Renal Endowment: Developmental Origins of Adult Disease

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he childhood shews the man / As morning shews the day," wrote John Milton in the 17th Century (1). At the end of the following century, Étienne Geoffroy St-Hilaire, using avian eggs, carried out a series of interesting experiments that suggested that alterations in the environment (e.g., temperature) could influence subsequent development and vasculature in the resulting birds (2). One might proffer additional examples, but it is very clear that humans have understood for centuries, at least in social terms, that events in earliest life preordain much of what occurs in later life. In 1966, back when we guest editors were still pursuing our education, Dubos et al. (3) published a paper about the influence of environment on development, which they proposed to call "biologic Freudianism," and began their treatise with the reference to Milton just quoted. During the 20th century, not only Dubos but also McCance and Widdowson (4,5) and others (6) recognized that early events, often subtle, influence later developmental outcome. However, during the past two decades, new epidemiologic, biochemical, and molecular techniques have emerged, providing new tools with which to address this concept. The issue of how changes in the intrauterine environment might influence adult health has been forged into a novel field of inquiry, now known by terms such as "perinatal programming" or "developmental origins of adult disease." This Frontiers in Nephrology provides three articles to apply concepts from this field to the kidney: A historical accounting that provides the conceptual foundation of the field (7) and reviews of relevant experimental and clinical data (8,9).

One way to consider the concept of perinatal programming and what it means is to consider its other names: Fetal origins of adult disease or developmental origins of health and disease. Organizations such as the Society for Developmental Origins of Health and Disease, which will have its Third World Congress in November 2005 in Toronto, Canada, attest to the high level of interest in the area. The developmental origins concept implies a response to adversity during development, and responses rarely have a single facet. Moreover, according to Gluckman and Hanson (10,11), one should consider both maternal and fetal responses to adverse conditions. The resulting adaptive response thus can be complex. In general, however, the fetus can respond to an unfavorable environment by maturing more rapidly, by conserving nutrients that will restrict or limit its growth, or by aborting. Obviously, fetuses that abort are not subject to develop health problems from fetal origin risks—they do not live to adult life. Thus, what is called fetal programming is probably the result of the other two responses: Attempts to mature more quickly and/or to restrict growth. In terms of the kidney, as the fetus adapts to altered conditions, there may be no renal consequences, or the kidney may be affected adversely (Figure 1) (12).
To provide insight into the renal and cardiovascular grounding of this hypothesis, Barker and Bagby provide a historical note (7). When Barker and his colleagues first proposed that there was a relation between birth weight and cardiovascular disease in later life (13,14), many doubted that the association would prove either important or durable. However, the observation has since been confirmed in many populations and, in recent years, amplified by the concept that nutrition, environment, and intake amplify or minimize the endowment contributed as a life dowry by intrauterine experience (reviewed in refs. 7,12,15). The level of importance of fetal origins, however, is still widely debated. For example, Huxley et al. (16) wrote an article entitled “Unraveling the Fetal Origins Hypothesis: Is There Really an Inverse Association between Birth Weight and Subsequent Blood Pressure?” These authors concluded that the observations attributed to fetal programming are explicable by random error, selective presentation of results, and inappropriate adjustments for confounding factors. Tu et al. (17) raised similar concerns, and some studies, such as those of Falkner et al. (18), did not find an association. However, those in the field present thoughtful responses (summarized in ref. 7) to explain discrepancies. Although it may be simplistic to assert that there is an invariant relation among birth weight, a surrogate, and developmental endowment, the weight of the evidence suggests an important interaction.

Experimental models of fetal programming abound, and many data point to a multifaceted way to understand the phenomenon. As Vehaskari and Woods (8) note at the start of the second paper in this special section, experimental models that are useful in understanding the fetal origins hypothesis should serve two purposes. Such models should provide a controllable construct that limits variation and simplifies genetic variation so that the outcome of the studies is straightforward. In programming, this means that experimental models should inform the observer as to whether the phenomenon is primary or secondary. In addition, such models should provide a system in which to uncover mechanisms. The authors detail the various models and manipulations that have been used.

As nephrologists, we are eager to understand the putative role of fetal programming or fetal origins in terms of human renal disease and cardiovascular disease. Much about programming is considered in terms of nutritional components. Certainly, the intrauterine milieu is influenced by the state of the mother—her nutrition but also her general health, activities, and level of stress. However, because the fetus can be nourished at the expense of the mother, the degree of nutritional deprivation and stress required to cause obvious impairment in humans seems to be substantial. Thus, an additional major factor in fetal development is the function of the fetoplacental/uteroplacental unit. Finally, the genetic makeup of the fetus may inform or shape its response to maternal factors. In the third article presented here, Hoy et al. (9) discuss available data in humans, bridging from the epidemiologic studies to nephron number and considering the relations between nephron number and renal disease and hypertension.

This growing field is not without other controversies. Too much emphasis has been placed on birth weight and subsequent disease. For one thing, birth weight may be considered a “crude surrogate” for changes during development (19). Altered organogenesis can occur in the absence of change in body size at birth. There is evidence that the kidney is particularly at risk. In models of protein-calorie restriction in which the kidney has been examined, kidney weight/body weight is particularly affected. Another issue is that genetic factors are important, both in the fetal response and in response during postnatal development. Finally, postnatal weight gain and the rate of this gain are important.

The prenatal influences of events in utero interact with postnatal events. Thus, individuals who were relatively small but who gain weight fastest after birth are at highest risk (20). Ross and Desai (21) recently made the point that over the course of evolution, various levels of environmental stress have affected both humans and animals. Among these, drought and famine have occurred many times over the millennia. When these extreme events occur while a woman is pregnant, it has been hypothesized that a “thrifty phenotype,” that is, a fetus with slow growth and relatively low birth weight, would be better able to survive. In the premodern era, the relative famine or drought often continued, and so the postnatal growth of the affected neonate would continue proportionally.

Nongenetic influences other than nutrition are also associated with lower birth weight in infants. Maternal smoking has been called the most important factor associated with fetal growth restriction (22,23). It is commonly held that children from poorer socioeconomic conditions and offspring of mothers who had pregnancy-induced hypertension are also at risk. Furthermore, those who are not breastfed, who have high sodium diets in infancy, and who are obese in childhood or adolescence tend to have higher BP in adulthood (24).

At this time, additional causes of intrauterine growth restriction have increased markedly, as higher risk pregnancies progress to term (25). To list a few examples, there is a higher rate of placental insufficiency in women who have previous
conditions that once precluded gestation, who have had previous cesarean sections, or who have had multiple gestations associated with in vitro fertilization. The postnatal rate of growth may be important in setting the course for future health.

It is important to reflect about what happens to the developing kidney and vasculature at different points in gestation to understand fetal origins more completely. Infants who are born early may still be undergoing nephrogenesis. Those infants, often to help them survive, of necessity receive a number of nephrotoxins. These may affect the final waves of nephron formation.

In humans, the complex interactions in which reciprocal inductive events occur between the ureteric bud and the metanephric mesenchyme, the two precursor tissues, are influenced by a myriad of factors. A host of genes are involved in the successive branching events that occur (26). In humans, the short-lived pronephros forms in the fourth week of gestation, and the mesonephros has formed by the end of that fourth week. By embryonic days 35 to 37, the metanephros has formed. Further development occurs over the next 29 wk, relatively speaking, many times longer. Nephrons are finished forming by week 34 of gestation.

The weight of the data on developmental origins of adult disease suggests that nephrogenesis, indeed, is affected by programming. It is important to remember that nephrogenesis is influenced by many genes and is accompanied by rapid remodeling and apoptosis. Experimentally, maternal protein restriction leads to metanephric apoptosis (27,28). The mechanisms may include increased expression of Bax and decreased Bcl-2 expression, which would cause increased caspase-3 activity.

The effects of the intrauterine milieu may also result in epigenetic changes, some of which might be permanent (25,28). Modifications in gene expression controlled by heritable yet potentially reversible changes in DNA methylation and/or chromatin structure form the basis of what is called epigenetics. DNA methylation, the postreplication process by which cytosine residues in CpG sequences CpG (cytosines and guanine connected via a phosphodiester bond) are methylated, forming gene-specific methylation patterns, may occur as part of programming. This process may result in changes in the developmental milieu becoming permanent and transmissible.

Thus, a combination of genetic influences and environmental conditions may lead to adaptive responses that have a significant impact on the kidney or cardiovascular system (Figure 2). The concepts of developmental origins of adult disease have relevance for all nephrologists. For example, pediatric nephrologists treat many small and premature neonates who have not yet finished nephrogenesis. These small newborns are at particular risk for later renal and cardiovascular disease. How to prevent such infants from developing disease later is an important mission that goes beyond nephrotoxins and nutritional stress in the neonatal intensive care unit. Learning how to maximize nephrogenic potential and maintain renal functional reserve should be a major research priority. Developmental nephrology has progressed to an understanding of many of the involved processes and the genes that control them. However, delineating how the sequence changes when the intrauterine milieu is altered remains incomplete. Understanding the factors that lead to later risk might potentially prevent much disease. For example, does the great increase observed recently in the incidence of focal segmental glomerulosclerosis (29) reflect an unfortunate confluence of genetic, environmental, and social factors leading to untoward effects on renal development? If so, then our ability to identify such factors or those who are affected by them would be extremely valuable. Knowing who is at risk would allow all who care for such people to recommend and prescribe a course of medical care that will maximize renal potential. There is much to be learned.

Figure 2. Hypothetical impact of genetics and environment on renal development and disease. Nephron endowment seems to be particularly sensitive to the impact of intrauterine growth restriction. If rapid somatic growth occurs subsequently, then the kidney may not be able to respond with an increase in nephron number. Resulting adaptive hypertrophy of existing nephron endowment renders the kidney susceptible to hypertensive and sclerotic events.

References
8. Vehaskari VM, Woods LL: Prenatal programming of hyp-