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Abstract

The introduction of the "fetal programming hypothesis," first in epidemiology, subsequently in a broad range of disciplines concerned with developmental biology, has generated new interest in phenotypic plasticity, the mechanisms that govern it, and its place in evolutionary biology. A number of epidemiological studies link small size at birth, assumed to be a consequence of constrained prenatal energy availability, with adverse effects on the risk of chronic diseases later in life. The cluster of chronic diseases associated with the metabolic syndrome and alterations of glucose metabolism are particularly implicated. Recent evidence suggests that epigenetic modification of gene expression affecting the hypothalamic-pituitary-adrenal (HPA) axis may be involved in these effects. In animal studies epigenetic alteration of HPA axis activity and responsiveness is associated with changes in adult behavior and stress responsiveness. The potential for similar effects to contribute to psychological and psychiatric outcomes has been explored in a number of contexts, including famine exposure, observed covariance with birth weight, and prenatal dexamethasone treatment of fetuses at risk of congenital adrenal hyperplasia. While fetal programming effects have now been widely demonstrated across species and human populations, the adaptive significance of these effects is still a matter of debate.

Life is integrated, cumulative, and continuous, not episodic, static, or discrete. Behavioral scientists rarely forget this, but biologists often do. Developmental biology is the one domain of the life sciences where the organism as a progressively unfolding phenomenon is a central concept. The reemergence of developmental biology as a vigorous discipline, intersecting in important ways with genetics (Badayev, 2008), evolution (West-Eberhard, 2003), and epidemiology (Barker, 1994; Gluckman and Hanson, 2006; Kuh, Ben-Shlomo, Lynch, Hallqvist, and Power, 2003), has injected new energy and new ideas into all those fields. Within epidemiology a seminal impact of this new attention to developmental biology has been in the formulation of the "fetal programming hypothesis," also known as the "fetal origins hypothesis," or, more generally, as the "developmental origins of health and disease" (DOHaD). Simply put, this hypothesis suggests that conditions very early in development, even *in utero*, can leave lasting imprints of an organism's physiology, imprints that may affect susceptibility to diseases with onsets that may occur many decades later (Barker, Eriksson, Forsen, and Osmond, 2002; Gluckman and Hanson, 2005).

The concept of fetal programming is, of course, not new. Behavioral endocrinologists and neuroscientists, for example, have long recognized "organizational effects" of prenatal androgen hormones in "programming" certain aspects of reproductive axis function and reproductive behavior that emerges later in an animal's life (Nelson, 2005). "Critical periods" in development, including fetal development, are familiar

concepts in psychology even as they are in biology. So rather than being a radically new concept, the ascendancy of the fetal programming hypothesis should be seen as representing a new appreciation for these kinds of effects together with a deeper understanding of the mechanisms that produce them and the significance they may play for individuals and species.

The question of the potential adaptive significance of fetal programming is an important one, both theoretically and practically. It affects the way in which the phenomena clustered under the DOHaD aegis are integrated in a broader context of evolutionary biology and the practical responses and interventions that might be made to affect health outcomes (Gluckman et al., in press). It is a question that is still keenly debated, however (Ellison and Jasienska, 2007; Jones, 2005; Kuzawa, 2005; Worthman and Kuzara, 2005).

The purpose of this paper is to briefly review the fetal programming hypothesis and the mechanisms thought to underlie it, to position the hypothesis in relation to psychological outcomes, and to comment on the theoretical framework that some have proposed to unite the hypothesis with cotemporary evolutionary theory. There is only space for brief review of these topics. Other, more extensive reviews of various aspects of the fetal programming hypothesis and its implications may be found in (Bateson et al., 2004; Gluckman, Hanson, Cooper, and Thornburg, 2008).

Fetal programming in human epidemiology

The fetal programming hypothesis in its contemporary form was stimulated by the work of Barker and colleagues who reported that rates of ischemic heart disease in England and Wales were more closely related to mortality conditions when heart patients were born than to recent conditions (Barker, Winter, Osmund, Margetts, and Simmonds, 1989). This led to hypothesis that maternal conditions in the prenatal period might have an important impact on the emergence of later vascular disease, and to the use of size at birth as a proxy for prenatal conditions (Barker, Osmond, Golding, Kuh, and Wadsworth, 1989). The relationship between size or relative thinness at birth and the risk of a group of chronic diseases including heart and vascular diseases, adult-onset diabetes, and the cluster of conditions known as the "metabolic syndrome" has since been observed in numerous different populations (Barker, 1995; Eriksson, Forsen, Tuomilehto, Osmond, and Barker, 2000; Eriksson, Wallander, Krakau, Wedel, and Svardsudd, 2004; Ismail-Beigi, Catalano, and Hanson, 2006; Rich-Edwards et al., 1999; Rich-Edwards et al., 2005). The effect of birth size is not simply a confounded effect of postnatal conditions, but it does interact with them to influence chronic disease outcomes. Thus, in several studies, small size at birth followed by rapid postnatal growth has been associated with the greatest risk for the cardiovascular-metabolic cluster of chronic diseases (Bahargava et al., 2004; Barker, Osmond, Forsen, Kajantie, and Eriksson, 2005; Ong, 2006).

The effects associated with birth size are not trivial. British babies under 6 pounds at birth, for example, are at a five-fold greater risk of type II diabetes as adults even after adjusting for adult body mass index (Barker, 1995). Given the interaction

between prenatal and postnatal conditions in influencing risk and the rapid rate at which environmental, and particularly nutritional, conditions are changing throughout the world, the fetal programming hypothesis has particularly worrisome public health implications (Gluckman and Hanson, 2008; Gluckman et al., In press). Studies of migrant populations from developing to developed countries indicate that a dramatic shift in the nutritional environment between gestation, childhood, and adult life may underlie the elevated risk for heart disease and diabetes that such populations face (Barnett et al., 2006; Beaulieu et al., 2007; Candib, 2007; Daryani et al., 2005; Dwivedi, Agarwal, Suthar, and Dwivedi, 2004; Foucan et al., 2006; Lob-Corzilius, 2007; Misra and Misra, 2003; Misra and Vikram, 2004; Misra, Endemann, and Ayer, 2005; Pousada et al., 2006; Schwingel et al., 2007; Trayhurn, 2005; Tull, Thurland, and LaPorte, 2005). Rapid nutritional transitions in the developing world may be accompanied by similar increase in chronic disease burden, if the fetal programming principle holds true.

The public health implications of the fetal programming hypothesis have motivated a large number of studies into the mechanisms that underlie the association between prenatal conditions and the cardiovascular-metabolic cluster of chronic diseases. One suggestion made by Baker and colleagues is that insufficient energy during fetal development might result in biased portioning of available energy designed to buffer brain development (D. J. Barker et al., 2002). The development of other organs, including kidneys, pancreas, and adipose tissue might be compromised instead. Small babies have fewer nephrons in their kidneys (Brenner and Chertow, 1993; Mackenzie and Brenner, 1995) and fewer beta cells in their pancreases (Breant, Gesina, and Blondeau,

2006), and lower fat cell number (Breant et al., 2006) than their larger at birth peers, supporting this notion. Many of the deleterious adult outcomes of small birth size, however, appeared to be related to altered insulin sensitivity and activity of the hypothalamic-pituitary-adrenal (HPA) axis (Fowden and Hill, 2001; Phillips, Barker, Hales, Hirst, and Osmond, 1994; Symonds, Budge, Stephenson, and Gardner, 2005). Both of these systems are key modulators of energy metabolism. Considerable attention has been focused, therefore on the degree to which insulin sensitivity and HPA axis reactivity may be established *in utero*, the potential for maternal nutritional status to affect these aspects of metabolic physiology, and the cellular mechanisms by which these effects are mediated.

Epigenetic programming of energy metabolism

The term "epigenetics" refers to non-heritable modifications of genetic material in somatic cells that persist through the process of mitotic cell division. Epigenetic modification of gene expression has recently been identified as a likely mechanism underlying fetal programming of metabolic set-points and sensitivities (Godfrey, Lillycrop, Burdge, Gluckman, and Hanson, 2007; Lillycrop et al., 2007). Epigenetic mechanisms effect quasi-permanent changes in the gene expression patterns of different tissues and are a key part of cellular differentiation during normal embryogenesis and fetal development. Among the specific processes that have been identified are histone acetylation, DNA methylation, and micro-RNA inhibition of gene translation (Baek et al., 2008; Goldberg, Allis, and Bernstein, 2007) (Figure 1). Histones are structural proteins

that organize the tightly coiled packaging of nuclear chromosomes. When acetyl groups are attached to specific lysine residues of histone molecules, the binding of DNA to those histones is modified making the neighboring regions available for transcription. The de-acetylation of histones, conversely, prohibits transcription of affected stretches of DNA. Promoter regions for many genes include cytidine-guanosine sequences, or CpG sites, that are potential site for the attachment of methyl groups. When promoter regions of genes are heavily methylated, the attachment of transcription factors necessary for the initiation of transcription is inhibited. Conversely, the de-methylation of promoter regions enhances gene transcription. Micro-RNAs are short segments of RNA molecules that complement portions of the mRNA that is produced by gene transcription. When this complementarity leads to binding of the micro-RNA to upstream segments of the mRNA translation of the mRNA into protein is inhibited. Histone de-acetylation and promoter methylation are among the regular mechanisms by which the fate of developing cell lines is determined (Cavalli, 2006; Henckel, Toth, and Arnaud, 2007). Once established in a given tissue, the patterns of histone acetylation and promoter methylation are usually not altered during the life of an organism (but see Fraga et al. 2005 for contrary evidence). Germs cells, however, generally retain a totipotent epigenetic patterning (Morgan, Santos, Green, Dean, and Reik, 2005).

Epigenetic patterns of gene expression are thus largely established *in utero* and are thus potentially subject to modification by maternal condition. A number of studies in animal models have focused on epigenetic regulation of expression of the glucocorticoid receptor (GR). When GR is expressed at high levels in a given tissue, that tissue

becomes more sensitive to glucocorticoid signaling, i.e., lower concentrations of glucocorticoid are necessary for a given level of tissue response. When GR expression is inhibited, tissues become relatively insensitive to glucocorticoid signals. Experiments in rats have shown that alteration of maternal diet can influence the epigenetic regulation of GR in the liver by affecting the activity of the key enzymes methyltransferase-1 and histone-deacetylase (Lillycrop et al., 2007). The result is an altered sensitivity of postnatal gluconeogenesis to cortisol signaling. Similar alteration of the expression of the gene for peroxisome proliferator-activated receptor alpha (PPAR-alpha) has also been demonstrated, resulting in altered lipid metabolism (Lillycrop, Phillips, Jackson, Hanson, and Burdge, 2005). Kidney GR expression and angiotensin II receptor gene expression in the adrenal gland also show modified epigenetic regulation in response to altered maternal diets, affecting both the development of nephrons *in utero* and blood pressure responses later in life (Pham et al., 2003). Expression of GR in the hypothalamus is also epigenetically modified in rats in response to maternal diets, leading to altered HPA activity and stress responses after birth (Sebaai et al., 2002).

The identification of a core set of mechanisms mediating many aspects of the fetal programming of blood pressure and energy metabolism has focused research into possible interventions (Wyrwoll, Mark, Mori, Puddey, and Waddell, 2006). Understanding how maternal nutritional status alters the activity of the fetal enzymes mediating histone de-acetylation and promoter methylation may yield insights into ways in which enzyme activity might be buffered from maternal condition. Alternatively, it may be possible to reverse deleterious epigenetic patterns after birth. Recent research in

rats has indicated that leptin administration to the pups of undernourished dams may undo the changes in PPAR-alpha expression induced *in utero* (Gluckman et al., 2007; Vickers et al., 2005). If the period of sensitivity for epigenetic regulation of key genes extend into the postnatal period in humans, similar interventions may be possible.

Although the primary focus in epidemiology has been on the cardiovascular-metabolic disease cluster, prenatal effects on other chronic disease outcomes have also been reported. Breast and reproductive tract cancers and osteoporosis have drawn considerable attention as candidates for the effects of fetal programming (Barbieri, 2008; Michels and Xue, 2006; Michels, Xue, Terry, and Willett, 2006; Zhou, Dowdy, Podratz, and Jiang, 2007). This in turn suggests that the expression patterns of steroid receptor genes may also be subject to epigenetic regulation (Fleury, Gerus, Lavigne, Richard-Foy, and Bystricky, 2008; Jordan, 2007; Leader, Wang, Fu, and Pestell, 2006; Wu, Strawn, Basir, Halverson, and Guo, 2006). Non-pathological correlates of birth size have also been reported, including variation in adult patterns of ovarian steroid production (Jasienska, Thune, and Ellison, 2006; Jasienska, Ziomkiewicz, Lipson, Thune, and Ellison, 2006). Of particular interest in the present context are correlations with psychological and behavioral outcomes. Because of the involvement of the HPA axis in many behavioral patterns and responses, it is reasonable to expect that maternal condition might, though the epigenetic modification of HPA axis function, influence temperament, stress responses, and potentially psychiatric outcomes after birth in interaction with the effects of postnatal conditions.

Fetal programming of psychological and psychiatric outcomes

The most elegant example of epigenetic modification of behavior by early environments is not strictly an example of fetal programming, but offers clear documentation of the epigenetic processes that determine the effect. Meaney and his colleagues have focused on maternal behavior in rats, describing individual variation in the pattern of arch-backed nursing intense licking and grooming of pups (Meaney et al., 1994; Meaney et al., 1991). Pups who receive greater degrees of maternal stimulation show less anxiety in open field tests and other indices as adults. Females who receive greater stimulation as pups give greater amounts of stimulation to their own pups, inducing the same low-anxiety behavioral phenotype in their own offspring. The entire effect appears to be mediated by epigenetic alterations in histone acetylation and methylation of the promoter region of the GR gene in the hippocampus of the rat pups depending on the type of maternal behavior they receive (Meaney and Szyf, 2005a; Weaver et al., 2004). High stimulation results in greater GR expression in the hippocampus, which is in turn associated with greater sensitivity to corticosteroid feedback, a pattern that persists into adulthood (Weaver, Meaney, and Szyf, 2006). (Note that in this tissue the effect of glucocorticoid signaling is to suppress hypothalamic release of corticotropin releasing hormone (CRH), leading to lower pituitary release of adrenocorticotropic hormone (ACTH) and lower secretion of glucocorticoid from the adrenal cortex. Thus "greater sensitivity" to corticosteroid signaling results *lower* amplitude fluctuations of the HPA axis in response to stress, not greater.) Adults who receive high levels of maternal stimulation as pups thus show relatively low HPA

reactivity to stress, while the reverse is true in those who receive less stimulation as pups. This appears to correlate with their behavior in open field and other tests, and with the maternal style that females may display toward their own pups. In this way a stable difference in HPA axis sensitivity is transferred across generations through females based on an "inherited" epigenetic pattern. Interestingly, the epigenetic pattern is passed on not as such, but through first being translated into a behavioral pattern in the mothers, and then back into an epigenetic pattern in the offspring. Recently the same group has documented the effect of maternal behavior to similarly program reproductive axis activity through epigenetic effects on steroid receptor expression (Cameron et al., 2008; Champagne et al., 2006). Although the example of rat maternal behavior is not an example of "fetal" programming, it is an elegant demonstration of the potential for programming of the HPA axis to have behavioral consequences (Champagne et al., 2008; Meaney and Szyf, 2005b).

One of the most impressive studies to implicate fetal programming in psychiatric outcomes is the work of Ezra Susser and colleagues on the follow-up of individuals conceived during the Nazi occupation of Holland at the end of World War II (Susser, Hoek, and Brown, 1998). The so-called "Dutch Hunger Winter" provides a rather gruesome "natural experiment" in which pregnant women, along with the rest of the civilian population, were subject to extreme food deprivation during a relatively discrete period (Susser, Hoek et al., 1998). Ezra Susser's parents conducted seminal studies of the effects of this famine resulting, among other things, in the recognition of the importance of folate nutrition in pregnancy in avoiding neural tube defects (Stein, Susser, Saenger,

and Marolla, 1972). The younger Susser undertook to determine whether less debilitating effects on nervous system development as a consequence of famine exposure *in utero* might have consequences for psychiatric risk after birth. He found a clearly significant elevation of risk of schizophrenia and related disorders among those whose mothers went through the peak of the famine during their second trimester of pregnancy (Susser, Brown, Klonowski, Allen, and Lindenbaum, 1998; Susser et al., 1996; Susser and Lin, 1992). Subsequent work with individuals born during discrete famines in China has yielded similar results (Susser, St Clair, and He, 2008). Whether the mechanisms mediating these effects are epigenetic in nature remains to be determined (de Rooij et al., 2006).

Costello et al. (Costello, Worthman, Erkanli, and Angold, 2007) provide a second example of prenatal influences on psychiatric outcomes. They assessed a population-based sample of over 1400 boys and girls in western North Carolina for psychiatric symptoms on an annual basis between the ages of 9 and 16. They found that the rates of adolescent depression was over four times higher (38.1%) in girls who were low weight at birth compared to normal weight girls (8.4%), and seven times higher than in boys of any birth weight (4.9%). The well-known sex difference in adolescent depression was thus almost entirely accounted for by the higher risk in low weight girls. The effect was not diminished by consideration of perinatal, childhood, or adolescent adversities. There was an interesting interaction, however. Low and normal birth weight girls who experienced no subsequent adversities showed no incidence of depression. But with each additional adverse circumstance the rate of depression in low birth weight girls, but not

normal birth weight girls, increased significantly. The authors suggest that low birth weight girls are thus more sensitive to adverse circumstances later in life in terms of their risk of depression, a result that suggests possible alteration of physiological responses to stress, perhaps involving the HPA axis.

Animal evidence has long suggested that maternal "stress" during pregnancy is associated with behavioral outcomes in offspring (Burton et al., 2007; Clarke, Wittwer, Abbott, and Schneider, 1994; Kapoor and Matthews, 2008; Ohkawa et al., 1991; Weinstock, 1997). The nature of the "stress" applied may differ, but it is often assumed that the mother's HPA axis responds with higher levels of glucocorticoid hormones. It is unlikely that higher levels of maternal cortisol affect fetal physiology in humans, however, since the placenta is rich in 11-beta-steroid-dehydrogenase, which converts cortisol to inactive cortisone, thus buffering the fetus from maternal cortisol levels (Lakshmi, Nath, and Muneyyirci-Delale, 1993; McCalla, Nacharaju, Muneyyirci-Delale, Glasgow, and Feldman, 1998). Although positive correlations between baseline levels of maternal and fetal cortisol have been observed (Gitau, 2001), evidence of changes in maternal and fetal cortisol levels following invasive procedures indicates that maternal and fetal cortisol responses to stress are independent (Gitau, Fisk, Teixeira, Cameron, and Glover, 2001). Such buffering makes physiological sense since in late pregnancy the mother is essentially in a catabolic state while the fetus is in an anabolic state. Cross-talk between the energy metabolism of mother and fetus would be disastrous.

However, dexamethasone (DEX), a synthetic glucocorticoid, has long been

administered to mothers known to be carrying fetuses deficient in 21-hydroxylase and therefore at risk of congenital adrenal hyperplasia (CAH) (Forest, Betuel, and David, 1989; Speiser and New, 1994). Because affected CAH individuals are impaired in their ability to produce cortisol, inadequate negative feedback leads to overproduction of adrenocorticotropic hormone (ACTH) and hyperplasia of the adrenal glands. A secondary consequence is overproduction of adrenal androgens that can lead to varying degrees of genital androgenization (Pang, 1997). Some studies have indicated potential effects on childhood and adult behavior, including sexual orientation, as well (Arlt and Krone, 2007; New, 2004). DEX is often administered to head off these consequences, since it readily crosses the placenta, is not metabolized by 11-steroid-dehydrogenase, and interacts with GR receptors in the fetal hypothalamus to suppress excess production of ACTH and its corollary effects (Hughes, 2003).

In animal studies using prenatal administration of DEX as a treatment alterations of offspring behavior and HPA axis reactivity are observed. This suggests that the feedback sensitivity of the HPA axis may be partially regulated through the level of activation of the axis during fetal development. Awareness of this fact has led some researchers to suggest that the administration of DEX to mothers of CAH fetuses may be unwise until its programming effects are better understood (Hirvikoski et al., 2007; Lajic, Nordenstrom, and Hirvikoski, 2008; Miller, 1999).

Although maternal stress may not be communicated to the fetus via maternal cortisol, there are other pathways possible, including alterations of placental blood flow

(Gitau 2001) and changes in energy available for fetal growth. In addition, conditions that lead to fetal stress, such as restricted energy availability or invasive medical procedures (Gitau et al. 2001) may directly affect the level of activity of the fetal HPA axis, as opposed to the maternal axis, with potential programming consequences. Achieving a better understanding the potential for prenatal conditions to have lasting effects on an individual's physiology, with possibly serious implications for psychiatric risk, must be considered one of the high priorities for psychological research stemming from the fetal programming hypothesis (Kaplan, Evans, and Monk, 2008).

Is fetal programming adaptive?

Fetal programming as a phenomenon was first recognized through its pathological consequences, and most research continues to focus on the deleterious sequellae of small size at birth. Epigenetic regulation of gene expression, on the other hand, is hardly pathological; rather it constitutes one of the principal mechanisms of cellular differentiation during embryological development. Selection pressure on developmental processes should be very strong, since mistakes early in ontogeny can have broadly ramifying consequences. Thus it would seem logical, in one way, that epigenetic responses to prenatal conditions must themselves have been products of natural selection, representing adaptive responses to those conditions. Yet attention has been focused on prenatal programming principally through a recognition of its association with pathological outcomes.

Peter Gluckman and Mark Hanson have suggested that the apparent paradox of presumably adaptive developmental processes yielding pathological results can be resolved if (1) the adaptive processes are aimed at adjusting the organism's physiology to a "predicted" postnatal environment, and (2) if there is in fact a "mismatch" between the predicted and actual postnatal environment (P. Gluckman and Hanson, 2005; P. D. Gluckman and Hanson, 2004; P. D. Gluckman, Hanson, and Spencer, 2005). For example, fetal energy restriction may signal the fetus to permanently alter its own energy metabolism in anticipation of an energy restricted, postnatal environment. The fetus might upregulate GR expression in its hippocampus to enhance cortisol responses to energy restriction. If the postnatal environment is not energy restricted, however, this shift in metabolism may result in a tendency to obesity and poor glucose regulation. Thus the mechanisms of fetal programming might be adaptive in cases where *in utero* conditions are predictive of characteristics of the postnatal environment, but maladaptive when the prediction fails.

Others have argued that adjusting postnatal physiology on the basis of prenatal conditions would represent "hyper-responsiveness" to transient conditions and is unlikely to be the basis of an adaptive explanation for fetal programming effects (Jones, 2005; Rickard and Lummaa, 2007). Gestation is at best a nine-month "bioassay" of environmental conditions, and the fetal environment is highly buffered as well. Rather than establishing permanent physiological set-points and sensitivities on the basis of such a short period of information of limited relevance, wouldn't it be more adaptive to establish these set-points on the basis of a longer period of postnatal experience? The

force of this logic suggests that fetal programming effects are not in themselves adaptive, but are instead probably constraints of development akin to the "sensitive periods" that are observed in many developmental processes.

These perspectives may not be as antithetical as it seems at first. Yet if irreversible "decisions" must be made early in development, such as whether or not to silence or dampen the expression of certain genes in certain tissues, it may be better to make that decision in the light of whatever information is available, even if its correlation with future conditions is low. A different answer to this problem has been proposed by Kuzawa (2005). He suggests that conditions *in utero* may not merely reflect maternal conditions at the time, but also her own sensitivity to those conditions. For example, fetal energy availability may not only be affected by maternal undernutrition, but also by how sensitive the mother's own physiology is to variation in energy availability. Maternal sensitivity to energy availability in turn may be partly a consequence of the conditions *she* faced *in utero*, which in turn would depend on *grand-maternal* sensitivity to energy availability, and so forth. In this way fetal programming may not primarily be a response to transient conditions during gestation, but rather a response to a more cumulative signal of conditions across generations. Rather than representing hyper-responsiveness to transient conditions, fetal programming may represent a mechanism of developmental "inertia."

Interestingly, Barker himself does not subscribe to the view of fetal programming as adaptive (Barker et al., 2002; Barker, 1994). He sees these effects rather as disruptions

of optimal development with permanent consequences, developmental pathologies that may indeed be more frequent in evolutionarily novel environments.

Testing the Gluckman and Hanson hypothesis of "predictive adaptive responses" is difficult. One strategy might involve experimentally "matching" and "mismatching" postnatal environments to prenatal treatments and comparing the outcomes in selectively relevant currencies, such as survival or fertility. Other strategies may involve identifying outcomes *a priori* as constrained, pathological, or adaptive and then applying a test (Ellison and Jasienska, 2007; Jasienska, Thune, and Ellison, 2006). In the same way that a deeper understanding of underlying mechanisms can suggest opportunities for public health intervention, a deeper understanding of the functional significance of fetal programming may help us avoid unanticipated consequences.

Summary

Epidemiological evidence that prenatal conditions can be important determinants of adult health is now quite compelling. The rapidly developing field of epigenetics has elucidated important mechanisms by which tissue-specific patterns of gene expression that are stable over the life of an individual can mediate such effects. Many of the best examples of prenatal alteration of gene expression involve adjustments in the sensitivity of the HPA axis. In addition to the implications for metabolic disease, these changes can also affect behavior in animal models. They may also underlie the relationship between fetal energy restriction and the epidemiology of schizophrenia in humans. Animal

models suggest that more moderate effects of prenatal and even immediately postnatal conditions may affect adult stress reactivity, with potential implications for the spectrum of individual differences displayed, from variation in normal temperament to pathologies of HPA axis responsiveness. At the same time the potential for prenatal epigenetic alteration of HPA sensitivity has caused some to suggest caution in the use of drugs like dexamethasone *in utero*. It is likely that the literature and examples reviewed here represent merely the opening of a new area of research in developmental psychology, one that will bring it into closer and more productive interaction with research in human genetics, developmental biology, and evolutionary biology in the years ahead.

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Figure Captions

Figure 1: A schematic depiction of the three mechanisms of epigenetic modification of gene expression discussed in the text. Nuclear DNA occurs tightly wound about histone molecules. Attachment of acetyl groups (CH_3CO) to exposed lysine residues on the histone molecules loosens the association between the histone and DNA molecules, allowing transcription factors access to gene promoter regions. CpG sequences in gene promoter regions provide sites for the attachment of methyl groups (CH_3), which inhibits the binding of transcription factors. Micro RNA molecules are small RNA sequences that can bind to messenger RNA. When they do, they inhibit the translation of the mRNA into protein. In this figure, elements that promote gene expression are contained in ellipses; those that inhibit expression are contained in rectangles.

Alternate Figure Caption (if color figures are possible)

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