Developmental plasticity and human disease: research directions

P. D. Gluckman1,2 & M. A. Hanson3

From the 1Centre for Human Evolution, Adaptation and Disease, Liggins Institute, University of Auckland, Auckland, New Zealand, 2National Research Centre for Growth and Development, Auckland, New Zealand, and 3Centre for Developmental Origins of Health and Disease, University of Southampton, Southampton, UK


The conceptual basis of the ‘developmental origins’ paradigm has converged on the role of developmental plasticity responding to signals from the early environment, with heightened risk of disease if the induced phenotype does not match the later environment. Nevertheless, numerous questions remain, including the current burden of disease that can be attributed to early environmental factors; the pathways, mechanisms and windows of plasticity; the identification of early markers of environmentally induced change; and the feasibility, costs and benefits of intervention. A focused agenda of research is needed to convince policy makers of the importance of developmental factors in human disease.

Keywords: fetal growth retardation, insulin resistance, leptin, obesity, pregnancy, type 2 diabetes mellitus.

Introduction

Although it is nearly two decades since the first observations relating early environment to later disease were made, there remains debate and uncertainty as to how understanding the so-called ‘developmental origins (DOHaD) paradigm’ can be applied to improving human health. The questions that have emerged are multiple and there is now a broad and interdisciplinary research agenda. Despite some confusion and debate, there is now overwhelming epidemiological and prospective data relating early life events to the risk of heart and cardiovascular disease, type 2 diabetes, obesity, osteoporosis and other disorders in later life.

This relationship has been termed ‘programming’, but we generally resist the term – it implies a deterministic process and set of mechanisms akin to the genetic ‘programme’ of development and, as this review will highlight, its use may influence the mindset of investigators. We now consider the DOHaD phenomenon to be a subset of a broader and normal biological phenomenon – that of developmental plasticity – but one that can under some circumstances be maladaptive and lead to greater risk of disease. Developmental plasticity encompasses those processes that generate alternative phenotypes from a single genotype through the actions of environmental cues acting during development. They allow environmental influences to ‘tune the match’ of the organism to its expected environment beyond that achieved through natural selection (i.e. inherited genotype).

During the 1990s a considerable experimental literature emerged showing that the equivalent of the DOHaD phenomenon could be replicated experimentally in animals by manipulating maternal nutrition or fetal growth or by mimicking stress by administering glucocorticoids to the pregnant mother (reviewed in [1, 2]). The long-term effects do not necessarily require alterations in birth size. Indeed an important
concept is that alterations in birthweight are not necessary for early life events to induce other phenotypic changes with later consequences. Indeed, comparative studies point out that quite major phenotypic changes can occur as a result of subtle, but evolutionarily important, signals, as in the case of environmentally induced polyphenism in insects [3]. Recent mechanistic studies have focused on the possible role of epigenetic changes in mediating these events, either directly or indirectly.

However, whilst there is increasing evidence that the normal processes of developmental plasticity operate in humans and can be affected by the early environment and that this may influence later disease risk, the outstanding questions are multiple and important and require systematic and integrated consideration. This paper highlights the most important of these questions in the hope that it will assist the biomedical research community to focus their effort.

How important are early environmental factors in the ecology of human disease?

An ongoing debate [4, 5] arising from the epidemiological studies is how important this framework is to the prevalence of diseases appearing in middle and old age. The debate is confounded by several factors: some studies use only surrogates for disease risk (e.g. measures of blood pressure or insulin sensitivity) and birthweight itself is a very crude measure of the prenatal environment. Further, current models consider that there is an interaction of the prenatal, infant and later environments in generating disease risk, and this generally is not considered appropriately in most of these analyses. The problem is that the only population-based estimate that examines lifetime disease risk comes from a Finnish cohort born in the 1930s [6]. The relevance of that population to current populations is uncertain. Yet that study suggests that a very large component of the attributable risk of heart disease and diabetes lies in perinatal growth.

This issue of how important are early life events needs to be addressed in new ways as retrospective cohort studies will always have the issue of relevance to current populations. What are needed are better surrogates of both change in development induced early in the life-course and consequential change in disease risk, preferably from current prospective cohorts. As will be discussed, epigenetic measures may be useful markers of the former and measures of lipid deposition (particularly visceral fat) and metabolism in children might be very relevant early outcome measures.

A related issue comes from the tendency to examine the attributable risk in relation to a single outcome such as heart disease, whereas the experimental and clinical data demand a more holistic approach. Thus, an adverse early life environment can induce a cluster of outcomes, including visceral adiposity, central and peripheral changes in the regulation of satiety, food preference, fat metabolism, insulin sensitivity, endothelial dysfunction, altered tempo of development, altered nutrient compartmentalization and growth, neuroendocrine changes, mood disorders and reduced nephron and neurone number [7]. It seems likely that the concurrent environment, developmental factors and genotypic variation all influence the particular balance of organ and system changes reflected in the variation in the expression of this ‘metabolic phenotype’. Thus, it is more appropriate to estimate the global attributable risk arising from early life factors in relation to their contribution to the origin of the metabolic phenotype rather than to individual components.

A key issue is to what extent do genetic confounders play a role in understanding these relationships. Studies of glucokinase mutations led to the proposition of the ‘fetal insulin hypothesis’ in which mutations affecting glucokinase influenced both fetal growth and the later risk of metabolic disease [8]. Undoubtedly there are mutations in several genes related to insulin action that could have this effect, and further studies are needed of this genetic confounding. But as is discussed below, recent evidence would suggest that insulin resistance appears after and not before birth.

The effect of environmental influences must of course be influenced by the genotype. This is best illustrated
by studies such as those on PPARγ2 polymorphisms [9, 10] and by the demonstration that the effects of maternal constraint on birth size are dominant in first-born children whereas the effects of insulin gene polymorphisms are more evident in subsequent pregnancies [11]. The experimental data clearly exclude a prevailing genetic explanation for the DOHaD phenomenon. Further, a number of the polymorphisms reported may well be very population-specific. Thus we are left with the question: to what extent do polymorphisms interact with developmental cues in increasing or reducing disease risk and to what extent are these variations population-specific? The matter is further confounded by the recent recognition of epigenetic inheritance [12], making twin studies and simple familial linkage studies of more limited value.

How then could we define an environmentally induced change in the developmental trajectory prospectively and early enough in postnatal life to be useful in prospective epidemiological studies? Experimental studies show that environmental factors can change development without affecting birthweight [13] and this is also suggested from the Dutch famine studies [14]. Possibly epigenetic biomarkers can be identified, because where they differ between groups they are likely to reflect environmental influences [15].

The issue is further compounded by the potential existence of three developmental pathways of relevance. The first is that studied by Barker’s group and many others and which we now refer to as the ‘mismatch’ pathway – children born following a relatively deprived intrauterine environment which may or may not be manifest as impaired fetal growth and who may continue to show poor growth before showing rapid weight gain (e.g. [16]). We have suggested that it is the degree of mismatch that determines disease risk, but how that is defined (for example, which nutritional parameter, what measure of stress) is a challenge for the investigator.

The second potential pathway is that studied by Lucas and others, where rapid weight gain in infancy, generally as a result of formula feeding, appears to be associated with poor intermediate metabolic outcomes [17]. This may be a distinct pathway, but as all fetal growth is somewhat constrained [18] it may simply be a more acute form of developmental mismatch rather than a distinct pathway.

Thirdly, we need to note that infants of diabetic and obese mothers become obese and insulin resistant themselves by a distinct pathway [19]. The outcome for the infants of diabetic mothers is discussed below and is likely to represent a pathological pathway reflecting increased fat mass, probably arising in utero secondary to fetal hyperinsulinaemia [20]. The mechanisms operating in maternal obesity are less clear. In this regard it is important to note the often-overlooked relationships amongst food composition, food intake and satiety, which mean that the availability of a diet low in protein may result in consumption of a relatively high intake of fat and carbohydrate [21].

Our current need is to have measures in early life that will predict later disease risk arising from genetic, epigenetic and other factors. It is unrealistic to imagine that a single change in expression of a single gene, either because of epigenetic change or polymorphism, is prognostic of disease risk and we need new ways of integrating genetic, epigenetic and environmental information for such purposes.

These issues are problematic, but it is worth emphasizing that the only available estimates do argue that early life events are important both to life-long risk of ‘lifestyle’ disease [6] and to the development of obesity [22]. The weight of experimental evidence suggests that subtle insults can have lasting effects and that these effects, particularly in a ‘mismatched’ environment of, for example, an energy-dense diet with low energy expenditure, lead to heightened disease risk. The frustration for those interested in the DOHaD paradigm is that vested interest and a political focus on short-term outcomes restrict acceptance that these are important issues. But we must recognize that until we can answer these questions policy makers are unlikely to respond positively.

With uncertainty remaining in the human data, it is difficult to do the cost–benefit analyses that might
influence policy makers. One effort has been made to evaluate the cost of low birthweight in a third world population by using a life course approach [23], but that study has major limitations: the burden of chronic disease is underestimated, especially with respect to the range of diseases involved and the age at which they can develop, and birthweight was considered in a dichotomous fashion (less than or greater than 2500 g). The issues of babies of higher birthweight within the same populations, especially once these populations have entered socioeconomic and nutritional transition, were not considered. However the analysis did serve to highlight the point that even subtle changes in cognitive development may have a major economic impact. As will be discussed below, there is increasing reason to suspect that impaired early development both affects cognitive development negatively and increases the risk of adiposity gain in childhood. Perhaps cost–benefit could be modelled on these earlier outcomes in a developed population – our bias is that the effect would be great enough to merit increased policy and political attention to the DOHaD phenomenon. That fetal conditions can have lasting effects on adult achievement in a developed population – exposed in utero to the 1918 influenza pandemic in the USA [24].

Mechanistic perspectives

The experimental approach has generally been to take normal animals, subject them to a challenge in early development (fetal or infant) and study a narrow range of outcomes. There is a paucity of studies that consider the effects of prior intergenerational environmental history on the outcome – yet for reasons of selection or epigenetic inheritance this may be of importance in both animal and human studies. Most experimental work has utilized nutritional manipulation of the mother or infant, exposure to exogenous glucocorticoids, or maternal hypoxia, and all produce relatively similar outcomes. In human pregnancies these coexist frequently, for example poor nutrition, stress and maternal smoking. There is increasing interest in the role of xenobiotics, such as phyto-oestrogens, and these may well act through epigenetic developmental pathways [25]. Given that nutrition affects the placental glucocorticoid-inactivating enzyme 11β-hydroxysteroid dehydrogenase type 2 and that glucocorticoids can affect intermediary metabolism and glucose transporters, commonalities of effect are likely. It is possible that many challenges act through altered glucocorticoid exposure or through processes mediating oxidative stress. A convergent pathway seems likely, at least with regard to metabolic phenotype, given the strikingly similar outcomes to a variety of stimuli.

The focus on birthweight mistakenly led some to conclude that this phenomenon was one of extremes and therefore not important [26]. But this is clearly not the case. It cannot be over-emphasized that disease risk is associated with birth size across the full range of birthweights, and even if the analysis is restricted to babies above the mean for birthweight [27]. Thus the key issue must be: what is the range of cues operating in ‘normal’ pregnancies? Variation in maternal diet within the normal range can affect human pregnancy outcomes [28, 29]. The effects of parity [22, 30] led us to suggest that maternal constraint, the set of maternally determined environmental processes limiting fetal growth, is important [18]. If this is the case then demographic factors such as changing family size, maternal age and maternal dietary habits, combined with the nutritional and exercise transitions, can explain much of the changing incidence of lifestyle-related disease.

Other issues arise when considering the nature of the inducing cues. First, do cues always signal adverse environments, leading to subsequent metabolic compromise? This may not be the case. Recent studies in IVF offspring suggest that under at least some circumstances the offspring may be taller, leaner and have better lipid profiles [31]. Secondly, there is the issue of the cue arising from maternal hyperglycaemia and ‘overnutrition’. In evolutionary terms, fetal growth is limited by maternal constraint, which is likely to have developed to allow pelvic delivery. This and the other constraints on nutrient provision resulting from an uncertain food supply meant that fetal
adaptation would always be in the direction of coping with impaired intrauterine nutrition; maternal and fetal overnutrition would have been unlikely until the pathological circumstance of gestational diabetes appeared with excessive modern nutrition. We suspect that the outcome of gestational diabetes cannot be considered in adaptationist terms but rather is a simple sequence of fetal hyperinsulinaemia, larger fetal fat mass, greater infant obesity and its later consequences in an energy-rich postnatal environment. The different postnatal pattern of adipose development in larger infants supports this differentiation [19].

The mismatch concept highlights the role of postnatal amplification by energy-dense diets or low energy expenditure. Our experimental work shows that the degree of mismatch determines the magnitude of the developmentally induced changes [32]. In some cases – for example, expression of some neuropeptides associated with appetite regulation – the changes are only seen in the mismatched group [33]. This mismatch may be reflected in the rapid weight gain of those born to poor intrauterine environments and then given access to high energy intakes. But the problem with the use of the term ‘catch-up growth’ is that it is at best misleading, if not meaningless. It is often used to describe only weight gain, not skeletal growth. Weight gain in the absence of skeletal growth in most children is likely to represent metabolic abnormality. Clinical studies need to be precise as to what is being measured and future cohort studies should at a minimum consider gain in fat mass separately from gain in lean body mass and distinguish visceral from peripheral adiposity.

We have suggested that a key principle is that an early life cue may change the offspring’s physiological settings such that its response to a later environmental challenge is different. We have suggested that this process evolved as an adaptive phenomenon to match the individual to its environment, but that it can be maladaptive if the environmental prediction is wrong because of faulty transduction of the signal, maternal disease, maternal consumption of an unrepresentative diet (or indeed dieting to lose weight) or unpredicted environmental change. This model is discussed in detail elsewhere [34, 35] but it leaves several unanswered questions. First, how broad is the range of systems affected in an integrated manner? If the processes underpinning DOHaD are those of developmental plasticity then comparative studies would suggest that an integrated phenotype will emerge matched to the predicted environment. Clinical and experimental studies suggest this to be the case. It is clearly not a matter of a specific cue acting at a specific developmental time inducing (say) a reduction in nephron number – rather there is an integrated strategy to adopt a phenotype involving multiple systems. Thus an integrative biology approach is essential to understanding the phenomenon and to designing interventions.

A further question concerns the postnatal determinants of greater mismatch – what is the role of factors such as gain in fat mass, musculoskeletal growth, reduced exercise or continued stress? Indeed, we understand very little about the biology of compensatory linear growth and the change in metabolic compartmentalisation which favours visceral obesity following adverse environments operating in earlier life.

The original thrifty phenotype hypothesis was most clearly advanced to explain the link between small size at birth and later risk of type 2 diabetes. It posited that the foetus reduced its growth in an impaired nutritional environment, inducing insulin resistance, and that this then became manifest postnatally as metabolic disease in a high energy environment [36]. However, the hypothesis implied that impaired fetal growth was central, an immediate adaptive response to the poor in utero environment, leaving the offspring with a legacy with which it had to ‘cope’ later. At its simplest this would suggest that insulin resistance would develop before birth, which clearly it does not either experimentally [37] or clinically [38, 39] – if anything, poorly grown babies may be more insulin sensitive at birth, only developing insulin resistance many months or years later, suggesting that quite different processes are in play. The mechanisms underpinning this switch are speculative, but early insulin sensitivity may convey an advantage in ensuring sufficient muscle growth for survival and because
adequate infant fat appears to be important to buffering the infant brain at times of stress such as infection or weaning [40]. Thus the concept of a life-course strategy induced in development, and in this case involving greater insulin sensitivity followed by insulin resistance, seems a more satisfactory explanation.

Functional considerations can operate at one of the three levels: adaptationist/evolutionary, systems or mechanistic. The adaptationist model is reviewed in depth elsewhere [34, 41]. Key to it is understanding that developmental cues may be disruptive or plastic and that plastic responses may be delayed in relation to the inducer. We have advanced the arguments why we suspect that the mismatch pathway reflects a plastic response [7]. We propose that ‘programming’ is an integrated response involving life-history tradeoffs rather than a series of single cue/response relationships. But we have yet fully to understand the scope of the systems involved. We have argued [7] that the organism will make quite distinct predictive responses across a variety of systems depending on whether it foresees a safe or threatening environment based on maternally derived cues (Table 1). This evolutionary and life-history perspective is also useful in understanding gender difference, which seems almost universal in DOHaD studies but is often ignored. For example, the drive to achieve maximal body size in males to ensure reproductive success versus the need for extended fecundity in females may explain why components of the integrated response are often expressed differently between the genders.

The processes of developmental plasticity alter structure and function through effects either on tissue anatomy or micro-anatomy or on cellular activity within

<table>
<thead>
<tr>
<th>Table 1 Integrated responses to the predicted environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely responses to a secure environment</td>
</tr>
<tr>
<td>Investment for longevity (predictive responses)</td>
</tr>
<tr>
<td>Commitment to repair</td>
</tr>
<tr>
<td>Commitment to tissue reserve (e.g. neuronal and nephron number)</td>
</tr>
<tr>
<td>Investment for large adult size (predictive responses)</td>
</tr>
<tr>
<td>Greater bone mass</td>
</tr>
<tr>
<td>Greater muscle growth</td>
</tr>
<tr>
<td>Investment to resist threatening and difficult environment (predictive responses)</td>
</tr>
<tr>
<td>Altered hypothalamic–pituitary–adrenal axis</td>
</tr>
<tr>
<td>Altered behaviour, altered anxiety</td>
</tr>
<tr>
<td>Increased propensity to store fat</td>
</tr>
<tr>
<td>Central components</td>
</tr>
<tr>
<td>Increased appetite</td>
</tr>
<tr>
<td>Altered food preference</td>
</tr>
<tr>
<td>Reduced motor behaviour</td>
</tr>
<tr>
<td>Peripheral components</td>
</tr>
<tr>
<td>Altered hepatic development and function</td>
</tr>
<tr>
<td>Sarcopenia</td>
</tr>
<tr>
<td>Altered insulin release and action</td>
</tr>
<tr>
<td>Impaired action of growth hormone and insulin-like growth factors</td>
</tr>
<tr>
<td>Leptin resistance</td>
</tr>
<tr>
<td>Altered endothelial function</td>
</tr>
</tbody>
</table>
tissues. Both are probably mediated by epigenetic modulation of the expression of key developmental or regulatory genes by mechanisms involving DNA methylation, histone modification or small noncoding RNAs. Such modulation occurs throughout the period in which a system is plastic. Given that DNA methylation is the easiest of these changes to study, it is not surprising that evidence is accumulating for such modifications in genes associated with metabolism and endocrine regulation [42–44]. Such research may in time point to the fundamental processes, but in the interim provides insights into biomarkers. Studies will need to consider different classes of target gene: regulatory genes, growth-related genes (which are often imprinted) and mitochondrial genes, to name only three. The explosion of knowledge in epigenetics will lead to new tools and an understanding of how tissue specificity is achieved. Researchers will need to consider what are the targets at different times in development, from the egg and spermatogonia, through the early conceptus, stem cell differentiation, the placenta and specific organs as the organism matures.

They will also have to consider to what extent the wider concept of nongenomic inheritance plays a role [45, 46]. Not all this need be mediated by epigenetic processes. For example, girls born smaller have smaller uteri and this may be the mode of transmission to the third generation [47]. Female rats undernourished in utero have impaired uterine vascular responses to dilators, which will have impact on their adaptations to pregnancy [48]. Other examples could involve biochemical processes, for example growth-impaired F₁ offspring of F₀ mothers may develop insulin resistance, in turn affecting the F₂ generation when the F₁ mothers are pregnant [49]. The work of Meaney and colleagues [50] on intergenerational behavioural programming can be explained either by epigenetic inheritance or by behavioural intermediary mechanisms whereby altered maternal infant bonding leads to altered behaviour in later life, a process repeated when they in turn become mothers. We have pointed out [51] the potential for intergenerational switching of pathways whereby the offspring of a pregnancy with unbalanced nutrition are at risk of developing gestational diabetes, thus switching from a ‘mismatch’ pathway in one generation to the ‘infant of a diabetic mother’ pathway in the next.

We fear that much current research effort is at risk of repeating some of the errors of recent systems biology. The dominant medical model was often genetic, assuming single cause–single effect relationships. This is not the case in integrated developmental responses. Seeking linear relationships between cause and effect makes simplistic assumptions about effectors. To reduce the outcome to a single component ignores the many interacting systems which determine probability of health. It is important to note that biological systems are generally nonlinear and dynamic, producing discontinuous effects.

This discussion has focused on the ‘metabolic phenotype’ but there are data showing developmental induction of long-term effects in very different systems such as fluid and water balance [52], reproduction [53] and thermal homeostasis [54] as well as behaviour and cognitive function [55]. These have many analogies to metabolic induction by nutrient/stress signals. In evolutionary terms the parallels are striking and the question arises: do comparable processes explain induction of phenotype in different domains by similar cues?

**Intervention and reversibility**

The discussion above points to several approaches to prevention and intervention. Experimentally, manipulation of epigenetic processes by nutritional constituents administered during pregnancy, such as folate and glycine, has been shown to prevent the induction of altered trajectories by maternal undernutrition [44]. Reversal is a more complex issue. Recently, reversal of maternally induced behavioural attributes associated with epigenetic changes in hippocampal glucocorticoid receptors has been produced by drugs affecting histone acetylation [56]. Perhaps of most relevance to the current discussion is the recent finding that administering leptin neonatally to the offspring of undernourished mothers prevents the development of all components of the metabolic phenotype [57]. We interpret this study as tricking...
animals born thin into believing that they are in fact well nourished, because leptin is an adipokine secreted by fat. This study provides strong support for the adaptive and predictive mismatch model. It is compelling that the full spectrum of phenotypic changes was prevented for life by such neonatal leptin exposure. Other studies have reported specific treatment effects on organ systems, such as the effect of exendin-4 on pancreatic development [58]. At a population level we have suggested [59] that the mismatch paradigm argues for different public health foci in different populations at different points in nutritional and socioeconomic transitions – whether focused on antenatal prevention or postnatal intervention.

Whilst the desire for population intervention studies is clear, some key questions need to be asked. The argument for prevention is generally based on trying to optimize pregnancy outcomes in compromised populations. But what is an appropriate intervention? Two recent studies of nutrient supplementation in pregnancy, based on plausible assumptions of likely benefit, have had unexpectedly adverse outcomes [60, 61]. This highlights the need for caution in designing seemingly logical clinical intervention in the absence of solid preclinical data.

The alternative approach is to intervene in infancy or childhood. But many of the most compromised populations are now well into nutritional transition and in these there is a mix in the population of mismatched and fetally overnourished offspring. A single population-based approach may thus have limitations. It is a matter of faith rather than evidence as to the effectiveness of childhood diet and exercise programmes, and further research in this area must be a priority [62].

Thus the design of any intervention must be better informed by basic science. Fundamental questions in considering an intervention must include what kind, to whom and when in the life course, and whether the intervention is designed to affect a specific organ system (e.g., cognitive function) or reverse a range of phenotypic attributes. Further, how will efficacy be judged – on what surrogates and at what age? If the mechanisms are indeed epigenetic, could epigenetic biomarkers be useful surrogates of beneficial effects? These questions must be asked as interventions are designed.

Further, one must be cognizant of the varying ease of application in different populations. For example, the World Health Organization recently concluded that there would be much to gain for fetal health by delaying the age of first pregnancy until several years after menarche [63]. But there would be major cultural issues in implementing such a policy in many societies. The report also concluded that improved nutritional state at conception, optimizing maternal nutrition during pregnancy, avoiding smoking, malaria and HIV, promoting breast feeding and matching prenatal and postnatal growth were all important and desirable goals. However in each case other than smoking, we really do not have the knowledge or the strategies to design specific interventions to achieve these objectives. For example, we do not know how to define optimal nutritional state for mother and foetus, and we have a very limited idea of what would define nutritional ‘match’ across a life course. One clear challenge is how to establish effective nutritional interventions prior to conception. This requires population-based approaches starting in childhood and continuing into adolescence, addressing major social and cultural issues. It would require a focus on the education of child and family and greater empowerment of women whilst also involving men in the process. Yet all these factors need to be considered in an analysis that would compel policy change.

Final remarks

The DOHaD paradigm remains a challenge to the basic scientist, clinician and epidemiologist. Most researchers in the field believe that it is an important factor in human disease which will, in time, inform both population-based and individual approaches to improving health. It challenges the traditional medical model of disease causation and sees disease as the outcome of a mismatch between the processes of developmental plasticity and the environment in which the individual subsequently lives. It introduces new concepts into medicine: developmental plasticity,
Conflict of interest statement

No conflict of interest was declared.

Acknowledgements

We thank Dr Alan Beedle for his editorial assistance. The British Heart Foundation provided support for M.A.H. and the National Research Centre for Growth and Development supports P.D.G.

References


© 2007 Blackwell Publishing Ltd Journal of Internal Medicine 261; 461–471 469
Neonatal leptin

Longitudinal changes in

Developmental

et al.

et al.

et al.

et al.

et al.

Bateson P, Barker D, Clutton-Brock T

Ikenasio-Thorpe BA, Breier BH, Vickers MH, Fraser M. Effect

Miles H, Hofman PL, Cutfield WS. IVF children are taller with

Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman

Pham TD, MacLennan NK, Ciu CT, Laksana GS, Hsu JL,

Kuzawa CW. Adipose tissue in human infancy and childhood:

Ibañez L, Ong K, Dunger DB, de Zegher F. Early development

Gluckman PD, Hanson MA. Metabolic disease: evolutionary,

diabetes mellitus.

Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992;


Weaver IC, Meaney MJ, Szyf M. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. Proc Natl Acad Sci U S A 2006; 103: 3480–5.


Christian P, West KP, Khatry SK et al. Effects of maternal micronutrient supplementation on fetal loss and infant mortality:


Correspondence: Prof. Peter D. Gluckman FRS, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand.
(fax: +64 9 373 7497; e-mail: pd.gluckman@auckland.ac.nz).