Introduction

Fetal Origins of Developmental Plasticity

The finding that prenatal nutrition has effects on adult health has heightened interest in the mechanisms and consequences of developmental plasticity. While most fetal programming research has focused on the role of prenatal exposures in the development of cardiovascular disease, the evolutionary implications of these findings have received less attention. The articles in this special issue showcase the range of approaches that are currently being used to explore the evolutionary significance of fetal developmental plasticity, both in humans and animal models.

The study of developmental plasticity has occupied a special place in the history of human biological and anthropological research. Boas (1912) used the natural experiment of immigration to demonstrate the sensitivity of child growth to the environment of rearing, bringing into question the concept of the fixity of types that had dominated early anthropological thinking about human diversity. While Boas' agenda was explicitly nonevolutionary, subsequent research highlighted both the pervasiveness of plasticity and its adaptive significance in light of the myriad environments and ecologic challenges faced by human populations (Lasker, 1969; Frisancho, 1993).

Over the past 15 years the study of plasticity has experienced yet another minor revolution. The finding that birthweight is inversely related to adult rates of cardiovascular disease mortality led Barker et al. (1989) to hypothesize that the nutritional conditions that the fetus is exposed to in utero may have lasting effects on adult health, by permanently changing, or "programming," the structure and function of organs, endocrine systems, and metabolism—a novel form of developmental plasticity resulting from the sensitivity of fetal development to the maternal state. The hypothesis was initially received with skepticism, owing in part to the retrospective design of most early studies (Paneth et al., 1996). Support for the hypothesis grew as findings were replicated in longitudinal studies that included improved measurement of potential confounding variables in the postnatal environment (Rich-Edwards et al., 1999). At the same time, animal model research demonstrated that prenatal undernutrition or maternal stress induces physiologic changes in offspring that are similar to the patterns of disease risk observed in humans born small (Langley-Evans, 2001).

The fetal origins hypothesis revitalizes long-standing interests in nutrition during pregnancy and promises revolutionary approaches to public health, nutrition, and disease prevention. Notably, it proposes a key role for developmental plasticity in diseases that have, until now, been viewed primarily as adult ailments resulting from a combination of genetic susceptibility and an unhealthy adult lifestyle. Moreover, the hypothesis suggests that patterns of fetal growth and developmental plasticity may, in some instances, extend across generations. The intergenerational component of the hypothesis may make it particularly relevant for many populations in developing nations where dietary patterns, such as energy or fat intake, are changing rapidly within single generations (Popkin et al., 2001). Under such circumstances the metabolic imprint of a nutrient-poor prenatal environment may linger into adulthood to exacerbate the adverse health effects of societal changes in activity level, diet, energy balance, and other factors that contribute to cardiovascular disease (CVD) risk.

FETAL DEVELOPMENTAL PLASTICITY: BEYOND THE ORIGINS OF ADULT DISEASE

Even as the role of early environments in CVD has gained broad acceptance, the list of traits shown to be influenced by prenatal environments has outgrown this narrow focus on adult chronic disease. For instance, restricting the dietary intake of a pregnant lamb not only elevates blood pressure and impairs glucose tolerance in offspring, but also alters their postnatal growth trajectory, with prenatally malnourished offspring growing slower, maturing later, and attaining a smaller adult size (Engelbregt et al., 2004). Gonadal function, as reflected in testosterone production by the testes in males, or by the number of follicles and ovarian

Received 7 September 2004; Accepted 1 October 2004
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajhb.20090

steroid production in females (Ibanez et al., 2000; Cicognani et al., 2002), is also attenuated by prenatal growth restriction. Studies in humans and animal models provide evidence for an effect of prenatal stimuli on immune function (McDade, 2005), adult body composition (Li et al., 2003), and even lifespan (Cameron and Demareth, 2002). The growing list of postnatal functions shown to be influenced by the prenatal environment has made clear that fetal developmental plasticity is likely to have consequences for the organism's genetic fitness, beyond any effects on cardiovascular disease risk (Lummaa, 2003). What is less clear, however, is whether these responses are potentially adaptive and, if so, at what ages or developmental stages their benefits might be enjoyed.

The evolutionary implications of these responses have received little research attention, but may hold novel insights into the mechanisms of human adaptability. For instance, given that fetal programming occurs in utero, does the mother convey information to the fetus about the conditions of the postnatal environment that it will one day be born into? Several recent reviews propose such a scenario and suggest that the adverse effects of prenatal undernutrition on adult health may result from a mismatch between the actual postnatal environment and the postnatal environment predicted by the fetus in utero (Bateson et al., 2004). Alternatively, the postnatal effects of the prenatal environment may be little more than casualties—unavoidable impairments—triggered by responses designed to help the fetus survive a difficult pregnancy. Selection is strongest early in life, when prereproductive mortality is highest, and responses made by the fetus or infant that boost the chances of surviving this difficult period could be favored by natural selection, irrespective of their late life sequelae. These are but a few of the important questions raised by this new line of research.

The articles included in this special issue were presented at the annual meeting of the Human Biology Association, held on April 15, 2004, in Tampa, Florida. The symposium, entitled "The Fetal Origins of Developmental Plasticity: Life History, Adaptation and Disease," was organized to showcase the evolutionary significance of research on early life developmental plasticity, while providing a forum to discuss approaches that are currently being used to address these issues within human biology and related fields. The articles from this session reflect the breadth of issues related to this topic, and include forays into evolutionary theory, natural history, and such mainstays of human biological research as growth and development, nutrition, and immunology.

Current evolutionary perspectives on the significance of fetal developmental plasticity have emphasized the possible postnatal benefits of the fetal capacity to adjust nutritional requirements by modifying growth rate (e.g., Bateson et al., 2004). Using a life history framework, Kuzawa (2005) examines the costs and benefits of altering growth rate in response to nutrition in utero, and critically evaluates evidence that fetal nutrition might function as a reliable indicator of future nutritional environments in a long-lived species like humans. After reviewing the determinants of fetal growth, he hypothesizes that fetal nutrition may provide useful information to the fetus in the form of an integrated signal of nutrition as experienced by recent matrilineal ancestors.

For a complementary perspective on the postnatal significance of fetal developmental responses, Jones (2005) scrutinizes the assumptions of conventional life history models and their applicability to human life history, before introducing a stochastic demographic framework for evaluating the adaptive significance of different developmental trajectories. Among other conclusions of his analysis, Jones suggests that size at birth is likely to restrict the range of viable developmental strategies by influencing the severity of functional trade-offs.

Two articles from the session highlight how mechanisms for altering the developmental trajectory might work in other species, and hint at common themes across taxa that may inform our understanding of these responses in humans. Horton (2005) reports on her early work with high-latitude rodents, which was among the first examples of how developmental plasticity may be adjusted adaptively in response to the conditions of the maternal-uterine environment. In the highly seasonal environments inhabited by this species, circulating maternal melatonin levels mirror changes in day length and cross the placenta, thus allowing the fetus to "see" what season it will be born during, and thus alter its postnatal developmental trajectory. This animal model provides a concrete example of the adaptive

fine-tuning of offspring life history in response to ecologic information relayed in utero via maternal hormonal cues. Horton also reviews current work in rodents demonstrating a long-term effect of prenatal hormonal exposures on adult reproductive function and metabolic disease.

Crespi and Denver (2005) focus on the role of the stress hormone and hypothalamic–pituitary–thyroid axes as mediators of adaptive plasticity in amphibians. Their ground-breaking research reveals that the hormonal pathway allowing tadpoles to speed development in response to rapidly drying ponds is the same as that used by the human fetus to accelerate maturation and parturition in response to maternal stress. A highly conserved "larval/fetal escape route" is suggested, with phylogenetic origins predating the rise of placental mammals. The articles by Horton (2005) and Crespi and Denver (2005) highlight the important insights that may be gained into the evolutionary origins and function of fetal developmental plasticity by studying similar pathways in other taxa.

Additional perspectives on the fetal origins literature are offered by human biologists approaching the literature from the perspective of different functional systems and theoretical viewpoints. Pike (2005) assesses the preterm delivery literature for evidence that maternal investment in individual pregnancies is limited when chronic energetic constraint is present across the lifespan. The evidence suggests that preterm delivery may serve as a fetal response to an insufficient environment but ultimately is triggered by maternal neurohormonal cues of nutritional and even psychosocial stress. The costs of preterm delivery are high for both the mother and the fetus but also might be associated with benefits: the mother improves her reproductive opportunities and the fetus survives gestation in an insufficient environment.

Lampl (2005) further explores fetal accommodations and responses to stressful intrauterine environments in different conditions during pregnancy, including hypoxia, undernutrition, and maternal cigarette smoking. She suggests that oxygen and energy work in an integrated manner to influence fetal growth at the cellular level. Lampl concludes by questioning the assumption that metabolic "thriftiness" is a driving force of fetal adaptation, and proposes a nonlinear systems model of fetal plasticity that integrates genes, cells, organs, and organisms.

McDade (2005) addresses the importance of immune function as a component of the organism's maintenance expenditure and presents a life history framework for examining how the fetal and early postnatal environments influence the development of the organism's repertoire of immune defenses. His analysis explores evidence for a long-term effect of early environments on immune function later in life and highlights the life history trade-offs that the organism must negotiate when investing in costly immune defenses.

In a broad theoretical synthesis, Worthman and Kuzara (2005) examine the adaptive value of fetal programming and assess the manner in which neuroendocrine mechanisms negotiate the costs and benefits of altered metabolism and function across the life span. After proposing a developmental ecologic framework applicable to early environments, Worthman uses it to highlight the subtle complexities of the interaction between the environment and development and the range of variation in functional and health outcomes that such interactions may create.

Finally, Ellison (2005) synthesizes and critically evaluates some of the common themes that unite the session articles, and presents several compelling and original analyses of his own, including a neuroendocrine model of how the fetus might achieve different goals of energy partitioning.

The articles from this session showcase the many exciting research questions that converge on the problem of early environments and their lasting effect on the phenotype. We believe that a more complete understanding of the origins and evolutionary function of these developmental pathways will prove critical to clarifying not only their role in human adaptation, but also their maladaptive role in disease (Nesse and Williams, 1994). We hope that this collection of thematic articles will serve as a catalyst for future work in this promising new area of research.

ACKNOWLEDGMENTS

We thank Dan Brown (Past President) and Ellen Demareth (Past Secretary-Treasurer) for their gracious assistance and encouragement. All of the plenary session participants were great sports and conformed to tight deadlines and strict guidelines on topic

matter; thus, we owe them a special note of gratitude. Finally, we thank Peter Ellison for his insights and for the invitation and opportunity to publish the papers from the session in the *American Journal of Human Biology*.

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