A Critical Evaluation of the Fetal Origins Hypothesis and Its Implications for Developing Countries

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Professor David Barker and his colleagues at the MRC Environmental Epidemiology Unit in Southampton, U.K. have developed the theory that several of the chronic diseases associated with aging may be programmed in very early life (1). Their ideas were initially described as the fetal origins of adult disease hypothesis and, in spite of the existence of a significant body of earlier animal data pointing to the existence of early life programming, were met with much skepticism (2). This skepticism persists with regard to many of the details of the associations and the causal pathways (3,4), but few would doubt the basic conclusion that an organism’s nutritional experience during critical periods of ontogeny can have permanent effects on how it later responds to its environment. In short, the backbone of the theory has graduated from hypothesis to accepted biology even though the details remain controversial.

One of the central tenets of the early programming theory is that the effects are most pronounced when there is a mismatch between early nutritional deprivation and later nutritional affluence. In the West this is manifest in the fact that the detrimental effects of intrauterine growth retardation are most clearly seen in populations that have become overweight and obese in adult life (1,4).

The great majority of low-birth-weight babies, and, by inference, of growth-restricted fetuses, are born in developing countries (3). This might not be of great significance if these populations remain lean, fit and frugal, because studies under such conditions show very few risk factors for chronic diseases (hyperinsulinemia, hypertension, hyperlipidemia) and no detectable association with maternal nutrition during pregnancy (e.g., 6). However, with increasing affluence the obesity pandemic is now penetrating into many developing countries, especially in urban areas (7). Until this newfound affluence feeds through to produce larger mothers and larger babies, a process likely to take several generations, it is suggested that these developing-country settings are where the fetal origins theory is most relevant. It was for this reason that the Society for International Nutrition Research (SINR) convened a symposium at EB 2003 in San Diego to take a critical look at the evidence and explore the experimental paradigms that will be required to reach a better understanding of the basic biology, and hence of the health implications.

From frugal origins to affluent futures: human metabolism stressed by excess

Poor peoples in developing countries can be viewed as having been exposed to four phases in which nutritional deprivation may have imprinted itself on their metabolic makeup: an evolutionary phase with frequent famines selecting what J. V. Neel termed a thrifty genotype (8); an intergenerational phase in which the failure of women to grow to their full genetic potential imposes uterine restraint on the developing fetus; a fetal phase; and a postnatal phase. Any of the latter three phases might create what Hales and Barker have termed a thrifty phenotype in which the metabolic and endocrine control systems are tuned to expect a meager substrate supply and are ill-adapted for later nutritional excess (9).

Evolutionary selection of a thrifty genotype

An examination of historical records, such as those listed by Ancel Keys and colleagues in their seminal report on the biology of human starvation (10), is sufficient to make the point that the ability to survive starvation must have been a major factor in selecting the genetic makeup of modern humans, particularly in the ~12,000 y since the advent of agriculture, because this development made populations vulnerable to occasional catastrophic crop failures and famines (11). In the twentieth century most natural famines (i.e., excepting those caused by humans’ inhumanity to fellow humans) affected the Indian subcontinent and sub-Saharan Africa, so it is natural to assume that these populations may carry a greater preponderance of thrifty genotypes. This might be the case, but is not necessarily so, because an examination of the earlier
historical record shows that all of humanity has been regularly challenged by famine to a surprising degree (12); it may therefore be misleading to impute a greater genetic thriftiness in people from the developing countries of today.

It is noteworthy that Neel’s original speculation about the thrifty genotype arose from observations in relation to fetal overgrowth in mothers with gestational diabetes. The original concept was of a fetal thriftiness, even though many of the later interpretations have tended to focus on the idea that thriftiness was selected for by the ability of adults to survive starvation (c.f., the diabetes-prone Polynesians as survivors of long sea voyages). In fact a close look at the statistics of when during the life cycle most Darwinian selection occurs yields the surprising finding that most selection occurs prenatally (see Fig. 1). This may have important implications for our understanding of how genetic factors may contribute to the observed associations among size at birth, later growth and adult disease, and must be factored into our thinking (13,14).

**The intergenerational cycle of fetal growth restriction**

The early breeding studies of Walton and Hammond, in which dwarf Shetland ponies were crossed with Shire horses several times their size, showed conclusively the importance of the maternal uterine environment in constraining fetal growth so that the mother can deliver an appropriately sized offspring (15). Such effects also operate in humans, with small mothers (especially in southern Asia) producing small babies (16,17). The effects have complex modes of transmission from generation to generation, but, aside from the subtleties, it is clear that several cycles of good nutrition are required to ameliorate them. Until this has happened, populations of small mothers pose a real dilemma in terms of how rapidly and aggressively we should try to intervene with supplementary feeding initiatives, because there is some concern that acute interventions have tended to focus on the idea that thriftiness was selected for by the ability of adults to survive starvation (c.f., the diabetes-prone Polynesians as survivors of long sea voyages). In fact a close look at the statistics of when during the life cycle most Darwinian selection occurs yields the surprising finding that most selection occurs prenatally (see Fig. 1). This may have important implications for our understanding of how genetic factors may contribute to the observed associations among size at birth, later growth and adult disease, and must be factored into our thinking (13,14).

**Fetal growth restriction and the thrifty phenotype**

The possibility that fetal growth restriction may create a thrifty phenotype disadapted to later affluence has been described and discussed at length elsewhere and so requires little amplification here. Approximately 95% of the world’s low-birth-weight babies are born in the developing world, and the majority of these are growth restricted rather than premature (5), lending emphasis to the argument that Barker’s theories may be most relevant here.

**Postnatal growth restriction and the thrifty phenotype**

Most of the discussion of the early-life theory of adult disease has concentrated on fetal growth restriction, although even some of the earliest publications described associations with weight at 1 y of age (19). The subsequent interest in postnatal growth has tended to focus on rapid growth as a risk factor for later disease, especially where there is a pronounced divergence between fetal and postnatal growth trajectories (4,20–23). In many areas of the developing world, the combination of poor diet, persistent gastroenteropathy and infections leads to serious growth faltering in whole population groups and life-threatening malnutrition in a substantial subset. Figure 2 shows some fairly typical growth trajectories, in this case in rural Gambian children. At birth the babies’ Z-scores for weight and length are $\sim -0.8$. They grow rapidly during the first postnatal months when fully breastfed, then show a precipitate deterioration to $\sim -2$ $Z$ by the end of infancy. This implies that the postnatal stresses are actually greater than the prenatal stresses. It may be that such stresses have less impact on longer-term metabolic function because the great majority of the cell divisions required to create the fully differentiated organism occur prenatally; however, there may be plenty of remaining scope for entraining endocrine systems. The later consequences of this early growth failure merit closer examination to determine the extent to which they may contribute to the development of a thrifty phenotype.

The papers that follow address some key methodological and theoretical issues related to fetal origins of chronic disease, with an emphasis on the developing-country context, and include case studies of diabetes in India and hypertension in populations of African descent.

Cole’s paper (24) raises important questions about the interpretation of evidence of inverse associations of birth size
with later disease risk only after accounting for current size. Although such findings have been interpreted as evidence of fetal programming, Cole argues for the alternative explanation that rapid postnatal growth is the main risk factor. He then proposes use of life-course plots as a straightforward way to understand the role of size and weight gain simultaneously. He demonstrates the utility of this approach using data from longitudinal studies in Brazil and the Philippines. Life-course plots depict the effects of changing Z-scores for weight (and thus accelerating or decelerating growth) on outcomes such as blood pressure. When such plots reveal interactions of size and growth, they support the hypothesis that prenatal factors alter sensitivity to postnatal influences on growth.

Kuzawa (23) reminds us that although the central tenet of the fetal origins hypothesis involves nutritional programming, research in humans is most often based on birth size, which is a flawed indicator of prenatal nutrition. He proposes a supply-demand model that focuses more squarely on nutritional sufficiency. The supply-demand model suggests that supply (nutritional intake) will be highest in those individuals who fail to reach their growth potential in utero (i.e., when fetal demand outstrips maternal supply). He finds support for this hypothesis in the case of low density lipoprotein cholesterol in Filipino adolescent males. The supply-demand model is useful not only in the context of refining our characterization of exposures that lead to programming, but in understanding intergenerational processes.

The following two papers focus on chronic diseases with dramatically increasing prevalence rates in countries undergoing rapid development: diabetes in India, and hypertension in populations of African descent.

Yajnik (26) provides important evidence for how body composition is affected by the circumstances characteristic of developing countries in transition. The small birth size of Indian babies is associated with a deficit of skeletal muscle but not body fat. Similarly, the Indian adult who experiences relative nutritional excess has more central adiposity, but retains a smaller skeletal muscle mass. This phenotype has metabolic consequences and is associated with insulin resistance and type 2 diabetes. In its description of the Pune studies, Yajnik’s paper also provides an excellent example of a study design that can produce the kind of data needed for more rigorous testing of the fetal origins hypothesis in human populations. The Pune studies begin in pregnancy, then follow offspring for long periods of time during which diet and body composition are carefully assessed. Such well-controlled prospective studies are needed to establish a basis for causal inferences.

Forrester (27) notes the gradient of hypertension observed in populations with increasing adiposity and salt intake. He explores the possible underlying genetic and historical factors that might explain high rates of hypertension in populations of African descent, and considers the extent to which the risk factors as well as the outcome may be prenatally programmed. Forrester finds no evidence that hypertension in populations of African descent is any more likely to be the result of early programming than it is in other populations. Rather, the high rates of hypertension reflect a similar history related to increasing exposure to lifestyle factors associated with increased salt intake and obesity.

The papers share several common themes. First, they point to the importance of intergenerational influences on chronic disease. Second, they draw our attention to the need to fully characterize the nutritional exposures rather than relying on poor proxies such as body weight. Third, they support the notion that prenatal factors contribute to a phenotype that may be more sensitive to lifestyle factors associated with the development of obesity and the chronic diseases with which it is associated. Finally, they suggest important directions for future research, which should include prospective measurement of maternal nutrition during pregnancy, more refined indicators of fetal growth restriction, careful consideration of body composition and appropriate modeling of postnatal influences.

**LITERATURE CITED**