Novel Concepts in the Developmental Origins of Adult Health and Disease

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The seminal epidemiological observations of David Barker demonstrated that birth weight across the normal range is inversely proportional to the risk for hypertension, cardiovascular disease, and type 2 diabetes in adulthood (1). Increasing evidence suggests that either low birth weight or accelerated postnatal weight gain or a combination of the 2, may predispose the above diseases (2). As a consequence of these observations, David Barker developed a theory, the now eponymic “Barker hypothesis,” proposing that adverse events in utero induce compensatory responses in the fetus that reflect “developmental plasticity” during this critical period (3) and persist permanently, thus defining an altered phenotype not only at birth but also for a lifetime. In other words, altered developmental programming limits the range of postnatal adaptability, creating disease vulnerability (4).

Also called the “fetal or developmental origins hypothesis,” this provocative theory is both stimulating and challenging for evolutionary human biologists (5). Several themes that are fundamental to human biology emerge from an engagement with the possibility that alterations in fetal developmental programming can direct adult health consequences. Included among these are 1) the “tensions” among traditional concepts of genes and environments; 2) constraints and adaptation and the pathophysiology of disease; 3) mechanisms of energy mobilization, allocation, and fuel partitioning; 4) the mechanism of cellular “memory” of fetal events throughout the postnatal lifespan; 5) the importance of a life history perspective that embraces the notion of trade-offs; and 6) questions of environmental predictability or determinism. The insights that evolutionary biology provides about the “developmental origins hypothesis” illustrate the value of the field now known as evolutionary medicine.

The review by Sir Patrick Bateson (4) discusses developments in plasticity and brings together clinicians and evolutionary biologists. The primary observation is that individuals have many latent capacities that evolved from their specific genetic endowments but that specific capacities are expressed only under certain conditions. The principle is that developmental plasticity processes are triggered by the in utero environment. In an adverse in utero environment, pathological stunting represents a sign of a poorly adapted phenotype and forecasts an environmental maladaptation in postnatal life. Thus, for example, such children no longer have the ability to fully adapt to the affluent environment in which they are raised, a vulnerability that leads to the adult phenotype of the metabolic syndrome. Sir Patrick (4) does not favor use of the term “programming” of the developing organism because it implies that the programming instructions were provided by the environmental influences to which the individual was exposed. He suggests using the term “environmentally elicited” because the development of alternative phenotypes are elicited by environmental influences.

The “developmental origins hypothesis” clearly requires the fetus to make cellular, metabolic, and physiological adaptations in response to changes in its environment to prepare itself for postnatal life. Now well-described epigenetic modifications of gene expression may provide a basis for some of these changes (6,7). The “thrifty phenotype hypothesis” explained the association between insufficient in utero nutrition and the later development of type 2 diabetes (8). In this context, the second article in this symposium by Johan Eriksson (9) examines genotypic contributions to expressed phenotypes, showing the importance of gene polymorphisms to birth size and development of type 2 diabetes and hypertension. Dr. Eriksson delineates the interactions between intrauterine growth and genes in relation to adult disease outcomes. His first illustrative example, an important polymorphism in the peroxisome proliferator-activated receptor gene that results in a Pro12Ala missense mutation in the protein’s functional domain, protects against appearance of type 2 diabetes in low-birth-weight infants (10). On the other hand, he also shows that the K121Q polymorphism of plasma cell glycoprotein-1 gene is positively associated with type 2 diabetes and hypertension in adults born with low birth weight (11). Likewise, an angiotensin-converting enzyme insertion/deletion polymorphism is associated with type 2 diabetes in adults who were born small (12). These illustrative genotypic associations with low birth weight are beginning to provide insight into the loci of plasticity responsiveness at the DNA level and the mechanism(s) by which environmental conditions during development lead to individual variability in growth response and adult disease phenotype. Thus, these findings may eventually illustrate “developmental plasticity.”
when defined as a single genotype giving rise to a range of different phenotypes.

It is also plausible from experimental studies that a range of molecular, cellular, metabolic, neuroendocrine, and physiological adaptations to changes in the early environment produce a permanent alteration of the developmental pattern of cellular proliferation and differentiation in key tissue and organ systems that result in pathological consequences in adult life (13). Dr. Susan Bagby's article provides a clear proof-of-principle (14), advancing the view that low-birth-weight infants might have a permanently reduced nephron number, with resultant hypertension later in life.

Dr. Bagby's thesis, based on her significant data set, is that fetal developmental insults that are manifest by low birth weight include a corresponding reduction in nephron number. If postnatal growth is accelerated, the resultant increased body mass generates a correspondingly increased excretory load on a kidney with limited excretory capacity. In return, this induces tubular and glomerular hypertrophy with single-nephron hyperfiltration and renin-angiotensin II activation that maintain a normal glomerular filtration rate at the expense of developing hypertension.

In addition, the discussions during the Symposium raised many other possible contributing factors to the pathophysiology of adult disease phenotypes recognized as consequences of the “Barker hypothesis.” Developmental maturation of the hypothalamic-pituitary-adrenal axis has been shown to be susceptible to fetal programming. Thus, it is hypothesized that an adverse fetal environment alters the “set-point” of the hypothalamic-pituitary-adrenal axis, leading to increased activity of the hypothalamic-pituitary-adrenal axis and subsequent increased cortisol concentrations (15). Related recent work has also demonstrated similar “developmental programming of hypothalamic feeding circuits” (16) and of maternal care-giving behavior on the hypothalamic glucocorticoid receptor (17). Most importantly, in the latter case, there has been a recent further demonstration that such epigenetic programming can be altered by diet in adult life (18,19).

Additionally, oxidative stress has been hypothesized as a common link underlying associations between adverse fetal growth or preterm birth and elevated risks of certain chronic diseases (20). The mechanisms of oxidative stress programming may be through directly modulating gene expression or indirectly through the effects of certain oxidized molecules. Experimental investigations have well demonstrated the role of redox balance in modulating gene expression, and recent studies indicate that both the insulin functional axis and blood pressure may be sensitive targets to oxidative stress programming. Because oxidative stress levels are readily modifiable during pregnancy and in early postnatal periods (both plausible critical developmental “windows”), the hypothesis, if proved valid, will suggest new measures that could be very helpful in fighting the adverse consequences of adult hypertension, type 2 diabetes, and cardiovascular disease (20).

Barker’s seminal epidemiological findings, that people who were small at birth have an increased risk of cardiovascular disease, type 2 diabetes, and hypertension, has been of immense importance because it opened an entirely new field. The development of this field has identified key questions related to the relationships among in utero growth, genotype–phenotype expression, gene interactions, and environmental/epigenetic influences during critical periods of ontogeny. However, the field, although now unequivocally established, is still in its infancy, its own critical developmental period, so to speak. Thus, for most of the epidemiological observations central to adult human health and disease, we still lack specific mechanisms for the observed effects. Further, some very fundamental issues relating to the low-birth-weight phenotypes that signal adverse adult consequences have not yet been clarified in humans. For example, in the developed world, “small” infants have birth weights that are at the large end of the birth-weight scale in developing countries. Yet, these infants of similar birth weights exhibit different adult outcomes. How can this be explained? Also, after a gestation of normal length, an abnormally low birth weight may be the result of recognized genetic growth defects or the result of a restricted intrauterine environment as a result of anatomical conditions, abnormal uterine blood flow, or nutritional inadequacy. These infants are small for gestational age. On the other hand, if gestation terminates early, an infant may be born with a low birth weight that is the result of true prematurity, but with a weight that is appropriate for gestational age. Not surprisingly, the issue of birth-weight phenotype is further confounded by the fact that many infants who are born inappropriately small for their gestational ages are also born truly prematurely. How these different low-birth-weight phenotypes segregate in epidemiological studies of the developmental origins hypothesis has not been adequately studied. Research to define specific relationships among adult disease outcomes and low-birth-weight infants who are the consequence of intrauterine growth retardation and those who are the result of decreased gestational age, or both, is sorely needed. Similarly, careful systematic review of reported effects, including meta-analysis of available data when appropriate, is necessary to construct a defensible evidence-based, hierarchic classification of the variously described relationships.

Nonetheless, the “predictive adaptive response” hypothesis proposes that the degree of mismatch between the pre- and postnatal environments is an important determinant of subsequent disease. We believe that continued investigation of the mechanisms underlying current assumptions themselves underlying theoretical relationships of developmental origins of adult disease will immensely advance our knowledge of human ontogeny and its impact on adult health.

**Literature Cited**