

Wiley-Liss Plenary Symposium

Life History and the Early Origins of Health Differentials

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ABSTRACT Current epidemiologic models concerning the fetal origins of later health risk are evaluated from the perspectives of evolutionary and developmental biology. Claims of adaptive value for and biological status of fetal programming are critically examined. Life history theory is applied to identify key trade-offs in adaptive strategies that constrain developmental design to use information from the environment to guide ontogeny and establish cost–benefit trade-offs that weigh early survival advantage against remote or unlikely future costs. Expectable environments of evolutionary adaptedness, particularly of gestation, are characterized and their impact on human adaptive design discussed. The roles of neuroendocrine mechanisms in scaffolding life course development, negotiating ongoing cost–benefit trade-offs, and mediating their long-term impacts on function and health are reviewed in detail. Overviews of gestational biology and the postnatal physiologic, cognitive-affective, and behavioral effects of gestational stress identify a shared central role for the hypothalamic–pituitary–adrenal (HPA) axis. Rather than merely mediating stress responses, the axis emerges an agent of resource allocation that draws a common thread among conditions of gestation, postnatal environments, and functional and health-related outcomes. The preponderance of evolutionary and developmental analysis identifies environments as agents on both sides of the health risk equation, by influencing vulnerabilities and capacities established in early and later life course development, and determining exposures and demands encountered over the life course. *Am. J. Hum. Biol.* 17:95–112, 2005. © 2004 Wiley-Liss, Inc.

A major contribution to health policy during the last half century was the identification, by human biology and public health, of a close relationship between early environment and adult life expectancy. Specifically, growth in childhood and timing of puberty were found to be tightly linked to environmental quality, most particularly nutrition and health. In turn, adult differences in height attributable to developmental insults and trade-offs incurred early in life were definitively associated with differences in function, morbidity, and life expectancy (Martorell, 1989; Martorell et al., 1996; Mascie-Taylor, 1991; Ulijaszek, 1996). These insights yielded practical applications, including the widespread use of child growth indices as markers of child welfare and need for assistance (WHO, 1995). Over the last 15 years, epidemiologic identification of long-term health consequences of gestational outcomes widened the window of investigation to include the early origins of later disparities in well-being and health (Barker, 1991b, 1998). Reported associations of fetal and subsequent growth patterns with metabolic and cardiovascular disease and obesity have triggered an explosion of research effort aimed at illuminating the

burgeoning contemporary epidemics of these chronic conditions (Dodic et al., 1999; Laurén et al., 2003; Phillips, 2002; Symonds et al., 2003; Whitaker and Dietz, 1998).

The present report explores the convergence of three streams of inquiry to inform both old basic science questions and renewed public health concerns that these recent insights have raised. Epidemiology, life history theory, and developmental science (biology and ecology) each made enormous gains in the late twentieth century. Advances in these three areas leave us unusually well positioned to analyze the relationships of early environment, adaptation, and development with regard to later health risk. Beyond the significance for public health, assessment of the fetal origins scenario directly illuminates design issues in human development and life history.

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Received 7 September 2004; Accepted 1 October 2004

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajhb.20096

FETAL ORIGINS: DO EFFECTS IMPLY CAUSES?

The fetal origins hypothesis itself originated from epidemiologic research by Barker and colleagues with British public health records that revealed associations of low birthweight with subsequent risk for cardiovascular disease and its antecedents in the insulin-resistance syndrome (dyslipidemia, glucose intolerance, elevated blood pressure) (Barker, 1990, 1991a; Hales et al., 1991; Law et al., 1991; Phillips et al., 1993a,b, 1994). To account for these associations, the group proposed the fetal programming hypothesis, to the effect that early growth retardation results in adjustments or impairments in fetal development with permanent consequences for function and health risk. The thrifty phenotype hypothesis was advanced as one mechanism mediating these consequences, via altered glucose-insulin metabolism (Hales and Barker, 1992, 2001). By this view, the poor conditions of gestation that result in impaired fetal growth prompt an adaptive energy-sparing response by the fetus that impairs pancreatic development and increases insulin resistance. Postnatally, the resultant energy-sparing adjustments in metabolic regulation foster rapid growth, promote weight gain, and become overburdened when confronted with adequate-to-overnutrition, carbohydrate-rich diet, and sedentism. Thus, the fetal origins hypothesis expanded to include goodness of fit between phenotype and environment, in particular, a *mismatch between physiologic capacities established in early development and the environments in which they later must function*. Poor fetal nutrition is proposed to predict postnatal conditions that make the thrifty metabolism established in gestation a survival advantage under later conditions of poor nutrition. The problem arises when the prediction is wrong; hence, the association of small size at birth and early infancy followed by increased weight gain ages 3–11 years with an increased risk for adult coronary heart disease, diabetes, and hypertension (Gluckman and Hanson, 2004).

The fetal origins literature also directs attention to intergenerational transmission via the translation of maternal experience from gestation onwards into the environments of gestation and rearing for her offspring (Barker, 2001a). Constitutive of these environments are physiological (e.g., maternal meta-

bolic regulation), psychobehavioral (e.g., stress or smoking), and ecological conditions (e.g., poverty or unstable food supply). Given that the aforementioned relationships of birthweight with adult health have been found to hold across the range of normal birthweights, the effects of this form of transmission may be quite subtle. In this literature, “programming” is understood as a “setting” of physiological function by conditions operating during a sensitive developmental period to produce long-term effects on function and thereby on health outcomes (Godfrey and Barker, 2001; Lucas, 1991). Programming is thought to occur through “induction, deletion or impaired development of a permanent somatic structure as a result of a stimulus or insult” (Davies and Norman, 2002:386).

Recognition of the fetal origins of adult health by epidemiologists has heightened attention to gestational processes, particularly the nature of the fetal impacts responsible for observed postnatal effects on function and health, and the gestational conditions that exert these impacts. Descriptive epidemiology establishes association but not cause; the challenge is to specify the pathways that link context with function and health. The logic of fetal origins discourse makes a weak claim to adaptation on behalf of fetal responses but does not avail itself of substantial theoretical and empirical literatures that would permit stronger formulation and evaluation of this claim. We turn next, then, to such adaptationist considerations.

LIFE HISTORY

In evolutionary ecology, life history theory aims to explain phenotypic variation in terms of evolved design for fitness optimization (Stearns, 2000). Such design generates the species-specific suite of features (e.g., timing of maturity, litter size) that comprise its distinctive life course (Charnov, 1993; Promislow and Harvey, 1990; Ross, 1998). Life history analysis has reinstated mortality (juvenile and adult) alongside fertility as a primary constraint on life history organization (Charnov, 1993): selection pressures driving age-specific mortality and fertility operate synergistically on life history characters including target age at maturity, adult size, reproductive pattern (frequency, litter size, parental care), and senescence. These factors are important because they set the

cost–benefit trade-offs for allocation of two critical resources, time and energy. For example, if adult mortality is high, accelerated maturation and early reproduction are favored to ensure that reproduction will occur before death intervenes. Resources must be allocated among three domains: growth, reproduction, and maintenance. Energy intake minus the costs of staying alive (maintenance) sets the resources available for growth and reproduction (productivity). Allocation of resources to one domain meets some goals (e.g., increased maintenance to increase longevity) at the expense of ability to invest in other competing demands (e.g., increased growth to enhance adult size and competitive advantage or reproductive capacity) (Allal et al., 2004). Costs and benefits can accrue on different time schedules (Metcalf and Monaghan, 2001). For instance, maintenance may be shirked earlier on to get through a period of calorie restriction, at a deferred cost of later mortality risk. Mortality schedules determine the probability that an organism will survive to realize a time-delayed cost or benefit.

Fundamental to life history analysis is that every species is distinctive in how it handles trade-offs over time and space (Hill and Hurtado, 1995). Each species has evolved a set of genetic and epigenetic (gene/organism–environment) devices adapted to the environments it can expect to face in a lifetime (Brommer, 2000). This adaptive set, or life history strategy, instantiates a suite of mechanisms or algorithms for condition-dependent prioritization of resource demands and determination of how they are met across the range of expectable operating conditions. At the level of the individual, life history plays out as the product of ongoing dynamics between its phenotype and its environment (Valsinger, 1997). Thus, the course of life history is partly state-dependent, that is, driven by the current state of the organism which in turn is the product of prior conditions.

Two major difficulties that must be solved in the evolution of life history are the tension between plasticity and robustness and the problem of incomplete information. Any organism must be equipped to deal with life's immediate vicissitudes, even while it must get on with the overarching tasks of growing, surviving, and reproducing (Hoe, 1984). Capacity for adaptive change forms part of life history strategy and can be assessed by the norm of reaction, which is the range of phenotypes expressed by a given

genotype across a range of operating conditions (Stearns and Koella, 1986). The norm of reaction accommodates organism–environment interactions that result in change by design (adaptation), as well as inevitable random effects (tolerable cost or insult) (Finch and Kirkwood, 2000). Further, it incorporates non-genomic sources of individual variation that, as shall be seen below, are an inherent feature of complex developmental systems. Adaptation can be remarkably difficult to distinguish from insult (Andrews et al., 2002; Reeve and Sherman, 1993), for adaptation is defined as an evolved response to circumstances that is costly to mount but confers fitness benefits, while an insult is a tolerable cost that is chronically borne through impaired function or increased maintenance costs.

Human life history includes singleton births, altriciality, slow childhood growth, delayed maturation, large body size, long lifespan, and a corresponding set of mechanisms for resource allocation that mediate trade-offs and reaction norms (Hill and Kaplan, 1999). The pace and outcomes of human life history can exhibit substantial plasticity. A well-studied example is the secular trend to accelerated child growth and maturation under favorable conditions of nutrition and health (Eveleth and Tanner, 1990; Stearns, 1992; Worthman, 1999b). In life history terms, the conditions of good maternal health, low juvenile morbidity rates, and sustained good nutrition effectively increase productivity and reduce the relative cost of maintenance. The consequent increase in energy available for growth or reproduction results in increased growth and accelerated maturation. Favorable conditions also operate indirectly on age at maturity by signaling that resource availability is reliably good and that mortality risk is low. The norm of reaction for timing of maturation in humans is large: documented population median ages at menarche range from 12.3–18 years (Eveleth and Tanner, 1990).

Overall, life history theory is useful for providing an empirically grounded comparative time-integrated perspective that encompasses the entire life course (reviewed in Worthman, 2003). It identifies key cost–benefit trade-offs, permits hypothesis generation, suggests design criteria and constraints, and accommodates plasticity. Limitations include that it is largely nonphysiological and does not concern mediating mechanisms (Barnes and Partridge, 2003; Zera and Harshman, 2001), and that its account of phenotypic variation is hampered

by weak articulation between macro- and microevolutionary processes (Day and Rowe, 2002; Glazier, 1999). Given the interest in explaining individual variation, these are significant shortcomings.

IMPLEMENTATION OF DESIGN BY DESIGN

The gap between life history and organismic biology was bridged in part by recognition that life history must be effected through a set of physiologic mechanisms, supplied largely by neuroendocrine systems (Finch and Rose, 1995). These intensively studied systems are relatively well characterized. As reviewed in detail elsewhere (Worthman, 1999a, 2002, 2003), neuroendocrine actions both determine net energy availability (productivity) by regulating uptake and maintenance costs, and effect resource partitioning among maintenance, growth, and reproduction. They prioritize resource use through axial cross-talk, or the competing and synergistic actions of centralized (e.g., somatotrophic or hypothalamo-pituitary-gonadal (HPG) axes) and distributive (e.g., leptin, insulin) regulatory systems. And they negotiate short- and long-term resource allocation; for example, the HPG axis triggers the onset of puberty, and the hypothalamo-pituitary-thyroid axis down-regulates energy use with aging. Similarly, neuroendocrine action regulates key life history events by acting as pacemakers for growth, developmental transitions, reproductive effort, and aging. They also mediate the interface between individual and environment by regulating or modulating internal (physiologic) and external (behavioral) responses to contextual demands (e.g., thermal load, workload, psychosocial stress). Finally, in their role as pacemakers, neuroendocrine mechanisms mediate facultative adjustment of life history parameters.

Life history and fetal plasticity

The neuroendocrine architecture for implementing life history design can also be viewed as the architecture of resource allocation. Indeed, the elements of this architecture represent the evolved adaptive mechanisms that produce life history, effect trade-offs, and mediate plasticity. Turning now to the central present concern, fetal plasticity, we apply the perspective of life history, neuroendocrine architecture, and resource allocation (Fig. 1).

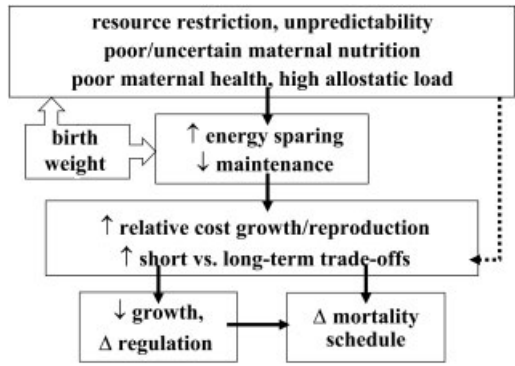


Fig. 1. A schematic life history analysis of fetal plasticity in resource allocation.

To cast the fetal origins hypothesis in life history terms, variability in birthweight attributable to malnutrition reflects resource restriction or unpredictability in utero that, in turn, is related to poor or uncertain maternal nutrition, poor maternal health, and/or high allostatic load (where allostatic load represents the mismatch between burden of demands and capacity for meeting that burden) (McEwen and Wingfield, 2003). These conditions necessitate fetal responses to cope with resource restriction by promoting energy sparing and energy reallocation. Reallocation responses include decreasing maintenance in order to sustain productivity for fetal growth and adjustments of apportionment within growth and maintenance to favor critical systems, especially the developing brain. The relative cost of growth and reproduction is increased and the trade-offs between the short versus long term are increased as a direct consequence of fetal responses and an indirect consequence of the conditions that signal poor environmental quality and increased risk to survival. Consequently, growth is slowed and metabolic regulation is adjusted to hedge against future shortages. Further, mortality risk shifts as a direct result of fetal adaptations that adjust trade-offs to favor current over future survival and anticipate chronic environmental risk. Mortality schedule also may shift as a direct consequence of altered energy use reflected in impaired growth and increased insulin resistance.

Whether the risk of mortality increases marginally or markedly depends on the goodness of fit between the energy-sparing phenotype and the postnatal environment.

Where expectations are met, enhanced capacity to function under poor conditions offsets the delayed costs (e.g., accelerated aging) incurred by reducing maintenance and altering trade-offs. But where expectations are not met and resources are abundant and stable, health is good, allostatic load low (including low energy expenditure in physical activity), and lifespan long, risk for obesity and metabolic dysfunction increases and the deferred costs to longevity fall due.

Cortisol and resource partitioning

If neuroendocrine systems define the architecture of resource allocation, one well-studied hormone plays a central role in this regard. Cortisol long has been called the “stress hormone,” but perhaps should be viewed as the traffic cop of resource partitioning. In that guise, it mediates apportionment of available resources (energy, time) among competing immediate, intermediate, and long-term demands. Glucocorticoids also regulate food intake and body weight (Dallman et al., 1993; Tempel and Leibowitz, 1994). A list of prominent actions of cortisol, a glucocorticoid released peripherally and regulated by a limbic-hypothalamo-pituitary-adrenal system, reveals the pervasiveness of its effects across multiple key systems involved in immediate function and survival (metabolism, immune responses, blood supply, atten-

tion), intermediate actions (repair, immunity, learning, energy storage), and long-term projects (growth and development, reproduction, memory) (Table 1) (Sapolsky, 1998).

In a comprehensive survey of the role of glucocorticoids (GC) in stress, Sapolsky et al. (2000) provide a detailed account of GC actions as modulating or preparative. Modulating actions regulate the response to a stressor, including permissive (priming initial phases of response by basal GC), suppressive (moderation of initial stress-activated responses to deter overreaction; stressor-induced rises in GC), and stimulating actions (enhance initial permissive actions; stressor-induced rises in GC). Stimulating and suppressive actions of GC effectively titrate widespread effects of GC to produce graded, conditional responses. Preparative GC actions modulate future responses to the stressor and provide a feed-forward capacity. The combination of modulating (reactive) and preparative (anticipatory) responses mediated by GC effectively integrate action across time and negotiate the balance of resource allocation in the light of prior, ongoing, and anticipated conditions. The diversity of stimuli to which the HPA axis responds attests to its regulatory and integrative functions (Table 1).

In sum, the broad swathe of conditions and systems monitored and regulated by cortisol suggests that regarding it as the “stress

TABLE 1. Regulatory scope of the limbic-hypothalamo-pituitary-adrenal (HPA) axis

Actions of cortisol

- Metabolic
- Immunologic
- Systemic
- Structural
- Reproductive
- Central

- glucose and lipid metabolism energy availability, use, storage
- immune function, inflammatory response
- vascular tone, fluid and electrolyte balance
- muscle and bone metabolism growth and development
- activity and action of the hypothalamo-pituitary-gonadal axis
- attention, learning and memory

Stimuli provoking HPA response

Reactive responses

- Pain (visceral, somatic)
- Neuronal homeostatic signals
- Chemoreceptor stimulation
- Baroreceptor stimulation
- Osmoreceptor stimulation
- Humoral homeostatic signals
- Glucose
- Leptin
- Renin-angiotensin
- Atrial natriuretic peptide
- Others
- Humoral inflammatory signals
- IL-1, IL-6, TNF- α , others

Anticipatory responses

- Innate programs
- Predators
- Unfamiliar setting
- Social challenges
- Species-specific threats (e.g., dark space)
- Memory programs
- Classically conditioned stimuli
- Contextually conditioned stimuli
- Negative reinforcement, frustration

hormone” represents too narrow a view of its roles. Substituting the word “demand” for “stressor” in the previous paragraph reveals cortisol’s capacities for resource allocation. Indeed, so central is resource regulation to HPA axis function that insulin-induced hypoglycemia is used clinically to assess its functional integrity (Pacák and Palkovits, 2001). Modulating actions and reactive responses of cortisol represent powerful and highly nuanced mechanisms for partitioning resources among the competing demands of multiple systems over a graded time course. Moreover, its anticipatory and preparative actions expand the comprehensiveness of its regulatory purview to context and behavior via evolved as well as learned programs.

Trade-offs of plasticity

The permanent changes in function or regulation specified by the fetal origins hypothesis may tailor phenotype to the conditions under which the individual operates, but they also increase vulnerability to the impacts of early conditions that are uncommon and transient (Finch and Kirkwood, 2000). Elements affecting trade-offs in irreversible adjustments to phenotype during ontogeny include: 1) predictiveness: the probability that the conditions of early development will predict future circumstances; 2) relative cost of error: the cost to the individual (in time, energy, survival, fitness potential) if the early environment is not predictive of the future relative to the cost of *failing* to adjust phenotype if it does predict to future; 3) cost of phenotypic alternatives: in particular, the physiologic costs of maintaining plasticity versus the adaptability costs of irreversibility; and 4) cost/benefit schedule: the fitness ratio of present gain to future pain sets the value of any trade-off (Houston and McNamara, 1992; Lindstrom, 1999; Metcalfe and Monaghan, 2001; Nylin and Gotthard, 1998; Shanley and Kirkwood, 2000).

Plasticity has limits, reflected in the reaction norm defined by the range of environmentally induced phenotypic variation possible for any given genotype. The point of physiologic regulation is production and maintenance of tolerable-to-optimal operating conditions for all ongoing systems in order to sustain the larger projects of staying alive, growing up, reproducing, and (for humans) having a social life. The neuroendocrine mechanisms largely responsible for

effecting life history are identical with those responsible for ongoing regulation of this kind. The components of these systems necessarily accommodate substantial changes in demand over different time courses (e.g., meal times vs. diurnal activity patterns vs. pregnancy). They also track different aspects of demand and function, which requires the means to coordinate or prioritize competing demands. A complex array of mechanisms is deployed to suit these purposes, including concentrations and distributions of receptors and receptor variants; components of second messenger and nuclear pathways; concentrations of circulating binding proteins; metabolic activity, conversion and clearance rates of hormones; use of multiple modulators (agonists, antagonists, cofactors); hierarchically structured feedback loops; and functional cyclicity reflected in chronobiology (reviewed in Worthman, 1990).

Functional setpoints along endocrine regulatory pathways have been implicated as prime mediators of the fetal origins phenomenon, and this brief review suggests numerous routes by which such mediation may occur. As such, adjustments to early resource constraint can be anticipated to comprise shifts in diverse elements of endocrine regulation along multiple endocrine axes.

Evolutionary bases of fetal plasticity

The question remains whether the functional correlates of birthweight reflect adaptive plasticity or tolerable insult. One approach is to consider the likely selective pressures operative in human evolutionary history, while another concerns design constraints on reproduction and development. These will be considered in turn.

Historical prevalence of gestational stressors. The selective forces operating in gestation can be approximated by estimating the historical prevalence of the conditions associated with impaired fetal outcomes. A focus here is on the probability of encountering dietary insufficiency. Comparative data from preindustrial societies as well as from the paleontological record are informative in this regard and suggest overall that food insufficiency was not rare in human history (Barrett et al., 1998; Goodman and Armelagos, 1989; Goodman et al., 1988). Indeed, dietary restriction was fairly common, depending on locale

and demography. Analyses of a sample of 115 preindustrial societies found that nearly half (47%) experienced frequent food shortages (one or more times per year), 25% had occasional shortfalls (every 2–3 years), and in only 28% were shortages rare (every 5–10 years) (Brown, 1987). In 113 of these societies, severity of food shortages when they did occur was mild in 37% of cases, moderate for 34%, and severe for 29%. Humans lack marked birth seasonality, and pregnancy lasts 9 months. Therefore, the probability that seasonal food restriction would occur during gestation was at least 75% where shortages were common and 25% where they were occasional.

Humans show various behavioral and physiological adaptations to dietary insufficiency, including preferences for calorie-dense foods (Kaplan et al., 2000). More pertinently, women exhibit striking energy-sparing capacities during periods of food shortage in pregnancy (Prentice and Goldberg, 2000). Pregnancy is an energetically costly endeavor that had been regarded as imposing rigid caloric demands (Prentice et al., 1987), but the advent of fine-grained, methodologically sophisticated comparative studies of energetics in pregnancy has yielded a more complex picture of widely varying energy costs of pregnancy linked to maternal energy condition (Poppitt et al., 1994). Reported mean population energy expenditure by women during pregnancy ranges from a low of –30 MJ to a high of 520 MJ per pregnancy across countries with low to high levels of affluence (Prentice and Goldberg, 2000). Birthweight is tightly scaled to maternal metabolic body size, suggesting that metabolic adjustments in pregnancy maintain a fetal weight proportional to maternal size. Such adjustments occur against a widely varying background of energy invested in pregnancy. Total weight gain in pregnancy reflects the degree to which mothers could build energy stores above and beyond the needs of the fetus. The percentage of total pregnancy weight gain taken up by birthweight goes from a low of 20% in affluent populations to over 50% in poor ones (Prentice and Goldberg, 2000). The necessity to negotiate pregnancy successfully despite potentially stringent resource limitations highlights the selection pressures to adapt to such conditions, and to do so at deferred cost to mother and fetus when adaptive capacity is saturated.

The comparative data on birthweight attest to powerful capacities for metabolic

adjustment in pregnancy to environmental quality, particularly calorie nutrition, but also reflect differences in micronutrient nutrition, activity burden, parasite and pathogen load, and placentation.

Constraints on developmental design. An evolutionary background informs fetal origins scenarios. The historic prevalence of energetic constraint argues for the likelihood of adaptive mechanisms to buffer early development from these potential insults to mothers and fetuses, while the centrality of epigenesis to development highlights the role of the environment in co-determining phenotype. One approach comes from longstanding work in evolutionary biology concerning the problem of inheritance (Gould, 1977). The intergenerational transmission of information is a major constraint for evolution, because reproduction involves not only production of a new organism but also implementation of an entire life course. The bottleneck is biological: a single fertilized cell must be amplified into an entire organism that is not only biologically but also behaviorally competent over the full life span of a species. In the case of humans, that life span is long and socially, behaviorally, and ecologically complex and variable. Too much information is required for a priori instructions (i.e., genetic programs) to be adequate for the task. Humans, for instance, have an estimated 30,000–40,000 genes, far too few to directly program ontogenetic processes (Consortium, 2001; Venter et al., 2001). The solution to this problem is to use other sources of information: context can package far more relevant information than genetic programs ever can. Indeed, the previous century saw not only great strides in genetics but equally significant progress regarding epigenetics, revealing mechanisms for capturing information from the environment to inform ontogeny, and hence reproduction (Bonner, 1974; Miklos and Maleszka, 2000; Oyama, 2000; van Speybroeck, 2002; Waddington, 1957).

Epigenesis involves nonlinear developmental processes comprising interactions within and among all levels of the organism and its environment, and thus includes but is not reducible to genes or genetic programs (Gottlieb, 1998; Jablonka and Lamb, 2002; Maleszka et al., 1998). Through epigenetic mechanisms, the environment instructs the organism during the construction of systems

that work in place. Ongoing activity (physiology and behavior) and structure of the developing individual act in concert with environmental inputs (conditions, stimuli, demands, resources) to drive ontogeny via throughputs and outputs. Major empirical insights into how epigenesis works come from developmental neurobiology (Changeux, 1985; Edelman, 1987), immunology (McDade and Worthman, 1999), and psychology (Gottlieb, 1991; Hofer, 1978; Meaney, 2001). Such work suggests that the evolution of epigenetic mechanisms often capitalizes on features of context that are reliably present and that genetic mechanisms often are used to establish time- and context-dependent ontogenetic conditions that can use the information these features provide. For instance, the complex wiring of the brain is achieved in part by cell-to-cell interactions and by timed waves of structural proliferation followed by selective pruning dependent on sensory inputs and/or behavior, such as incoming light for the visual system, or fetal movement for motor systems (Changeux, 1985; Levitt et al., 1998). Internal and external milieux furnish the genes with inputs requisite for regulating their activity. As agents in the architecture of life history, hormones permit activation or amplification of epistatic as well as pleiotropic effects (Finch and Rose, 1995).

By this view, development is canalized with respect to process but probabilistic with respect to outcome. The outcome, or phenotype, remains subject to selection. Consequently, the process of individual development is directly subject to evolutionary pressures on the adaptability and fitness of the resultant phenotypes. As such, epigenetic processes are products of selection, as are the reaction norms (ranges of phenotypes) they produce (Brommer, 2000).

Developmental ecology

The evolutionary perspectives applied in the previous section address the fetal programming scenario by illuminating assumptions about adaptation and developmental biology. They clarified the importance of environment and person-environment interactions in determining both the course of development and the fitness of resultant phenotypes. In this section, this ecological approach is applied first to the expectable environments of rearing and of function, with particular regard to gestation, and

second, to reevaluate the concept of fetal programming.

Expectable environments of rearing

A profile of the expectable environments of rearing (EER) for humans can be drawn from the paleontological record, comparative empirical work in behavioral ecology, and modeling of the environments of human evolutionary adaptedness (Bogin, 1997; Geary and Flinn, 2001; Kaplan, 1997; Kaplan et al., 2000; Konner, 2002; LeVine, 1989; Worthman, 2003). The EER includes the range of conditions normally encountered during development, constituted both by physical and social ecology (e.g., food types and availability, pathogen exposure, provisioning, language use). Conceptualization of the EER in terms of adaptively relevant environments is analogous to the widely used concept of the environments of evolutionary adaptedness (EEA) (Bowlby, 1969). Developmentalists' use of the EER (and Bowlby's original formulation of the EEA) contrasts with use of the EEA by evolutionary psychologists, who focus on fitness-enhancing cognitive-behavioral features evolved in the context of foraging (Irons, 1998). In our view, characteristics of the EEA comprise the full array of selection pressures (types, strengths, configurations) operating in human evolution to the present, and shape the entire suite of species-characteristic adaptations, from morphology to behavior (Reeve and Sherman, 1993). The regular presence of these conditions during the course of human history has both exerted systematic selective pressure on developmental design and established them as reliable sources of input to inform development. The EER constitutes the set of conditions that will be present and available to inform the development of a reasonably normal child in a reasonably normal situation that is compatible with survival and sustainable function. Insofar as life history strategy and developmental design evolve to capture information provided by parameters of the EER, they become dependent on rearing conditions, and therefore are subject to perturbations in the EER. Thus, for humans, gestation is an obligate component of the EER.

All environments vary, in space (patchiness) or time (periodic or episodic), and organisms must cope with or exploit that variation (Lytle, 2001). Plasticity is valuable to the degree that the environment varies:

organic design must equip members of a species to deal with such probable variation within their own lifetimes and across generations (Denenberg, 2000; Levine, 1957). Some characteristics do not tolerate variation (e.g., number of heads) and must be closed to ambient conditions, while others (e.g., immune function) must be acutely open to contextual cues. Developmental design requires dynamic stability, that is, robustness of functional trajectory through time along a course of planned change with conditional accommodation. Modeling of such systems suggests that they involve hierarchical, genetically informed processes (sequential, operating through time and space with multiple feedback loops) that are self-organizing and robust (Keller, 2002). As reviewed above, neuroendocrine systems exemplify the mechanisms that mediate just such processes.

Expectable environments of gestation

The adaptively relevant, expectable environments of gestation (EEG) is a subset of the EER composed of the characteristic conditions under which fetal development is designed to proceed. As noted, gestation is an invariant condition of human development. Such invariance provides a strong basis for the evolution of epigenetic mechanisms. Furthermore, although the presence of certain properties of gestation is invariant (e.g., warmth), the state of those properties is not (e.g., fever, postprandial thermogenesis). State variation in properties of the EEG can be due to both systematic (e.g., circadian rhythms) and stochastic sources (Finch and Kirkwood, 2000). But whatever the source, degree, and patterns of variation in EER, all contribute to a range of variability that fetal development must be designed to accommodate.

A preliminary, by no means comprehensive, overview of features of the EEG is outlined in Table 2. The nature of and variation in these features supply essential materials and information for fetal development.

The schema in Table 2 conveys a rather structural and maternocentric view of the EEG, whereas actually it is the fetus who largely drives pregnancy and effectively generates the EEG (Haig, 1993). The fetus and its placenta act to manage both maternal function and the materno-fetal interface to produce and maintain the conditions and

TABLE 2. *Expectable environments of gestation*

Biochemical properties (diverse, fluctuating)
Nutrients (glucose, amino acids, micronutrients, etc.)
Hormones, metabolic products, substances/toxins
Immune and inflammatory factors
Gas pressures, blood pressure, electrolyte balance and osmotic pressure
Geophysical properties
Gravity, magnetic fields
Maternal movement
Sensory inputs (tactile/pressure, acoustic, gustatory, light [dim])
Aqueous milieu
Maternal chronobiology
Maternal sleep/wake patterns (including work, meal consumption)
Diurnal and other cycles of physiologic activity
Maternal activity (work, meal consumption)
Temperature
Anatomic arrangements
Suspension in amniotic fluid (biochemical, chemical, and physical properties)
Placentation, materno-fetal interface

resources the fetus needs over the course of gestation, graded to its developmental needs and geared to determine the timing of gestation's end, in parturition. As detailed in Figure 2, endocrine mechanisms central to this process are mediated by the fetal brain, adrenal, and placenta acting in concert as the fetoplacental unit (detailed discussion in Challis et al., 1995, 2000; Murphy and Clifton, 2003).

Maturation of the fetal HPA axis proceeds throughout gestation and is buffered by adaptations that reduce the normal negative feedback of cortisol on the hypothalamus and pituitary (see reviews in Benediktsson et al., 1997; Blum and Maser, 2003; Challis et al., 2000; Mesiano and Jaffe, 1997; Seckl et al., 2000). Fetal buffering includes: 1) elevated circulating cortisol binding globulin (CBG) that diminishes cortisol bioavailability; 2) increased pituitary 11 β -hydroxysteroid dehydrogenase-2 (11 β -HSD-2), an enzyme that rapidly converts biologically active cortisol to biologically inactive cortisone and thereby diminishes cortisol bioavailability in the feedback loop; and 3) reduced glucocorticoid receptor (GR) production in the pituitary and hypothalamus that reduces bioimpact of cortisol feedback. Placental and maternal mechanisms also buffer the fetus from maternal cortisol. Maternal circulating levels of CBG are very high and bind over 95% of cortisol. Additionally, the placenta acts as a barrier to transfer of maternal cortisol to the fetus

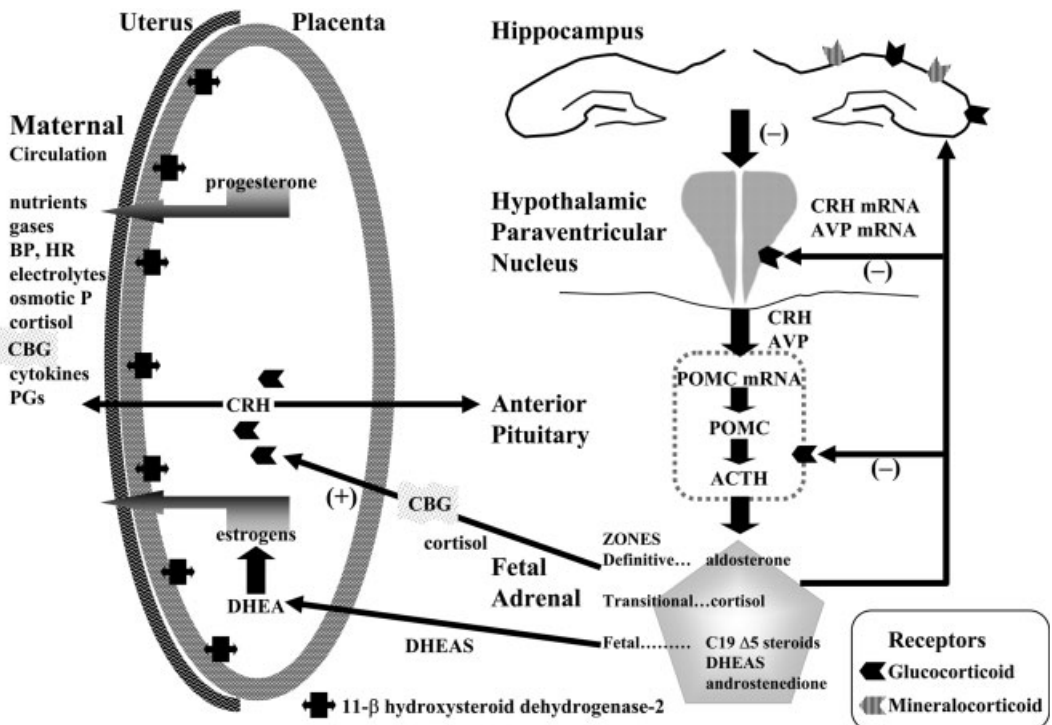


Fig. 2. The fetoplacental unit and the endocrine regulation of pregnancy. By weeks 7–9, the fetal-placental complex secretes an array of steroids, peptide hormones, neuropeptides, growth factors, and cytokines. From weeks 5–6 of gestation, the placenta produces progesterone and estrogens and secretes them into maternal circulation, creating the characteristic maternal endocrine profile of pregnancy and its attendant shifts in metabolism and resource mobilization, cardiovascular load adjustment, and preparation for lactation. Substrate for this massive output of steroid hormones comes via the placenta for progesterone and largely from placental conversion of adrenally produced C19 delta-5 precursors (DHEA/S and androstenedione) for estrogens. Pathways for HPA regulation run from limbic inputs to corticotropin-releasing hormone (CRH) release by the paraventricular nucleus (PVN) of the hypothalamus. In turn, CRH acts synergistically with avian vasopressin (AVP) from the posterior pituitary to regulate the production and release of adrenocorticotropic hormone (ACTH) by the anterior pituitary. ACTH stimulates fetal adrenal steroidogenesis, although both placental and pituitary CRH can also stimulate the fetal zone to produce DHEAS. The largest of the three zones in the fetal adrenal, the central, fetal zone, produces the C19 delta-5 precursors. The outer adult or definitive zone largely produces the mineralocorticoid aldosterone that regulates electrolyte balance. Between these two zones is the transitional zone that produces cortisol at relatively low levels for much of gestation. ACTH, adrenocorticotropic hormone; AVP, avian vasopressin; BP, blood pressure; CBG, cortisol binding globulin; CRH, corticotropin releasing hormone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; HR, heart rate; osmotic P, osmotic pressure; PGs, prostaglandins; POMC, pro-opiomelanocortin. Sources: Matthews (2000), Mesiano and Jaffe (1997).

due to high levels of 11β-HSD-2 that inactivates over 90% of incoming maternal cortisol, which is 2–10 times higher in maternal than fetal circulation (Murphy and Clifton, 2003). Indeed, clinical studies report that a 10-fold increase in maternal cortisol is associated with no change in placental conversion efficiency; consequently, wide variation in concentrations of maternal cortisol result in minor changes in fetal cortisol load (Challis et al., 1995). Only at the end of pregnancy (weeks 38–40) does fetal

11β-HSD-2 activity decrease (Murphy and Clifton, 2003). Concurrently, 11β-HSD-1 (which converts inactive cortisone into active cortisol) rises and consequently fetal cortisol increases, contributing to both fetal maturation toward term and the fetal stimulation of onset and progress of labor.

In addition, the placenta synthesizes and secretes large quantities of CRH into the maternal and fetal circulations. This action is reinforced by fetal cortisol. Contrary to the usual negative feedback relationship of

cortisol and CRH, fetal cortisol enhances placental CRH release to stimulate both maternal HPA activity and fetal pituitary ACTH and adrenal steroidogenesis. High levels of 11 β -HSD-2 in the placenta buffer the fetus from maternal cortisol and thus permit it to escape from presumed negative feedback from the mother. Therefore, maternal cortisol may reflect not only maternal but also fetal regulation and stress (Wadhwa et al., 1997).

To summarize, the expectable environments of gestation are determined not only by maternal factors, but also by fetal activity, particularly the endocrine activity of the fetus and placenta in which fetal adrenal plays a key role. This system is substantially buffered from maternal perturbations in cortisol. Other stress-related changes in maternal physiology that alter the list of circulating constituents on the left in Figure 2, such as in maternal blood pressure and peripheral gas exchange, are much more likely to mediate any impact of maternal stress on the fetus.

Fetal programming reconsidered

Fetal programming has been framed primarily in terms of gestational insult and postnatal pathology. But the above review of developmental biology and ecology draws another picture, in which fetal programming represents an inherent feature of fetal development. Insofar as fetal development relies on probabilistic epigenesis, fetal development *is* fetal programming because development itself involves establishment of regulatory dynamics within and across physiologic systems. The prevailing concept of fetal programming implies that there is an optimal setpoint that all systems will reach unless they are perturbed or *programmed* away from the presumed default outcome. The above reviews have shown that the situation is more complex than supposed, and that the outcomes of any gestation are contingent on the specific sequence of ecologies under which the process occurred. By this view, fetal programming largely comprises expectable outcomes of expectable environments of gestation, rather than insult and pathology. Any level at which feedback systems or regulatory elements are “set” effectively constitutes programming, even when the long-term effect is functional rather than pathological. This

insight shifts the explanatory focus from individual fetal outcomes to the conditions under which development occurs. Pre- and postnatal environments act on both sides of the fetal origins equation. They are agents in production of variation in fetal development as reflected in birthweight, while also defining postnatal operating conditions that shape demands and exposures, thereby influencing the health risks associated with such variation.

By this logic, the fetal programming concept focuses on a subset of condition-specific fetal outcomes and would benefit from a broader theory of fetal development and developmental design in relation to health risk. Life history perspectives suggest that conditions resulting in birthweight variation (maternal caloric restriction, dietary shifts, illness and parasites, psychosocial stress) have been common in human evolutionary history. The weight of selection pressure from these factors relates to the magnitude of threat to survival and fitness. Thus, fetal development should be adapted for optimizing chances of immediate survival, adjusting phenotype to information that predicts future conditions, buffering from conditions that do not predict but which likely impair future function, allowing phenotype to vary when variation in outcomes matters little for fitness, and minimizing impact when avoidance of impairment is not possible. Variation in birthweight within populations probably reflects all of these forces.

Adaptive design in neuroendocrine architecture furthermore would suggest that low birthweight should be characterized not by a single critical change, but by a set of dynamic shifts in that architecture that alter algorithms for resource allocation. As Herman and Cullinan (1997:169) noted in a recent review of stress regulation and the diversity of neuroendocrine responses to stressors, “the road to adaptation may well have many neurochemical and humoral forks.” The well-studied models of stress response suggest this metaphor is somewhat misleading: ontogenetic plasticity involves hierarchical and graded responses that integrate the overall balance of sensory inputs and central processing, rather than decision points on branching pathways (on/off, high/low) (Pacák and Palkovits, 2001). In accord with this view, variation in fetal outcomes has been associated with continuous gradients in health risk across the entire range of

birthweight. Furthermore, low birthweight presents a suite of changes, including pancreas (decreased pancreatic b-cell mass), kidney (decreased nephron numbers), liver (altered zonation, increased capacity for gluconeogenesis), body composition (increased fat, decreased muscle), metabolic regulation (increased insulin resistance, decreased glucose tolerance), and endocrine systems (decreased growth hormone, IGF-1 activity, and IGFBP-3, altered HPA activity) (reviewed in Barker et al., 2002; Byrne, 2001; Dodic et al., 1999; Hales and Barker, 2001; Holt, 2002; Matthews, 2002; Phillips, 2002; Seckl, 1998). Another ubiquitous selection pressure, infectious disease, has been linked to HPA development: prenatal exposure to endotoxin and cytokines alter multiple aspects of HPA regulation and action and induce other effects on metabolic regulation similar to low birthweight (Nilsson et al., 2002).

Gestational conditions and HPA development

If cortisol and its upstream neuroendocrine regulatory systems could best be characterized as resource allocators rather than simply stress mediators, then we would predict that variations in quality of early environments would be associated with adaptive adjustments in the HPA axis. Accordingly, a decades-long literature documents the effects of early environment on subsequent HPA function (Levine, 1957), and glucocorticoids are suspected to be responsible for the metabolic syndrome (Björntorp, 1995; Seckl, 1997). Birth cohort studies show associations between birthweight and HPA activity across the lifespan, from infancy to old age (Clark et al., 1996; Phillips et al., 1998, 2000). Low birthweight is associated with both increased basal and ACTH-stimulated cortisol (Levitt et al., 2000; Reynolds et al., 2001). Indeed, the conditions that lead to impaired fetal growth and reduced birthweight may increase sensitivity to glucose levels and insulin resistance: fasting plasma morning cortisol is negatively correlated with birthweight and length (Phillips et al., 1998). The metabolic syndrome in adults is associated with altered HPA function and regulation, including altered GR (Byrne, 2001).

Obversely, early glucocorticoid exposure affects multiple functional outcomes. Fetal exposure to cortisol is determined as much

or more by fetal responses to gestational conditions (e.g., availability of gases and nutrients), as it is by maternal HPA activity related to diet or undernutrition and psychosocial stress (Dodic et al., 1999; Welberg and Seckl, 2001). Whatever the route, cortisol strongly mediates impacts of gestational conditions on fetal outcomes. Hypothalamo-pituitary-adrenal activity increases with undernutrition, possibly to promote maintenance of blood sugar levels at the expense of fat storage (Symonds et al., 2003). In rat models, reduced maternal dietary protein intake in pregnancy and lactation results in decreased GR expression and activity in pups. The effects of maternal psychosocial stress on fetal outcomes has recently come under intensifying scrutiny (Paarlberg et al., 1995; Wadhwa et al., 1996, 1998; Weinstock, 1996). Social support and security have been positively associated while negative life events and perceived stress are negatively associated with gestational outcomes (reduced birthweight, preterm delivery). Elegant experimental work with rhesus macaques has demonstrated neuroendocrine mediation of these effects, with a central role for the maternal HPA axis (Schneider and Moore, 2000; Schneider et al., 2002). In turn, brain development is highly sensitive to GC exposure (Welberg and Seckl, 2001). Moreover, a substantial body of animal and clinical research establishes a widespread postnatal impact of prenatal GC (Matthews, 2000; Takahashi, 1998; Weinstock, 2001; Young, 2002). Enduring postnatal effects are pervasive and include reduced birthweight; increased HPA activity; decreased volume and altered regulation in hippocampus; accelerated maturation of dopaminergic systems in forebrain and noradrenergic tracts in brainstem, forebrain, and cerebellum; decreased hypothalamic serotonin and transporter activity; altered immune function; increased fussiness and irritability; increased behavioral reactivity and sensitivity to novelty; and multiple specific cognitive-learning deficits.

By way of overview, it can be concluded that perturbations in early environments are associated with variation in outcomes constituted as a suite of adjustments that run from molecules to behavior to life expectancy. In its role as mediator of resource allocation among systems and through time, cortisol and its related HPA regulatory pathways can be expected to shift to accommodate

the resources (constraints, opportunities, information) afforded during early development. Consistent with this expectation, the quality of early environment has been associated with pervasive alterations in structure and function of the HPA axis, which in turn have been linked to cognitive (mood, memory) and behavioral (social behavior, behavioral reactivity) changes that affect lived experiential worlds (stress, anxiety, security). Early environments thereby affect life history in two of its senses, the autobiographical and the adaptationist.

ENVIRONMENT AND EVOLUTIONARY MISMATCH

The above review has identified environment and environment–person interactions as active agents on pathways to differential health. Traditional epidemiological, biological, and medical approaches have focused on proximal causes and consequences of individual variation, but the less well-characterized role of context (social dynamics, political economy, history) in moderating and mediating these dynamics has become an important site for inquiry. Turning to environment, then, stressors on early development have prevailed throughout human evolution; as a component of the EER, stressors that threaten early survival or long-term fitness have acted and continue to act as major selection pressures to which the fetus and its mother must be adapted. The preceding analyses of trade-offs in life history raise the possibility that present health consequences of differential fetal outcomes represent the resurfacing of costs deferred in early trade-offs. The fetal programming scenario proposes that permanent alterations in metabolic regulation under early adversity were adaptive by virtue of establishing an energy-sparing phenotype adapted to present and future (Hales and Barker, 2001). We note in passing a recent report contravening this adaptive scenario: men not thin at birth were resistant to later effects of poor living standards on cardiovascular disease (CVD), by contrast with their peers who were thin at birth, gained weight in childhood, and had high CVD risk (Barker, 2001b). Nonetheless, the problem has been why such permanent changes should be adaptive if they do not pay off in future, yet do exact a future cost.

The solution is that a permanent advantage need not be present for a trade-off choice to be adaptive; there simply has to be an early benefit (survival) with little or no probability of paying a long-term fitness cost (Finch, 1990; Rose and Mueller, 1998). Fitness is the currency of trade-offs: although the literatures on fetal origins are rightly concerned with longevity and human suffering, conditions that have little or no effect on fitness are subject to very weak selective forces. As a result, trade-offs conferring early fitness advantage while incurring delayed costs will be selectively favored. The problem arises when survivorship improves and the costs must be paid. The morbidities associated with fetal origins are all chronic conditions of middle and older age, and have little impact on fitness. Deferred costs have resurfaced as life expectancy has increased (Worthman and Kohrt, 2005).

The probability that the phenotypic consequences of earlier trade-offs will have deleterious effects, even in deferred terms of secondary chronic morbidities (diabetes, heart disease), also depends on later environments. Existing evidence suggests that the widespread and sustained presence of a trio of contemporary conditions—dietary change and chronic overnutrition, early and persistent sedentization, and reduced morbidity and pathogen/parasite load—is unique in human history (Eaton et al., 1997; Trevathan et al., 1999). Moreover, the material and social ecologies of everyday life have changed dramatically, suggesting to some that the conditions of crowding, stratification, social fragmentation, and labor generate unique pressures of psychosocial stress. Selection therefore would not have operated on these conditions, and thus we cannot expect to see adaptive responses to them, although we might see exaptive ones that build on existing adaptive capacities developed for other purposes (Gould and Vrba, 1982).

Another trade-off concerns cognitive performance. Poor or stressful early environments demonstrably induce changes in cognitive style and capacity (attention regulation, memory, learning), emotion regulation (moodiness, irritability), and social relationships (novelty aversion, avoidance and/or aggressiveness). Such effects historically may have exacted little functional cost. Although foraging societies present strong

cognitive, emotional, and behavioral demands in subsistence, social, and life history (maturation, reproduction) pursuits (Hawkes et al., 1997; Hill and Hurtado, 1995; Kaplan et al., 2000), contemporary demand may be quantitatively and qualitatively distinctive. The present use of formal education, literacy and novel forms of information transmission and use, stratification of opportunity by rigorous performance selection, forms of labor and work trajectory, and number and complexity of interactions with relative strangers form a distinctive set of cognitive challenges with concomitant demands for emotion regulation and social behavior. In this scenario, the impacts of early stress may put future performance at risk and erode function and mental health.

CONCLUSION

Although the fetal origins hypothesis continues to be critically evaluated and revised, its practical potential is large and its scientific impact significant. The hypothesis has spurred new empirical work and fostered reevaluation and integration of existing ideas and knowledge about an important set of issues. But two aspects of the model remain underspecified, the assumptions about evolved design and adaptation, and the mechanisms in developmental biology behind variation in birthweight. In that vein, the present exercise has deployed epidemiologic, evolutionary, and developmental perspectives to evaluate the hypothesis. But it has also yielded insights into the several domains as they pertain to the early origins of later differences in health.

The adaptationist life history perspective identified two prominent trade-offs concerning early development under resource restriction, between early fitness benefits from survival versus later fitness costs in reproduction and health, and between use of environmental inputs to inform development versus resistance to environmental insults. In this view, birthweight is not simply a crude index of resource availability: it reflects cumulative fetal and maternal decision-making concerning trade-offs in resource allocation informed by the conditions that unfolded across gestation. Epigenetic processes in fetal development permit sensitive use of ambient conditions and are linked to placento-fetal neuroendocrine mechanisms that drive maternal and

fetal resource allocation over the course of gestation. These dynamics are heavily buffered from adverse conditions such as nutritional insufficiency via adaptations that reflect the high prevalence of such adversities throughout human history. But the limitations of buffering arise in part because the later functional and health costs of growth adjustments to poor prenatal nutrition, reflected in birthweight, were rarely or never paid. Two changes have operated in tandem to alter this schedule of early benefit versus deferred cost. First, altered living conditions changed demands on metabolic regulation and, second, increased life expectancy increased the likelihood that differences in ability to meet those demands would emerge in chronic conditions such as obesity, secondary diabetes, and coronary heart disease. Moreover, selection against such secondary conditions remains weak because their fitness costs are low, although their personal and social costs now are high.

In accord with existing fetal origins assumptions, environment emerges as a critical variable determining the significance of birthweight for later health and longevity. But in contrast to the fetal origins model, environment also plays a necessary, positive role in guiding fetal development and maternal response in pregnancy. Analysis of expectable environments of rearing and particularly of gestation demonstrates the degree of plasticity by design. From this vantage, fetal programming should be considered an integral part of fetal development, as constituting the neuroendocrine architecture of resource allocation that defines capacities for adaptation through transient and permanent phenotypic adjustments. Thence, the epidemiological findings informing the fetal origins model can be viewed as individual manifestations of social conditions and practices that alter equations of benefits (increased early survival, decreased infectious morbidity and mortality, childhood sedentization in school followed by adult sedentization at work) and costs (emerging noninfectious morbidities consequent to changed lifestyle and increased survivorship) (Trevathan et al., 1999).

Moving to lessons for developmental biology, the fetal origins literature has stimulated an outpouring of data that document a major role for the HPA axis in organization of the conditions and course of fetal development, as well as in postnatal resource allocation that

translates fetal outcomes into long-term consequences for function and health. These insights converge with another literature concerning stress to suggest the need to systematically revise our view of cortisol from “stress hormone” to “triage hormone.” The HPA axis, reflected in cortisol and its actions, emerges as a key player in the neuroendocrine architecture for implementing life history. A thorough review, reintegration, and reconceptualization of the massive literatures on cortisol (developmental, behavioral, physiological, genetic-molecular, and comparative evolutionary) is called for and should seriously advance our understanding of many, presently disparate problems, including psychobiology of temperament, developmental epidemiology of mood and behavioral disorder, clinical uses of glucocorticoids, trauma and resilience, ... and the fetal origins of health.

At the least, the impact of increased prenatal GC on birthweight, brain, behavior, learning, and cognition suggests the practical need to reconsider the 1994 NIH recommendation of GC treatment in weeks 24–34 for all women at risk for preterm delivery (Matthews, 2000, 2002). With regard to lessons for evolutionary biology, such impact also suggests a possible cycle of Lamarckian effects whereby environmental insults that produce increased stress vulnerability and other functional stigmata potentiate subsequent stress in pregnancy with consequent transmission of the phenotypes of vulnerability to the next generation (Drake and Walker, 2004). Lamarckism notoriously involves intergenerational transmission of phenotypes via environmentally generated responses rather than genetic means. Although Lamarckism was discredited for failure to identify credible mediating mechanisms and its use to blame the victims of circumstance, a growing and robust empirical literature suggests that such transmission operates through an array of evolved mechanisms (Gottlieb, 1992; McDade and Worthman, 1999; Meaney, 2001). This emerging evidence promises to turn the tables of Lamarckian analysis from victim blaming to social critique, by identifying how social and material conditions produce differential well-being.

In closing, variation in birthweight manifests a plasticity inherent to developmental systems reliant on probabilistic epigenesis that establish individual-environment dynamics based on evolved expectations and trade-offs. The consequences of developmen-

tal variation reflected in birthweight reveal an underlying architecture of life history regulation that links early environments with later function, behavior, and health. As such, endocrine function instantiates the sum of prior and ongoing development and mediates life history trade-offs across the life course. The dynamics between these systems and conditions of the environments in which they function compound through time to set schedules of early versus later cost and benefit. Such systematic synergy with context suggests that the origins of the fetal origins of health differentials derive from ongoing material and social ecologies of individuals and their societies.

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