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Invited Comment

Genetics, Altruism, and the National Children's Study

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In July 2008, with a smile, a handshake and the signing of informed consent, future mother #000 001 will become the first person to enroll in the National Children's Study (NCS). This woman will be between 18 and 45 years of age. She will be either in the first trimester of pregnancy or planning soon to become pregnant. She will reside in Queens County, NY or Duplin County, NC, the two very disparate locations that have been selected as Vanguard Centers for the study. She and her family will be embarking on the most ambitious investigation of risk factors for child health and disease ever undertaken in the United States.

NCS is a prospective, multi-year, hypothesis-driven epidemiological study. It was authorized by the US Congress through the Child Health Act of 2000 and is directed by the National Institute of Child Health and Human Development. It will identify a nationally representative sample of 100,000 children born over the next 5 years in 105 counties across the United States. It will follow this birth cohort from pre-pregnancy or early pregnancy through age 21.

The goal of NCS is to discover and characterize adverse exposures in the environment—with particular emphasis on exposures in utero and in early childhood—that contribute to causation of disease, as well as beneficial environmental factors that enhance children's health. "Environmental exposures" are defined broadly to include chemical, biological, behavioral and social factors. The intent is to develop an evidence-based blueprint for disease prevention and health promotion.

To assess environmental exposures, each prospective mother and father will be invited to provide a comprehensive lifetime history at the time of enrolment. Samples of blood, hair and urine will be collected for chemical and other analyses from each mother at least twice during pregnancy; a cord blood sample will be obtained at birth; and biological samples will be obtained from each child at specified ages. These samples will be analyzed for over 100 chemical contaminants—metals, chlorinated organics, pesticides, solvents, and plastics chemicals—and for other markers of environmental exposure; aliquots will be stored at −70 degrees for future assays of still unrecognized hazards.

To assess genetic susceptibility factors that may modulate the impacts of environmental exposures on health and disease, biological samples collected from each enrolled mother, father and child will be processed to obtain and preserve DNA (from the nuclear and mitochondrial genomes) as well as RNA. Serial collection of these genetic specimens will permit assessment of dynamic changes in the epigenome (e.g., changes over time in DNA methylation and chromatin remodeling) that are suspected to mediate gene–environment interactions through temporal and spatial control of gene activity. These serial analyses will also enable systematic examination of dynamic changes in multiple gene products thus permitting detection of perturbations in biological networks even prior to manifestation of disease phenotypes. Aliquots of these samples will be stored in the National Children's Study Data Repository to permit future investigations of genetic factors using still undiscovered techniques.

The authors are investigators in the Queens, New York (1) and Orange County, California (2) Vanguard Centers of the National Children's Study.

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The NCS is needed because rates of many common diseases are increasing in American children, because evidence is accumulating that environmental exposures are partially responsible for these alarming trends, and because too little is known about the developmental origins and potentially preventable causes of these illnesses:

- Asthma incidence and mortality rates have more than doubled [Centers for Disease Control and Prevention (CDC) 1998; Gauderman et al., 2004].
- Despite declining mortality, annual incidence of acute lymphocytic leukemia increased by 61.7% from 1973 to 1999 [Robison et al., 1995].
- Incidence of primary brain cancer increased by 39.6% from 1973 to 1994 [Schechter, 1999].
- Rates of some birth defects, such as hypospadias and gastroschisis have increased in frequency over the past 30 years [Paulozzi et al., 1997; Williams et al., 2005].
- Recognition rates of both rare and common neurodevelopmental disorders (e.g., autism and attention deficit hyperactivity disorder) have increased dramatically over the past decade. These conditions, including mental retardation, learning disabilities and dyslexia are expected to affect at least 5–10% of the 4 million babies born in the United States each year [Grandjean and Landrigan, 2006; CDC, 2007; Froehlich et al., 2007].
- Prevalence of childhood obesity has trebled in the past decade [Strauss and Pollack, 2001; Freedman et al., 2006].
- Incidence rates of chronic neurodegenerative diseases of later life such as Parkinson disease and dementia have increased markedly, raising the possibility that toxic exposures in early life may be of etiologic importance [Cory-Slechta et al., 2005].

Previous large, prospective epidemiological studies have yielded invaluable gains in knowledge of disease causation and have guided successful programs of evidence-based prevention. The Framingham Heart Study is perhaps the best known of these. It was established in 1948 at a time when heart disease and stroke were epidemic. The goal was to identify preventable risk factors for cardiovascular disease (CVD). Within a few years, data from Framingham identified cigarette smoking [Dawber, 1960], elevated cholesterol and hypertension as preventable causes of CVD [Kannel et al., 1961, 1978]; later analyses documented the importance of elevated triglycerides, sedentary lifestyle, and diabetes. This information provided the blueprint for the reductions of greater than 50% in incidence of CVD that have been achieved in the United States over the past four decades [CDC, 1999].

The NCS has multiple strengths. The large sample size coupled with repeated, prospective measurements of a broad range of exposures and outcomes will facilitate simultaneous examination of the effects of multiple chemical exposures; of interactions among chemical exposures; of interactions among biologic, chemical, behavioral, and social factors; of interactions between environmental and genetic factors; and of gene **x** environment **x** time interactions. The prospective design, in which information on exposures is obtained in real time as exposures occur, eliminates the Achilles heel of environmental epidemiology, the need to reconstruct past exposures. The fact that the birth cohort is nationally representative will permit comparison of findings with data on past and future US populations as well as with data from other countries.

Recruitment and retention are the two great challenges confronting NCS. How can 100,000 families of diverse cultural backgrounds from across the United States be enrolled in a standard protocol requiring them to divulge sensitive information on exposures and to provide multiple biological samples, including samples for genetic analyses? How can these families' participation in a complex, time-consuming, government funded-study be maintained for 21 years?

While there is no complete answer to these questions, two papers published in this issue of *The American Journal of Medical Genetics* give grounds for cautious optimism. These reports from the University of Chicago [Joseph et al., 2007; Niedich et al., 2007] explore the attitudes of pregnant and post-partum women, most of whom were members of under-represented minorities living in inner city Chicago, about donating biological samples to a mother-infant specimen bank that would include genetic samples. Although the investigators made it clear to mothers that they and their children would likely not benefit individually from participation, the mothers nonetheless expressed substantial enthusiasm about joining the study. Mothers overwhelmingly expressed optimism that the research would yield significant results, and indicated confidence that the research team would keep medical information private. Although these reports suggest that participants may have "therapeutic misconceptions" about the possibility of receiving individual benefits—misperceptions that will need carefully to be addressed in the NCS consent process—still these findings suggest the presence of widespread altruism among these mothers.

These encouraging findings corroborate positive experience gained over the past 8 years in three prospective epidemiological studies of pregnant women and their children that were designed as precursors to the NCS. These investigations, which are assessing developmental outcomes of prenatal environmental exposures, were conducted in

Harlem and East Harlem, New York City [Rauh et al., 2006; Wolff et al., 2007] and in California's Central Valley [Eskenazi et al., 2005]. They have successfully recruited nearly 1,500 children. Despite the challenges of poverty, mobility and cultural diversity, they have retained over 70% of this number and generated important information on the adverse consequences of prenatal exposures to organophosphate pesticides. This experience provides more cause for cautious optimism.

Despite the enormous potential of the NCS to enhance the health of America's children, its funding has been in jeopardy. In 2006, after 4 years of planning, NCS was not included in the President's budget. Funding was restored in 2007 only after bipartisan action in the US Congress supported by a broad-based coalition that included the American Academy of Pediatrics, the U.S. Conference of Catholic Bishops, the American Chemistry Council, the Learning Disabilities Association, and the March of Dimes. A similar pattern is emerging for 2008, in that again the NCS was not recommended in the President's budget, but again both houses of Congress strongly support full funding.

The NCS provides an extraordinary opportunity. The studies reported here hold out the realistic hope that altruism still exists in the United States and that NCS will succeed. If NCS receives the funding that it needs, it will begin within 3–4 years to produce early data on pregnancy outcomes that could tell us how to save children's lives and how to improve health of the future population of the United States. It represents our generation's best hope of preventing disease and promoting good health in the generations of children yet to come.

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