Our Once-in-a-Lifetime Opportunity

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Longitudinal studies of the determinants of children’s health are complex, costly, infrequent, and incredibly valuable. It has become clear in recent years that the periconceptional environment plays a surprisingly large role in the health of the resulting child. This short introduction to this mini-monograph briefly recapitulates the articles included herein and reminds us that adequate forethought and planning will result in a study that could shed new light on the earliest determinants of children’s health and thereby fill critical data gaps. Key words: editorial material, National Children’s Study, reproductive epidemiology. Environ Health Perspect 112:67–68 (2004). doi:10.1289/ehp.6733 available via http://dx.doi.org/[Online 24 September 2003]

The “Retrospectroscope” shows us that the 1990s hosted the emergence of some concepts that have fundamentally altered our appreciation of many aspects of biology and medicine. The two concepts that immediately come to mind are Barker’s hypothesis and endocrine disruptors (EDs) (or, more deliberately, endocrine modulators). Barker and his colleagues (1995) observed that infants who are small at birth have increased likelihood of suffering from coronary heart disease in late middle-age. Their subsequent refinements of this hypothesis focused on the metabolic changes that become a permanent part of that individual (i.e., the metabolism becomes imprinted) (Osmond and Barker 2000). EDs are molecules that interact with hormone synthesis or receptor systems in the fetus. This agonist or antagonist activity in the fetus imprints the development of all systems that depend on that hormone and alters their function throughout life [see Colborn (2002) for recent overview].

The implication of these findings is that many more health outcomes might be programmed in the fetus than we previously appreciated. This appears to be true for several systems in the body not just the heart or the reproductive system [overview in Phillips (2002)]. If this is true, the implication is overwhelming: There are enormous health care costs that can be averted if we can learn what makes healthy babies and implement those lessons. In 2000, the United States spent $1.26 trillion on health care (U.S. Bureau of the Census and Centers for Medicare and Medicaid Services 2002). If even a fraction of this can be avoided, the economy would directly benefit and consider—perhaps even a fraction of this can be avoided, the economy would directly benefit and consider—perhaps almost all available benefit.

Is it possible to actually enroll couples before conception and to harvest the information that their recruitment will offer? The second article (Buck et al. 2004) is a review of the numerous studies that have handled very large amounts of data after preconception prospective pregnancy studies and shows it is indeed possible. In addition, new technologies are available that can allow the timely identification of when conception occurred, so that day-specific exposures can be captured and studied in relation to a spectrum of health endpoints. After a thorough review, Buck et al. (2004) show that study subjects will tolerate a significant burden of study tasks, including specimen collection and processing.

Specimen collection and processing will be a central part of the NCS as it tries to link exposures to health outcomes. Another article in this group (Rockett et al. 2004a) evaluates the real burden imposed on study participants, reviews which specimens have been collected successfully, and previews the use of less commonly used samples and the value they offer. The benefit of well-thought-out and well-timed sample collection is that it allows us to draw a much tighter relation between exposure and outcome. This becomes more

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important as our societal use of persistent organic pollutants declines and more of our environmental exposures are to compounds with shorter half-lives. No longer will a single blood or fat sample, for example, effectively recapitulate all the significant exposures of the past 6 months, so any large prospective study should be carefully thought through as to the types of biological samples that will be needed and when they should be collected. This is particularly true when trying to link preconceptional exposures with health outcomes years later.

The working group also realized that they could limit the scope of their attention to include only the current parental generation or extend it to include reproductive measures associated with these children as they matured. When faced with a rare opportunity to collect multigenerational data in humans, it is easy to see why the scope of their questions broadened to include the reproductive systems of the second generation, at least as it might be addressed within the confines of this study. As noted above, the possibility that EDs could affect human development and reproductive function has been leading the children’s health issue. One of the end points determined by fetal hormone levels in animals is the onset of puberty. There have been very few reports of factors that directly or indirectly change the age of human puberty (e.g., Teilmann et al. 2002). One of the challenges in this area is that the onset of puberty is still largely marked by gross external anatomic observations in the clinic and takes advantage of none of the revolution in endocrinology or molecular biology that has occurred over the past 20 years. For a large study such as the NCS, reducing the number of office visits and relying more on remote specimen collections could allow for more data to be collected and at lower cost.

The fourth article in this series (Rockett et al. 2004b) focuses on the current methods used to identify puberty and then explores some of the promising avenues for research in this area, noting that the study has some time to develop methods for remote monitoring of puberty before those methods will be needed.

Finally, the NCS study will generate huge amounts of data. Many of those end points will be unique in the sense of not having been collected together in previous studies. By nature of its time-dependent, highly interrelated processes, successful human reproduction and development poses some unique methodologic challenges for researchers. The last article in this mini-monograph (Tingen et al. 2004) answers questions and suggests strategies for study design and analysis sensitive to the unique aspects underlying research into human reproduction. This intersection of behavior (intercourse timing and frequency), sociology (pregnancy intentions, child spacing), and biology (male and female fecundity related to nutrition, hormonal milieu, and exposure) makes this a particularly challenging problem further complicated by the couple-dependent nature of reproduction. These complexities must be addressed in the study planning stages if any longitudinal prospective study will have a hope of accomplishing its goals.

This mini-monograph does not (and could not) address all the issues being raised in the planning of the NCS, but we believe it does address some of the critical issues that need to be tackled early in the formulation of the study. These articles not only raise questions and problems, but answer them. This mini-monograph shows us a) why preconception enrollment is important, b) that preconception enrollment is entirely feasible, c) that we can and must develop new tools to help monitor hormonally driven events in the study subjects, and d) that the collection of relevant data coupled with the sound analysis of specific end points will significantly increase our confidence in the answers. Only a well-formulated approach to such a huge and magnificent opportunity will leave our descendants smarter and better-positioned to reap the rewards of all our investments.

REFERENCES


