

*Wiley-Liss Plenary Symposium*

## Evolutionary Perspectives on the Fetal Origins Hypothesis

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**ABSTRACT** The fetal origins hypothesis, or Barker hypothesis, is both stimulating and challenging for evolutionary human biologists. While evidence of a correlation between conditions around the time of birth and later health outcomes has been presented before, the more recent evidence of a connection between fetal growth and chronic disease risk later in life has attracted considerable attention among epidemiologists and human biologists. Several themes that are fundamental to human biology emerge from an engagement with the fetal origins hypothesis. Among them are the tension between concepts of pathology, constraint, and adaptation; the importance of a life history perspective that embraces the notion of trade-offs; the question of environmental predictability; and the mechanisms of energy mobilization and allocation. Bringing the insights of evolutionary biology to bear on the fetal origins hypothesis illustrates the value of the field now known as evolutionary medicine. *Am. J. Hum. Biol.* 17:113–118, 2005. © 2004 Wiley-Liss, Inc.

Developmental plasticity is a fundamental concept in human biology, as the articles in this plenary symposium amply demonstrate. Indeed, one could easily organize an entire course in human biology using the topics touched on in this symposium. The purpose of this brief article is not to reprise all the excellent material in the individual contributions to this symposium, but rather to draw out and comment on a few of the important themes that run through the symposium set as a whole. Even as these studies represent human biology in microcosm, the themes that run through them are fundamental not only to this plenary session, but to the entire discipline of human biology.

## THE BARKER HYPOTHESIS AND ITS ANTECEDENTS

The so-called Barker hypothesis (Barker, 1994), also known as the fetal origins hypothesis or the fetal programming hypothesis, provides a primary motivation for many of the articles from the symposium, and for the symposium itself. The significance of the Barker hypothesis to the epidemiological community lies in the statistical correlation that Barker and his colleagues demonstrated between conditions prevailing at about the time of birth and early infancy and morbidity and mortality due to chronic diseases late in life. Two prime examples are the relationship observed between coronary heart disease mortality

and weight at 1 year of age, and the relationship between the incidence of adult-onset diabetes and birthweight (Barker, 1995). The strength of the relationships observed for some chronic diseases drew the immediate attention of epidemiologists, suggesting the presence of significant risk factors early in life and possibly new prevention strategies. At the same time, these relationships drew the interest and curiosity of human biologists, suggesting as they did important linkages between life history stages. Epidemiologists, then, were drawn to these observations for their potential value in understanding pathology. Human biologists were drawn to them for their potential relationship to normal biology and more fundamental aspects of human life history.

Of course, like most important ideas, the Barker hypothesis has its antecedents, both in the realm of epidemiology and in the realm of human biology. Forsdahl (1977) published an article in 1977 noting that regional variation in coronary heart disease mortality among Norwegian men 40–70 years old in 1970 was more highly correlated with infant mortality rates in 1896–1925, when the cohort

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was born, than with conditions prevailing at the incidence of the disease. Similarly, I noted in 1981 the close correlation between the infant mortality rate for birth cohorts in Norway over the past century and the average age at menarche for women in each birth cohort (Ellison, 1981). Despite these foreshadowings, Barker and colleagues deserve credit for calling major attention to these developmental relationships and their importance to an understanding of human disease.

The tension between an epidemiological perspective that is rooted in notions of pathology and dysfunction and a human biological one that is rooted in notions of integration and adaptation is reflected in many of the articles from this symposium set, and even in Barker's own interpretation of the biology underlying his observations. On the one hand, low birthweight is taken by Barker to be the consequence of maternal undernutrition and an inability to allocate sufficient energy to support the adequate growth and development of all fetal organ systems, resulting in physiological deficiencies that lead to chronic disease in later life. On the other hand, Barker advanced an explicit trade-off hypothesis suggesting that the sparing of fetal brain development under conditions of low energy availability leads to the deficits in the growth of other organs systems underlying the elevated risk of chronic disease (Barker, 1994). At play, then, are three concepts that seem different, and even fundamentally opposed, and yet come to coexist in the interpretation of the linkages between early life conditions and adult chronic disease: pathology, constraint, and adaptation. Is the predisposition to adult disease of a low birthweight child a consequence of pathological dysregulation of normal development, a failure of developmental homeostasis: a physiology that is "broken"? Or is it a consequence of normal, "healthy" physiological process operating under external constraint (lack of sufficient energy), resulting in sub-optimal outcomes: physiology trying to do something that it can't accomplish? Or is it the consequence of an adaptive response to certain challenging conditions, producing a trade-off that might be worse compared to what is possible under better conditions, but one that is in fact "optimal" for the circumstances at hand: physiology successfully accomplishing its mission? This is a tension that an epidemiologist may choose largely to ignore, since which of these interpretations

is correct does not materially affect the predictive power of early life conditions as risk factors for adult disease. For a human biologist, however, the tension is fundamental, not only to an understanding of the phenomenon of "fetal programming," but also to the entire domain of human biology and its relationship to human health.

#### TRADE-OFFS IN EVOLUTIONARY BIOLOGY AND LIFE HISTORY THEORY

The key to resolving this fundamental tension, as many of the articles from this symposium suggest, lies in the concept of necessary trade-offs that underpin evolutionary life history theory. Jones (this issue) cites the trade-off framework originally introduced by Gadgil and Bossert (1970), which posited that energetic resources available to any organism must be partitioned among competing physiological domains. The three domains that they identified as the first level of partitioning are growth, maintenance, and reproduction. But this tripartite categorization represents only the first level of partitioning. Within any of these three domains additional trade-offs can be identified, and several are alluded to in this symposium. For example, Barker's hypothesis identifies a trade-off in fetal energy allocation between brain growth and somatic growth. McDade (this issue) notes the trade-off that is encountered by the developing immune system, one of our foremost maintenance systems, between propagation of cell-mediated immunity versus humoral immunity. Energy allocation in the reproductive domain faces multiple trade-offs that are well documented in the field of reproductive ecology. Pike (this issue) identifies several of these, including the trade-off that mothers face between investments in current versus future offspring.

In the context of life history theory, developmental programming seems to many to require a similar analysis in order to be understood as functional. In 1990, noting the empirical association between the tempo of childhood growth and adolescent maturation in human females on the one hand and subsequent levels of adult ovarian function on the other, I suggested that the reproductive system might be coupled to juvenile growth as if the latter provided a "bioassay" of prevailing conditions of energy availability (Ellison, 1990). Set points for adult ovarian function might be established with the information

provided by this "bioassay" as one of the primary conditioning variables. Several of the articles from this symposium suggest that fetal programming may reflect a similar phenomenon, whereby energetic conditions experienced by the fetus are used to determine set points for subsequent developmental trajectories. The downstream consequences of this physiological coupling, in terms of increased susceptibility to chronic diseases in mid to late adulthood, may only be one side of a trade-off that also includes optimization of development to prevailing conditions.

It should be noted that construing the phenomena of fetal programming in this way, as facultative adjustments to developmental trajectories in order to optimize energy allocation later in life, differs from Barker's own interpretation. Barker (1995) identifies the trade-off in energy allocation as occurring between contemporary alternatives, investment in fetal brain, or investment in fetal soma, with downstream effects being consequences, not objectives, of this trade-off.

#### ENVIRONMENTAL PREDICTABILITY

Although appealing in many ways, understanding fetal programming as a facultative developmental adjustment generates difficulties as well, as noted by several symposium participants. One important sticking point is the notion of environmental predictability. The period of childhood and adolescent growth may provide a valuable "bioassay" of prevailing energetic conditions for setting adult ovarian function because it integrates the experience of a decade and a half, perhaps with extra weight given to the years leading up to reproductive maturation. Such integrated information may provide a useful basis for predicting energetic conditions during the prime reproductive years of a woman's life. But does fetal growth integrate a sufficient amount of information to justify the establishment of long-term developmental set points?

The answer to this question depends on the assumptions one makes regarding environmental predictability, or the temporal grain of uncertainty in environmental conditions. If environmental predictability were low, then it would be difficult to argue that integrating information over 9 months of pregnancy provides a sufficient basis for optimizing long-term developmental set-points. The strategy only appears to make sense if there is a high

correlation between the conditions faced by the pregnant mother and those that will characterize the environment in which her offspring mature. Horton (this issue) provides an excellent example of high predictability in her presentation of the influence of photoperiod cues on reproductive seasonality in rodents. If, however, the tempo of change in environmental conditions is rapid and unpredictable, the likelihood of achieving optimal trajectories by conditioning on fetal growth is low.

Many human biologists assume that the grain of environmental uncertainty has been fairly fine over the course of human evolution, and that predictability is low across relatively short periods of time (e.g., seasons to years). Such an assumption makes an adaptive view of fetal programming problematic. It would appear to be maladaptive to make developmental trajectories and adult physiology overly sensitive to cues that may have little correlation with later environmental conditions. Several of the articles from this symposium point out this paradox.

Kuzawa (this issue), however, suggests that there may be value in adopting the alternative assumption regarding the grain of environmental uncertainty. If the tempo of environmental change is slow, on the order of decades to generations, then resetting developmental trajectories for each generation on the basis of achieved fetal growth might be adaptive. Kuzawa invokes the concept of "developmental inertia" to suggest that, rather than making developmental trajectories hyperresponsive to short-term fluctuations in environmental conditions, fetal programming might buffer development from such abrupt changes, linking biological set-points across generations by tying fetal developmental trajectories to maternal biology.

Kuzawa's perspective is both novel and promising. It places the phenomenon of fetal programming within the framework of evolutionary human biology in a satisfying way. It also suggests that correlations may be uncovered linking developmental trajectories and adult health outcomes to conditions even further back in time than the fetal period, correlations that link developmental trajectories across generations. Intergenerational research may be difficult to implement, but may hold important keys to understanding human life history dynamics and predispositions to chronic disease. Intergenerational

linkages in physiology may even yield new insights into the phenomena of secular trends and other slow-tempo, multigenerational changes in human biology. If intergenerational effects become well established, they will constitute a new domain in the temporal continuum of adaptive response to environmental challenges, intermediate between more conventional developmental adjustments occurring within an organism's lifespan and genetic change in populations across generations. This is an exciting and challenging prospect for human biologists to consider.

It should be noted, however, that the various temporal domains of adaptive adjustment are not mutually exclusive. Environmental challenges occur on many time-scales simultaneously. It is one of the remarkable features of organismal biology that responses can occur on many time-scales simultaneously as well. Deconvoluting the reality of environmental change and uncertainty into trends and patterns with different timescales is an exceedingly difficult problem. But it appears that evolution has honed our physiology to do just that with remarkable success.

#### ENERGY MOBILIZATION AND ALLOCATION

Because trade-offs in energy allocation between competing alternatives play such a fundamental role in life history theory, the mechanisms of energy mobilization and allocation are also central. Several of the symposium articles focus on these mechanisms at some length, with particular emphasis on the physiological regulators—chiefly hormonal—that channel energy allocation within the organism (Crespi and Denver; Horton; Lampl; Worthman; all this issue). Two hormonal axes in particular feature in several articles: the hypothalamic–pituitary–thyroid (HPTh) axis and the hypothalamic–pituitary–adrenocortical (HPA) axis. These two hormonal axes share many features in common: short-chain peptides released by the median eminence of the hypothalamus into the hypophyseal portal system trigger the release of tropic protein hormones from the anterior pituitary. The tropic hormones travel through the systemic circulation to target their respective glands (thyroid and adrenal cortex), which in turn secrete small, lipid soluble hormones, thyronines or corticosteroids. These lipid soluble hormones are transported through the blood by specific and nonspecific

binding proteins from which they disassociate to enter target cells, there to interact with nuclear receptors of the same superfamily and thereby regulate gene transcription. Both axes are regulated by negative feedback at both the hypothalamic and pituitary levels. And most importantly for the present discussion, both have powerful effects on energy metabolism.

Thyroid hormones can be thought of as global energy regulators in humans. Decreases in thyroid hormone levels generally cause reduced energy turnover throughout the body, with broad consequences, reducing cognitive function, immune function, reproductive function, physical activity, thermogenesis, and growth processes. Increased thyroid hormone levels have the opposite effects. Corticosteroids have similar effects but on a shorter time-scale, mostly mediated by their actions on carbohydrate metabolism, increasing the mobilization of glucose into the blood and biasing any storage of glucose toward glycogen and away from fat and protein. Corticosteroids also have potent antiimmune and antiinflammatory actions and antagonize the effects of sex steroids at many levels of the reproductive system. Thus, corticosteroids are situated, functionally, to help regulate the trade-off between concurrent anabolic and catabolic processes. Thyroid hormones are situated, functionally, to help modulate the overall rate of energy consumption, affecting both types of processes.

Given this broad characterization, we might expect to find the HPTh axis involved in fetal programming if the goal of adaptive adjustment is an overall acceleration or deceleration of energy turnover to match environmental conditions. If, on the other hand, fetal programming is a matter of shunting energy to support brain development at the expense of other tissues, we might expect to find the HPA axis involved. Raising the set point for the HPTh axis would accelerate fetal growth in a global way, while raising the set point for HPA axis activity would increase levels of blood sugar, favoring brain development, at the expense of energy allocation to the accumulation of other tissues. Coupling increased HPTh activity to decreased HPA activity would intensify the former effect, while coupling decreased HPTh activity to increased HPA activity would intensify the latter effect. Focusing on these two major energy regulation systems as aspects of fetal physiology might therefore shed important light on

both the function of fetal programming as well as the mechanisms underlying it.

In their article, Crespi and Denver (this issue) provide a wonderful illustration of these metabolic regulatory systems at work controlling trade-offs in energy allocation and precipitating the developmental cascade of amphibian metamorphosis. For tadpoles developing in vernal pools and other transient water sources, shrinking pool volume leads to reduced oxygen availability and precipitates a "metabolic crisis." The physiological response to this crisis includes an upregulation of the HPA axis to increase the availability of metabolic fuel. This fuel comes from the catabolism of other tissues, however, undermining further growth and reducing survival probability. HPA activation alone cannot, therefore, be a long-term solution to the crisis. Instead, the high levels of corticotropin-releasing hormone (CRH) that are released from the hypothalamus to stimulate HPA activity also act to release thyroid-stimulating hormone (TSH) from the pituitary, which in turn stimulates thyronine production by the thyroid. The global acceleration of growth and development triggered by this system precipitates the metamorphosis from an aquatic to a terrestrial soma and physiology.

A very similar cascade is involved in the onset of human parturition. Elsewhere (2001), I have described the "metabolic crisis" faced by the developing fetus as it approaches term. The increasing energy demands of the developing fetus, and in particular the fetal brain, begins to outstrip the flow of energy across the placenta. At this "metabolic crossover" point the fetus upregulates its own HPA axis to increase the supply of metabolic fuel available to support its ravenous brain. The increase in corticosteroids flowing to the fetal side of the placenta triggers a positive-feedback response by cells that produce CRF locally in the placenta. This signal in turn leads to a cascade of events including the increased production of placental prostaglandins leading to the initiation of parturition. Even as the tadpole is propelled from its watery crèche onto the land by events that are released by a shift in energy allocation away from growth and towards survival, so the human fetus is propelled from its watery gestational environment into the cold light of day by a similar shift in energy allocation. Crespi and Denver (this issue) show that manipulation of the

oxygen content of the tadpole's pool can advance or retard metamorphosis. In the same way conditions that advance or retard the metabolic crossover for human fetuses, conditions such as maternal diabetes, gestation at high altitude, maternal undernutrition, or multiple pregnancies, can advance or retard the onset of parturition in predictable ways (Ellison, 2001).

It is possible that shifts in energy allocation govern other important transition points in human life histories, such as puberty (Ellison, 2002) and postpartum resumption of ovarian function (Ellison and Valeggia, 2003), and even more gradual transitions such as senescence. As in the case of amphibian metamorphosis and human parturition, shifts in energy allocation can be both the precipitating causes and the more lasting consequences of these developmental transitions. An interesting question touched on by many of the symposium participants is whether there is a functional integrity to human life histories that would link the timing of early developmental transitions to the timing of later ones. If small birth weight is a result of an earlier onset of the metabolic crossover that precipitates parturition, will it also be linked to alterations in the timing of puberty, or to set-points for adult energy metabolism or gonadal function? This is an alternative framing of the Barker hypothesis making more explicit its relationship to both the proximate mechanisms and the functional outcomes that are the domain of life history theory.

#### EVOLUTIONARY MEDICINE AND THE CONCEPT OF HEALTH

The focus of the Barker hypothesis, and of this symposium, is on the consequences of fetal programming for subsequent health outcomes. By grounding the Barker hypothesis in evolutionary biology, the symposium participants also locate this central aspect of the Barker hypothesis within the domain of evolutionary medicine. The perspective of evolutionary medicine is broader than that of traditional medicine and public health in many ways, including its embrace of the reality of biological trade-offs. This perspective helps to resolve the tension referred to earlier between the concepts of pathology, constraint, and adaptation by recognizing that "health," in the unqualified sense, may never be attainable. Traditional medicine

tends to operate on the basis of an implicit dichotomy between states of “health” and “disease,” seeking means to identify disease states and return them to healthy states. But evolutionary medicine highlights other sets of alternatives that may often represent the realistic alternatives faced by an organism. Those alternatives may, for example, contrast disease state 1 (say, osteoporosis) with disease state 2 (say, breast cancer). It may not be possible to simultaneously reduce the chances of both disease states, producing a conundrum for physicians and patients alike. Or the alternatives may be health now versus health later, muscle growth now versus prostate cancer risk later. Health as a single, attainable, and sustainable state may be a heuristic, but ultimately unrealistic, concept. Fetal programming—adjustments in subsequent development and physiology that are correlated with, and perhaps precipitated by, the course of

fetal development—will likely be best understood and integrated into the broader perspective supplied by evolutionary medicine.

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