EARLY ANTECEDENTS OF ADULT HEALTH

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The era of the past 50 years has been extremely productive for epidemiology. In particular, the epidemiologic approach that we often refer to as “risk factor epidemiology”¹ has uncovered a wide range of important determinants of the major causes of morbidity and mortality in this country. Many of the signal discoveries made possible by risk factor epidemiology concern the behaviors or characteristics of adults and their relationship to the risk of ill health in later life. Examples include the relations of smoking to lung cancer, diet to heart disease, and estrogen to osteoporosis. The methodology used to explore these relationships, generally involving the measurement of risk factors and outcomes at the individual level, has greatly advanced over this same era.² At the same time, these methods have often limited the inquiries of epidemiologists to questions that, while important, do not address the full range of important determinants of human health and disease.

In the hope of overcoming such limitations while retaining the strengths of risk factor epidemiology, epidemiologists have begun to branch out in other directions. One dimension in which the field is expanding is in the level or unit of analysis.¹⁻⁴ Epidemiologists have, for example, increasingly brought skills to collaborative ventures that examine causes of ill health at the genetic, biochemical, or cellular level. At the other end of this spectrum is work such as that presented by Dr. Kaplan in this volume, which examines the social causes of ill health. These social factors may operate as “causes of causes”—that is, they may be mediated by the individual-level behaviors they influence. Alternatively, it has been proposed that social determinants of health may have a more direct effect on health, mediated, for example, by stress-induced changes in neuroendocrine systems. The key point is that, insofar as our methods of inquiry have focused

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on individual behaviors or traits in adults as determinants, our ability to move our understanding up or down the chain of causation has been limited.

A second dimension in which epidemiology is increasing its breadth is that of time.⁵ Epidemiologic studies have most often been limited to studying causes that can operate in the time span of the career of an epidemiologist or even a funding cycle. Hence, we know a great deal, for example, about the effects of adult smoking on chronic obstructive pulmonary disease and the effects of pre-term birth on growth and development in childhood. We know much less, however, about how, for instance, maternal smoking during pregnancy might affect the health of offspring over the life course. Hence, just as we need to expand our unit of analysis from the individual to the community level, so too, we would argue, we need to expand our time reference to examine exposures from the very early prenatal period and their effect across the life course. It is on this life course approach to epidemiology that we direct the rest of our remarks. Those who seek a more in-depth review of this topic might also consult a recent book edited by Kuh and Ben-Shlomo.⁵

It has long been recognized that the prenatal period is a time of rapid development, during which the fetus is vulnerable to a range of toxic or metabolic insults that can result in manifest and lasting health impacts in the newborn and child. A recent example is the recognition that a relative deficiency in dietary folate increases the risk of neural tube defects, especially in the presence of a genetic predisposition.⁶ This knowledge has created the opportunity to intervene with folate fortification of foods to ensure adequate dietary folate during the critical early prenatal period.⁶

The discovery of the link between dietary folic acid intake and risk of neural tube defects was facilitated by the relatively short time interval between prenatal exposure and the manifest outcome in the newborn. More challenging from an epidemiologic point of view is the study of connections between prenatal exposures and health outcomes that may only be manifest when an individual is an adult. Such "latent" effects of prenatal and early childhood exposures have long been suspected, but only in the last 10 years have compelling studies begun to emerge.

This type of research has important public health implications. Chronic diseases in adults still constitute an enormous public health burden despite enormous strides in identification of lifestyle risk factors and medical treatment. One limitation we currently face in interventions to prevent chronic disease is that it is very difficult to achieve sustained changes in long-ingrained behavioral patterns related to diet, exercise, smoking, and alcohol consumption. Interventions that could be directed at pregnant women and children during critical developmental

windows might prove to be simpler and more powerful measures than are currently available to improve the health of adults.

RECENT RESEARCH IN LONG-TERM, LATENT EFFECTS OF EARLY LIFE EXPOSURES

Dr. David Barker of the University of Southampton in the United Kingdom has been especially influential as both an active investigator and a strong advocate of the importance of early life factors as determinants of adult health. A compendium of publications by Dr. Barker and his colleagues recently was published under the title, *Fetal and Infant Origins of Adult Disease*.⁷ In some studies, Barker employed an ecological approach to link indicators of health in early life to adult health. One such study was based in three textile towns in northern England: Burnley, Nelson, and Colne. The towns were similar with respect to the distribution of occupations in the early part of this century and with respect to the distribution of social class in 1971. In the early part of the century, however, residents of Nelson benefited from better-quality housing and less crowding than in Burnley, with Colne falling between the other two. A correlate of this variation in living conditions was a similar trend in infant mortality rates between 1911 and 1913: they were lowest in Nelson and highest in Burnley, although the three towns had similar infant mortality rates between 1968 and 1972. Barker found that the gradient in cardiovascular disease between 1968 and 1978 among adults aged 55–74 years closely paralleled the infant mortality rates at the time when the adult residents of those communities were infants and children. Barker inferred that higher infant mortality rates were a proxy for poor prenatal maternal health and nutrition, which in turn predisposed individuals to cardiovascular disease as adults.

Using a combination of ecological and cohort approaches, Dr. Barker has published approximately 300 papers related to the early antecedents of adult health. The central thesis that emerges from this work is that the early life experiences of an individual—extending back to the early prenatal period—are major determinants of the main causes of ill health and mortality in adult life, and that this relationship explains much of the social gradient in mortality from chronic disease.

This same life course approach has been used in efforts to examine the antecedents of adult mental illness, specifically schizophrenia.^{8–10} Schizophrenia is in many ways an ideal condition for exploration of early life factors. It cannot be diagnosed until adult life, yet appears to have a number of early manifestations that suggest a neurodevelopmental disorder. In other words, it appears to arise from disordered growth of the brain early in life, even in the prenatal period,

due to environmental factors, genetic factors, or some interaction between the two.

How does one examine what these early environmental factors might be? Because of the relative rarity of schizophrenia, one would need to assemble a cohort of tens of thousands of individuals. Prenatal exposures would need to be measured, and, as schizophrenia cannot be diagnosed before adulthood, this large cohort would have to be followed for at least 20 to 30 years. The logistics, expense, and time span required to complete such a study would seem to make it infeasible. As with Barker's work, the solution required seeking out a population of adults and a means of learning something about their early life experiences from existing information.

In this case, the circumstance was the Dutch hunger winter, which occurred at the end of World War II. The large cities of western Holland were at that time under Nazi occupation. After the Allies lost a key battle at Arnhem in September 1944, these cities were subject to a blockade by the occupying Nazi force. The result was a famine in a previously well-nourished, industrialized population. Three unique aspects of this famine created the opportunity for later research. First, it was well circumscribed in time. Second, the famine was well documented. The nature of records kept were such that it was possible to determine the food ration available to pregnant women during various times in the prenatal period. Finally, it occurred in a nation in which the health system facilitated tracking health outcomes into adulthood for the individuals who were exposed prenatally to the famine (and for comparison cohorts born just before and just after these individuals). This allowed for examining rates of schizophrenia in these cohorts and relating them to exposure to prenatal famine at specific times in pregnancy. Because these cohorts were born so close in time in a fairly homogeneous society, exposure to prenatal famine could be isolated as a factor that differed among the cohorts. While the rate of schizophrenia with respect to time of birth was generally stable during this period, the cohort of individuals exposed to famine early in gestation had a markedly increased risk of being diagnosed with schizophrenia 30 and 40 years or more after that exposure.

The Dutch famine study shares some of the limitations that characterize much of the research of Barker and others concerning early life exposure and adult health. Because the exposure data used were not collected for epidemiologic research, they tend to be imprecise or even mere proxies for the exposure of interest. In the case of the Manchester, England, area mill towns, Barker used infant mortality as a marker of the average state of fetal nutrition in each community. In the Dutch famine cohort, average caloric intake during pregnancy was

available, but not nutrient intake for individual women. Furthermore, data on other perinatal and childhood factors—potential confounders and modifiers of the relation of interest—were generally lacking.

Overcoming these limitations requires a design that would have seemed impossible until recently: the prospective enrollment and follow-up of individuals from early in the prenatal period until the age when adult chronic diseases begin to emerge. From beginning to end, such a study would generally span a period longer than the career of a researcher. Now, however, the opportunity to conduct essentially just such a study in a more feasible time frame is emerging for two main reasons. First, during the 1940s, 1950s, and 1960s, a number of birth cohort studies were established in the United States, the United Kingdom, and elsewhere.⁵ For the most part, these studies were motivated by an interest in the antecedents of developmental and learning problems among children, rather than as a plan to study the early antecedents of adult health. Nonetheless, prospective data were collected at that time, and, in some instances, foresightful investigators collected and preserved biologic specimens for future use.

The second factor that enabled the conduct of prospective life course studies today is the availability of improved methods for identifying early markers or risk indicators for chronic disease. This is especially true for cardiovascular disease; noninvasive imaging studies and metabolic tests are available that can be applied in cohorts too young to develop clinical cardiovascular disease except in rare cases. It is, therefore, possible to carry out an informative study of early antecedents of cardiovascular disease even in the relatively young cohorts born during the 1950s and 1960s and enrolled in prospective studies in the United States.

Two contemporaneous cohort studies, both funded by the National Institutes of Health (NIH), were initiated at that time. One was the Collaborative Perinatal Project (CPP).¹¹ In the CPP, pregnant women were enrolled when they sought prenatal care at 12 centers around the country during the years 1959 through 1966. The growth and development of their offspring were assessed through age 7 or 8. The CPP sample comprised approximately 58,000 pregnancies. The Child Health and Development Studies (CHDS)¹² were similar in concept, though differing in some details from the CPP. Mothers were enrolled during pregnancy by the Kaiser Foundation Health Plan in Oakland, California; approximately 20,000 pregnancies were included. The CHDS mothers were of somewhat higher socioeconomic status than the CPP mothers. In both the CPP and CHDS, detailed data concerning the pregnancy, labor, and delivery were carefully recorded, and prenatal serum samples were obtained, frozen, and stored to this day. These attributes, together with the large and diverse populations they in-

clude, make these studies unique resources for the study of early antecedents of adult health.

At the Center for Urban Epidemiologic Studies (CUES) at the New York Academy of Medicine, we are just beginning to plan collaborative follow-up studies of the offspring from the CPP and CHDS studies. We believe that these studies represent the best opportunity yet to conduct informative research that examines the relation of prenatal and early childhood factors to adult health.

Thus, we believe that a new era in epidemiology may be emerging. This era will be characterized by an expansion of the boundaries within which epidemiologists have hypothesized and examined causal relations. On the one hand, causes of ill health that operate at the community, or even societal, level, as others discussed at the sesquicentennial symposium, will be examined as never before. On the other hand, the time span across which causes are studied will be extended across the entire life course. This change will allow epidemiology to come closer to fulfilling its mission: the identification of preventable causes of premature death and disability.

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