-term participation, and community involvement*.

- *Ethical principles of anonymity.* Not all participants may want it known that they are involved in a research project. The Study should be careful to ensure the anonymity of participants, particularly in settings such as apartment buildings.

- *Community consultation.* Once community engagement strategies have been developed with input from key community members, they will be presented to communities for additional comment and feedback.

- *Evaluation of community engagement approaches.* Community engagement approaches will be documented and evaluated. The Study will report on the relative success and pitfalls of the various approaches.

- *Incentives.* The use of incentives for Study participation has been discussed but has not yet been determined.

- *Training of Study personnel.* Study scientists such as Principal Investigators will not be directly involved with Study participants. Community health workers will be most involved with the participants—going into homes, collecting samples, and completing questionnaires. Much of the Study's success will depend on the quality of community health worker training, as well as the health workers' ability to equitably inform researchers. Training may be necessary to teach and establish equitable relationships among health workers and researchers and improve communication among these Study personnel.

NCSAC Recommendations

The NCSAC strongly supports community engagement that is consistent with the Study design and goals. It applauds the efforts of the Recruitment, Retention, and Community Outreach Working Group and supports continued efforts by the Vanguard Centers to engage communities. The NCSAC recommends that the Study make continued efforts to support Vanguard sites with technical support, training, and help to assist in community engagement activities. In addition, the NCSAC would be interested in receiving periodic updates on the Study's progress in community engagement and would be pleased to help through its Community Engagement Subcommittee.

Report on Human Subjects Activities: Implications of Revealing Findings to Participants

Dr. Fleischman

Revealing findings is one aspect of community engagement and relates to keeping promises to participants and their communities.

Revealing Findings. The Study Plan states that "the Study is committed to revealing relevant and important information to participants and their families…to protect the health and well-being of the children who are participants…the Study will provide individual-level data…on environmental exposures, physical and psychological examination findings, and routine laboratory test results. Some data…will be of uncertain relevance to the health or well-being of individual participants. Such data will not be routinely reported to participants."

In addition:
- Scientifically valid and clinically relevant findings will be revealed to individual participants/families.
- Clinically "critical" findings will be revealed in a timely manner.
- Participants will be educated and helped to interpret findings.
- Scientifically valid aggregate findings will be revealed to participants and the general public through presentations, newsletters, Web sites, journal publications, and other media.
- Revealing site-specific findings will require sensitivity to community concerns.

During its September 20–21, 2005, meeting, the NCSAC agreed on the following statements:
- The Study should inform participants and families about all medically or clinically relevant individual findings regardless of whether there is an available intervention.
- The Study should have methods to identify in a timely manner clinically critical findings, with appropriate "red flags," and as best as possible, involve personal physicians and families in dealing with these clinically critical findings.
- When participants might wish to know clinically relevant but not clinically critical findings, the participants should be offered the findings.

During its January 24–25, 2006, meeting, the NCSAC agreed on the following statements:
- The Study has an obligation to share clinically relevant individual-level data with individual participants and families.
- There is also an obligation to share community-level data of importance with the broader community at each site.
- There may be potential risks to individuals and to the entire community of revealing information found in the Study.
- What constitutes "clinically relevant" and who decides what data are revealed is unclear at present.

On March 22, 2006, a group of consultants that included representatives from the Vanguard Center IRBs, Principal Investigators, IRB chairs, and liaisons met to discuss Study human subjects issues. The purpose of this meeting was to mitigate differences among local IRBs and to address any concerns early in the process.

The group generated the following points to consider:
- Revealing information has the potential to increase the level of risk to participants, even possibly increasing the risk of the Study above "minimal."
- Revealing information is a potential intervention.
- Informed consent must be clear on the intentions concerning revealing findings

Revealing Findings to Individual Participants. Based on the issues discussed during the March 22, 2006, consultation, Dr. Fleischman offered the following recommendations with regard to revealing findings to individual participants:

- Reveal results of individual clinical information including routine physical, psychological, and laboratory tests.
- Reveal clinically critical information in a timely manner.
- Reveal results of environmental exposure assessments when there is a known relationship between exposure and a significant negative health outcome or predisposition to disease.
- Do not provide genetic information or other information of uncertain clinical relevance to participants or families—except in the unusual circumstance that clinically relevant information may impact on the health and well-being of the Study participant in the future. Such information should be provided optionally after informing participants that the information is available.
- The Study should develop a process for serially examining the data being developed and determine which information is potentially clinically relevant and useful. Such information should be provided optionally to participants after informing participants that the information is available. As best possible, personal physicians should be involved in revealing such findings.
- The informed consent must include language that clearly describes the process of revealing findings to participants.

NCSAC Recommendations

- *Revealing results.* The Study should reveal all medically or clinically relevant information to participants. This information should include physical, psychological, and laboratory tests that are routinely performed in clinical practice.
  - Information of uncertain relevance or utility should not be revealed.
  - Clinically critical information should be measured and revealed in a timely manner.
  - The Study should have a process to determine which information being collected is medically or clinically relevant and will be revealed to the participants.

- *Revealing results of environmental exposures.* The Study should inform participants of environmental exposures with known and accepted risk and discuss with participants the clinical relevance of such exposures.

- *Authority for known risks.* Since, in many circumstances, a definitive authority for known risk exposure has not been established, establishing such an authority will be the responsibility of the Study based on the best available evidence.

- *Genetic information.* The Study should not reveal genetic information, except in the unusual circumstance of information that is of "clinical relevance and utility" to participants and families.

- *Involvement of participant's clinician.* Discussion and interpretation of findings may benefit from involvement of the participant's clinician. Because participants may not want to be

informed of all findings, they should be given options about which findings will be revealed to them.

- *Principles, policies, and processes.* The Study should articulate its principles and policies about revealing findings to participants through the informed consent process. Rules and regulations such as the Federal Privacy Act and the Health Insurance Portability and Accountability Act should be considered. Policies regarding the identification of relevant information, how the information is released/made available, and how the relevance of the data are explained or interpreted should be established. One approach for revealing information would be transmitted information from the Study Centers to a participants' personal physician or health care provider, who would in turn reveal the findings to the participant and provide interpretation or explanations about the findings. Processes and policies for revealing findings to third parties such as other family members will need to be established.

- *Access to health care.* One of the possible benefits to Study participants is access to health care. Although health care will not be routinely provided to participants, Study sites will have relationships with health care providers so that referrals for medical or clinically appropriate care can be made. The Study sites' relationships for referral were stipulated in the RFPs.

Day Two

Welcome and Recap of Day One

Dr. Fleischman

Dr. Fleischman welcomed participants to the meeting's second day and reviewed the highlights of the first day and the agenda for the second day.

School Exposure Assessment and Its Challenges

Moderator's Introduction

David J. Schonfeld, M.D., NCSAC Member, Cincinnati Children's Hospital Medical Center

Dr. Schonfeld noted that the Program Office is finalizing details of the Study protocol to address the prepregnancy and pregnancy periods and the first 2 years of children's lives. The next phase in protocol development will include the assessment of exposures in childcare, daycare, and school environments. Children are exposed to a tremendous range and almost unlimited variety of environmental conditions in schools. Schools have far-reaching and profound impacts—potentially both positive and negative—on the health and development of America's children and youths. As children grow older, the content of school curricula becomes less important than the social influences of peers in school settings. Therefore, the issue is not whether the Study should assess school environmental exposures but what exposures will be assessed and how they will be assessed. The current challenge is how to optimize school-based exposure measurements within the framework of the Study.

Optimizing Interactions in the Classroom: Experiences from Two National-Level Studies

Robert C. Pianta, Ph.D., University of Virginia

Dr. Pianta described the experiences of two large-scale, national-level observational studies of classrooms: (1) National Center for Early Development and Learning Multistate Prekindergarten (preK) Study (NCEDL) and (2) the NICHD Study of Early Child Care and Development (SECCYD). This presentation summarized what was learned from these two studies in terms of substantive results and considerations for logistics, planning, and data collection for the Study. Dr. Pianta discussed the study methods, decisions, and results as related to describing the classroom experiences of children in preK through 5th grade. The studies assessed how children's experiences related to structural features of classrooms and the ways in which these experiences mattered to children.

Characterization of the Two Studies. Collectively, NCEDL and SECCYD observed 1,000–1,200 classrooms at 5 levels: preK, kindergarten, grade 1, grade 3, and grade 5. The aggregate data were compiled from a total of 5,000 classrooms, which makes this the largest set of systematic standardized classroom observations in U.S. schools. These two studies offer a national view on classrooms. To date, there have been no nationally representative studies of classroom environments, either using children as the sampling frame or classrooms as the sampling frame. The study sites were ethnically and economically diverse. The first grade observations were made in 700 schools in 300 school districts. The classroom was the unit being sampled, not individual children. There were 10 SECCYD sites in 9 states, and the preK study sites were in 6 states.

Observational Issues. Observations and large-scale applications in classrooms often require trade-offs and decisions. No system can address every concern. Key issues for large-scale work include:

- Multiple versus single occasions
- Length of the observational "window"
- Time of day/content of instruction
- Unit of analysis—global or micro (for example, time sample, event sample) or both?
- Classroom level or child level
- Training demands and reliability—increase with scale
- A system applicable across diverse settings (a key issue for the Study).

Methodology. The choices for observation systems include time of day, classroom-level versus child-level focus, and time-sampled codes (setting and activities, teacher behaviors, and child behaviors). When assessing classroom quality, observational codes can be selected because they predict children's social and academic skills. "Value added" effects control for family, parent, and child factors; prior functioning; and prospective and experimental designs. The methodology should offer confidence that indicators relate to what matters for children's development. Global scales are almost always better predictors than the quantity of exposure to a given type of instruction. CLASS was the global rating scale to analyze the aggregate data from the two studies.

CLASS. CLASS focuses on (1) how teachers and students interact, rather than on physical or structural attributes of schools and classrooms and (2) intentionality—what the teacher is doing to promote the positive emotional, social, and academic development of students in the classroom. Factor analysis of all CLASS scales indicate three broad constructs: emotional support, organization/management, and instructional support.

Exposure to Activities and Practices. The vast majority of interaction/activity is whole group or individual seatwork. There are few, if any, social or instructional interactions between teacher and individual child. Mostly activities involved literacy. There was exceptional variation from classroom to classroom. There is no "typical class."

Allocation of Activities. In grades 1–5, children spend high levels (30 percent) of their time in "business/routine" activities such as managing materials and routines. These grade levels spend high levels of their time focusing on "basic skills," with the levels increasing from grade 1 to grade 5. For these grade levels, the ratio of listening/sitting/watching to doing is 10:1.

Summary and Correlates of Descriptive Results. There was exceptional variability within and across grades, generally passive instructional environments. There was little to no association with teacher experience or training, teacher salary, or small associations (.10–.20). Larger classes were more structured; smaller classes were more social and had higher instructional quality. Family income/education was related to more positive ratings. The teacher's sense of self efficacy related to more positive ratings. Children needing access to stable high-quality instruction typically did not receive it. Schools operate more as moderators of risk than as promoters of general development.

Lessons Learned. The experiences with NCEDL and SECCYD have shown that:
- Large-scale observational assessments are feasible.
- Norms for classrooms are a reasonable goal.
- The largest cost-center is the "classroom visit."
- Dimensional rating systems that focus on interaction and classroom process yield better validity and can be standardized for training.
- Within and between days and across months, the variation of quality dimensions is not large.

Considerations for the Study. Dr. Pianta noted the following considerations for the Study's assessment of classroom settings:
- The Study's large scale is conditioned by the sampling frame (that is, multiple children in a given school or in a given classroom)
- A minimal observational window is two cycles of 20–30 minutes each.
- Videotaped data collection is possible.
- Cost-center is the visit. (To save costs, can multiple aspects of the setting be sampled by the same person?)
- The Study should consider selecting/observing a representative subsample.
- Web-based training and certification of coders can be a way to address the challenge of many, widely distributed observers.
- The Study should consider which grade(s) it wants to assess.

- The Study needs to determine the point of contact for consent (that is, the school district/school board, the school/principal, or the teacher).
- The cancellation rate for NCEDL and SECCYD was about 10 percent. Although individual children may not be present, the Study may still want to observe the classroom.
- The overall successful collection rate from classroom observations is lower than that for laboratory or home visits.
- About 25 percent of children switch schools during the course of the school year.
- The minimum lead time for planning and implementing a classroom observational study is about 6–8 months.

After Dr. Pianta's presentation, he responded to comments and questions that addressed the following topics:

- *Parental permission.* If an observational study focuses on an individual child, parental permission/consent is not required for all other children in a classroom.

- *Classroom access.* A two-pronged approach can be used to contact schools and gain access to a classroom. The first approach involves contacting a school district, describing the plan for classroom observation of individual children, informing the school district that there will be parental consent, and asking what is necessary to gain classroom access. The second approach involves contacting the child's teacher to set up the actual visit.

- *Responses to requests.* School district responses to requests for observational studies are varied but generally positive. Community engagement during the planning phase of an observational study will help to make the school districts aware of a study purpose and benefit. Community engagement generally leads to a higher response rate. Challenges to requests include different consent forms for every school district, teacher, and parent. By informing school districts that the child is the unit of interest, requests for observational studies that emphasize a focus on child development generally lead to positive responses.

- *Requests for study findings.* Dr. Pianta explained that there were no requests from parents, schools, or school districts for NCEDL findings. Had such requests been made, they would have been denied. Protection of information can be stipulated in study protocols.

- *Consent issues.* Because it is a national project of national interest, the Study could benefit from support and endorsement from the U.S. Department of Education. Informing school districts, principals, and teachers that a classroom observational study is endorsed and supported by the U.S. Department of Education would improve consent.

- *Public versus private schools.* The variations in activities in public versus private schools were similar. There were few differences in outcome measures for public and private schools.

- *Teacher reports versus observation.* Teacher reports of standardized measures of a child's social competence, problem behavior, and academic functioning show little concordance with observational results, with the exception of more global rating scales (for example, a child's self-reliance in the classroom). Aggression and misbehavior are low-frequency events

and have almost no association with teacher reports. Many of these behaviors occur outside the classroom, and teachers may underreport such behaviors if observed.

- *Teaching quality.* Observed teaching quality has little or no association with schools' indicators and markers of the quality of teaching.

- *Peer-group interactions.* Both NCEDL and SECCYD collected peer-interaction data. Peer interactions in schools are more successfully sampled in contexts in which they are most likely to occur, such as lunch rooms and playgrounds during recess. Sociometric data such as popularity and sociability are best collected in the classroom. Teacher-reported tools and tools for children reporting on each other are available to collect such data. Global rating scales are effective and valid in assessing observational data from lunch rooms.

Research Challenges: Assessing Children's Environmental Exposures in Schools

John L. Adgate, Ph.D., University of Minnesota School of Public Health

Dr. Adgate briefly described his experience with probability sampling of children in school settings. He noted some issues of environmental assessment in schools such as study design and hazards, presented some relevant results and lessons learned from the Schools Health Initiative on Environment, Learning, and Disease Study (SHIELD), and discussed the challenges and potential solutions for assessing children's environmental exposures in schools.

Study Design and Schools. Exposure measurements in epidemiological studies generally include hierarchies of exposure information (for example, cost and ability to classify and estimate exposures, data collection approaches, and important toxicant exposure events). Hierarchical exposure assessments are basically a series of nested studies. The Study is a prospective study of a probability sample that is essentially numerous nested studies. SHIELD was a nested study of about 150 children. Sampling included blood, urine, indoor air, and personal air. The study had a variety of response rates for its measures. The key issues for school environment studies are (1) tracking children over time and space, response rates, and representation within all racial and ethnic groups; (2) finding subjects at the upper end of exposure distributions; and (3) determining the best allocation of measurement resources.

Importance of School Studies. Children spend 35 or more hours a week at school, and there are many potential exposures of interest. Conducting studies in schools helps identify, contact, recruit, rerecruit, and monitor children for additional studies. Working in schools develops partnerships with schools and communities that promote retention and overall study success. There is a perception that school exposures are important.

Hazards for School Children. Children can potentially be exposed to a variety of biological, physical, and chemical hazards in schools. Biological hazards include allergens, fungi, bioaerosols, and endotoxins. Physical hazards include accidents, which are the leading cause of death in children and adolescents. Each year, 4 million child/adolescent injuries occur in school settings. Chemical hazards include outdoor/indoor air pollutants and pesticides.

SHIELD. This study was a school-based probability sample from two diverse inner-city Minneapolis, MN, schools. There was little difference in environmental quality between the two schools. Multiple environmental stressors were measured inside and outside the subjects' bodies, with a big emphasis on biomarkers and personal dosimeters. The study had greater success at recruiting children from non-English-speaking (71 percent) than English-speaking (42 percent) families. The study had high retention rates once the subjects were enrolled.

Research Challenges. The challenges for assessing children's environmental exposures in schools include:

- Mobile population, especially low-income households, which have a higher frequency of moving
- Wide variety of languages
- Maintaining contact with study participants(via telephone/e-mail)
- General lack of trust for researchers
- Range of "unconventional" lifestyles and living arrangements
- Retention/representation.

Improving Retention. Working with schools can help retain study subjects. Studies can provide resources that schools can use. Trained, professional study staff should be involved with school staff. Child-friendly phlebotomists and school nurses are one of the key factors in retention. The study should be a trusted organization/consortium. Schools can help a study with tracking, which will help with retention.

Process Issues. The main process issues for schools are administration (for example, permission/insurance, IRBs, neighborhood/community involvement, Family Educational Rights and Privacy Act of 1974) and data collection (for example, timing, sample locations, amount of sample collected). Dr. Adgate suggested that the Study pick a limited number of schools/school districts within an area, based on defined criteria, to preserve the Study's main goals. Process issues for individuals include incentives, neighborhood/community involvement, and communicating and interpreting results.

Final Thoughts. The Study needs school involvement to meet its long-term retention and compliance goals. Schools are a nexus of subjects and communities. The biggest challenge will be deciding how and with which schools to work within the probability sample framework. This is a complex interaction of time, resource, logistical, and statistical power considerations.

After Dr. Adgate's presentation, he responded to comments and questions that addressed the following topics:

- *Differences in recruitment success*. SHIELD recruiters represented every racial and ethnic group represented in the two schools. Recruiters targeted individuals from their own racial/ethnic group, and schools were the platform for recruitment. Some of the recruiters were school language assistants and were highly respected at the schools and within their community. All recruiters were persistent, but some were less successful than others. Several community groups were contacted, but they expressed little interest in the study. A general lack of trust of researchers may have contributed to the differences in recruitment success, and the collection of blood and urine samples may have been deterrents. Dr. Adgate

explained that immigrant groups/communities tended to be more connected and socially cohesive than English-speaking groups/communities. Immigrant groups/communities perceived schools and school nurses as "trustworthy" and were willing to participate in a "school study." African Americans in the school district had the highest socioeconomic levels and had a low interest in study participation.

- *Venipuncture.* Local anesthetics for venipuncture were not used in SHIELD.

- *Public discovery of environmental samples.* Training for crisis preparedness often includes public discovery of positive environmental samples, which raises concerns about child health. Releasing environmental information—particularly about samples that exceed regulatory levels—may generate high levels of anxiety and may even lead to irrational actions such as school closures. Because there are very few regulatory standards for indoor exposures such as allergens and dust, positive samples in schools should not necessarily trigger concerns about health. There are regulatory standards for outdoor air quality, and positive samples of airborne pollutants from school playgrounds (for example, heavy metals) may trigger health concerns and actions such as school closure.

- *Home versus school samples.* SHIELD did not collect outdoor air samples at the schools. Indoor air samples were collected at the schools as well as the study participants' homes. Levels of airborne agents such as dust and allergens were generally higher in homes than in schools.

- *Smoking.* Smoking was not allowed in the study schools, and SHIELD did not assess second-hand smoke in the schools.

NCSAC/General Discussion

The discussion included questions and comments about the following topics:

- *Schools' expectations of studies.* Dr. Pianta explained that the investigators framed the psychosocial studies as focusing on children's development as they progress through school and that schools play a significant role in developmental outcomes. This framing emphasized the common goals of the studies and the schools. Dr. Pianta said that in his studies he has observed tremendous variation in the quality of schools' physical environments. Many schools may exceed thresholds of communities' expectations of physical quality and environmental health and safety. Assessing the health and safety of school environments tends to trigger greater sensitivity and scrutiny of such studies. Dr. Pianta stated that schools would have different expectations for the two types of studies (psychosocial versus physical). Dr. Adgate said that one of the expectations of the Minneapolis schools was not to be "blindsided" by findings that may exceed environmental standards. The schools were informed of the findings on a regular basis.

- *Descriptive assessment of schools' heating, ventilation, and air conditioning (HVAC) systems.* Dr. Adgate said that the Minneapolis studies assessed HVAC and plumbing systems. Because of their age differences, there were differences in these systems at the two

schools; one was a "clean air school" with a newer, more efficient HVAC system. There appeared to be little difference between the plumbing systems.

- *Criticism of schools.* Dr. Scheidt asked whether any groups or individuals had contacted or pressured the studies in order to find some fault with the schools. Dr. Adgate replied that some adults in the schools complained of nonspecific problems, and they were concerned with causes of the problems and interested in identifying the sources of the problems. Dr. Pianta noted that results of psychosocial studies (for example, demonstrating that a teacher's classroom activities matter more than a teacher's academic credentials) may pressure schools about teacher training and expenditure of resources.

- *After-school programs.* Dr. Pianta said that he has conducted studies in before- and after-school childcare environments. There are standard protocols for observing and assessing children in out-of-school environments.

Support for the National Children's Study

Eileen Ouellette, M.D., J.D., President, American Academy of Pediatrics

Dr. Ouellette thanked the NCSAC, the Program Office, and other Study personnel for the opportunity to discuss the Study and the commitment of the American Academy of Pediatrics (AAP) to the future of children's health research. Pediatric research is the foundation for the care and critical treatments that are often taken for granted, such as surfactants for infants in respiratory distress or placing babies on their back to reduce sudden death syndrome. The Framingham Heart Study and the Women's Health Initiative have provided valuable information about adult health outcomes. The Maternal-Infant Health Study was one of the first longitudinal studies of children's health. Its goal was to follow children from pregnancy to 7 years of age. It was abruptly terminated 40 years ago, a casualty of the Vietnam War. Although crude by present standards, and in spite of its truncation, the study provided important information in areas such as febrile seizures and the antecedents of cerebral palsy. Much important information, however, was lost when the Maternal-Infant Health Study was terminated.

The Study has the opportunity to add to the current knowledge of how to improve the health care of children and adolescents. The Study's findings will influence medical care and health care decisions for children for decades to come. For this reason, AAP strongly supports the Study. In a time of burgeoning health care costs and limited resources for health care research, including pediatric research, prevention is a cost-effective approach. Carefully conducted research has the potential to identify important and even life-saving interventions. The Study is unique because it will investigate multiple determinants of children's health, including biological, environmental, and sociological factors. In addition to measuring a broad variety of environmental exposures and establishing linkages with a large number of outcomes, gene-environment interaction and gene expression are very important elements of the Study. There has never been a longitudinal study of this scale in the United States that has simultaneously examined all of these factors and their relationships.

The determinants of many adult diseases begin during childhood. Findings from the Study will enhance the ability of primary care and subspecialist pediatricians to improve the health of adults

by improving the health of children. The Study represents a critical step forward toward preserving the health and well-being of the next generation. Although the Study is bold and ambitious, it must move forward. Despite its 25-year timeline, data will be generated with the first several years of the Study.

AAP strongly urges Congress to provide the necessary federal funding to continue the crucial work of the Study. Much time, effort, and money has been devoted to the planning and early implementation of the Study. AAP members have been instrumental in requesting funding for the Study's planning phase and are also actively participating in the Study's early implementation at the Vanguard Centers. AAP members will convey information about the Study's planning and early implementation to members of Congress in an effort to provide sufficient funding for subsequent years. The Study needs $69 billion in fiscal year 2007 to move forward to the implementation phase. The costs of the Study are dwarfed by the costs of treating the diseases and conditions that the Study expects to address. Six of the chronic diseases that the Study plans to examine—obesity, injury, asthma, diabetes, schizophrenia, and autism—cost the nation more than $600 billion each year. If the Study could reduce the incidence of these chronic conditions by only 1 percent, it would pay for itself several times over.

The potential benefits of the Study are clear to the pediatric community. AAP, with its 60,000 member pediatricians, is committed to fighting for ongoing and new funding for the Study. So far in 2006, AAP has organized two Congressional briefings to discuss the importance of the Study with key budget and appropriations staff members. AAP has been instrumental in facilitating 50 organizations to sign a letter to Congress requesting full funding for the Study. AAP has submitted written testimony on child health funding that specifically addresses the Study. AAP members have been engaged through the Academy's advocacy network and have e-mailed more than 150 members of Congress asking them to support full funding of the Study. AAP has issued a news release in response to the President's proposal to phase out the Study in fiscal year 2007. All major pediatric organizations and several national health organizations are working with AAP to support the Study. AAP will continue its efforts until it is certain that the Study will receive the sustained and robust federal support that it needs, not only in fiscal year 2007 but over the 25-year length of the Study.

The Study is a major undertaking that is well worth the costs and efforts. Pediatricians of the future will be better able to care for children as a result of the Study's findings. Children in the United States and around the world will benefit from the Study, and ultimately adult health care will also benefit. Although there has been much progress in children's health over the last 75 years, many questions about how to promote children's health remain. AAP stands behind the Study as it endeavors to answer the many questions about children's health and fully realize its goals.

NCSAC/General Discussion

The discussion included questions and comments about the following topics:

- *Contacting members of Congress.* During their meetings, NCSAC members are special government employees and are forbidden to lobby Congress on behalf of the Study. Outside of meetings, they are private citizens and can contact members of Congress. Contact

information is available from a variety of private sources. Dr. Ouellette commented that e-mailing is the most effective means of communicating with Congressional members.

- *Issues and concerns of AAP members.* Dr. Ouellette reported that one of the members' greatest concerns is that the scope of the Study is too broad and has the potential to reduce available funding for R01 grants. Dr. Scheidt explained that funds not spent on the Study will not be allocated to the funding pool for R01 grants. Funding for the Study and R01 grants is not competitive or mutually exclusive.

- *Dr. Alexander's presentation on children's environmental health.* Dr. Eaton reiterated her suggestion that Dr. Alexander be asked to present on children's environmental health to AAP's fall meeting. Dr. Ouellette promised to follow up with this suggestion, to the extent that she can.

- *Benefits to practitioners.* Fernando A. Guerra, M.D., M.P.H., commented that some practitioners may not understand the potential benefits that the Study offers. He said that practitioners need to know how pediatric research results can affect practice and improve health outcomes. Dr. Guerra asked what AAP is doing to inform practitioners about the benefits of pediatric research. Dr. Ouellette explained that AAP communicates information on the application of pediatric research findings to practice in several ways, such as its Web site, newsletter, and other publications.

- *Training of pediatricians.* Barbara Anne Nabrit-Stephens, M.D., M.B.A., suggested bridging the gap between research and practice by engaging pediatricians in training and making them aware of the Study. Dr. Ouellette replied that AAP has a very active residents' section with about 10,000 members. This section will meet for an entire day at the fall AAP meeting. It was suggested that Dr. Alexander address these AAP members during their meeting. Dr. Scheidt noted that the Study envisions various training programs at the Study Centers, and a grant for a training program at one of the Vanguard Centers has been awarded.

- *Informing other organizations.* Edna R. Ranck, Ed.D., commented that the early childhood field should be made aware of the Study, and she offered to provide the names and contact information of relevant early childhood groups and organizations.

NCSAC Members

Alan R. Fleischman, M.D., NCSAC Chair, The New York Academy of Medicine
Marion J. Balsam, M.D., NCSAC Executive Secretary, NICHD, NIH, DHHS
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Robert E. Chapin, Ph.D., Pfizer Inc.
*Frank Chervenak, M.D., Weil Medical College of Cornell University
Giselle Corbie-Smith, M.D., M.S., University of North Carolina, Chapel Hill (participated via telephone)
Janet Currie, Ph.D., Columbia University
*George Daston, Ph.D., Proctor and Gamble

Allen Dearry, Ph.D., ex officio member, NIEHS, NIH, DHHS
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Liliana J. Lengua, Ph.D., University of Washington
*Bruce Levin, Ph.D., Columbia University
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Cynda Hylton Rushton, D.N.Sc., R.N., F.A.A.N., Johns Hopkins University Medical Institutions
P. Barry Ryan, Ph.D., Emory University
David J. Schonfeld, M.D., Cincinnati Children's Hospital Medical Center
Peggy M. Shepard, West Harlem Environmental Action, Inc.
Robert F. Spengler, Sc.D., ex officio member, Office of Public Health Research, CDC, DHHS
Alan M. Zaslavsky, Ph.D., Harvard University

**Did not attend.*

ICC Members in Attendance

Elizabeth H. Blackburn, B.S.N., Office of Children's Health Protection, EPA
Amy Branum, M.S.P.H., National Center for Health Statistics, CDC, DHHS
Woodie Kessel, M.D., M.P.H., Office of the Secretary, DHHS
Sarah Keim, M.S., NICHD, NIH, DHHS
James J. Quackenboss, M.S., Office of Research and Development, EPA
Peter C. Scheidt, M.D., M.P.H., NICHD, NIH, DHHS
Kenneth C. Schoendorf, M.D., M.P.H., CDC, DHHS

Program Office Scientists in Attendance

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Richard Callan, M.P.H., NICHD, NIH, DHHS

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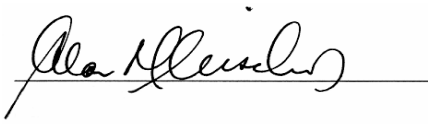
Grace Yang, M.P.A., National Opinion Research Center

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.



07/31/06

Date

Alan R. Fleischman, M.D.
Chair
National Children's Study Federal Advisory Committee