Physiol Rev 94: 1027–1076, 2014
doi:10.1152/physrev.00029.2013

EARLY DEVELOPMENTAL CONDITIONING OF LATER HEALTH AND DISEASE: PHYSIOLOGY OR PATHOPHYSIOLOGY?

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Hanson MA, Gluckman PD. Early Developmental Conditioning of Later Health and Disease: Physiology or Pathophysiology? *Physiol Rev* 94: 1027–1076, 2014; doi: 10.1152/physrev.00029.2013.—Extensive experimental animal studies and epidemiological observations have shown that environmental influences during early development affect the risk of later pathophysiological processes associated with chronic, especially noncommunicable, disease (NCD). This field is recognized as the developmental origins of health and disease (DOHaD). We discuss the extent to which DOHaD represents the result of the physiological processes of developmental plasticity, which may have potential adverse consequences in terms of NCD risk later, or whether it is the manifestation of pathophysiological processes acting in early life but only becoming apparent as disease later. We argue that the evidence suggests the former, through the operation of conditioning processes induced across the normal range of developmental environments, and we summarize current knowledge of the physiological processes involved. The adaptive pathway to later risk accords with current concepts in evolutionary developmental biology, especially those concerning parental effects. Outside the normal range, effects on development can result in nonadaptive processes, and we review their underlying mechanisms and consequences. New concepts concerning the underlying epigenetic and other mechanisms involved in both disruptive and nondisruptive pathways to disease are reviewed, including the evidence for transgenerational passage of risk from both maternal and paternal lines. These concepts have wider implications for understanding the causes and possible prevention of NCDs such as type 2 diabetes and cardiovascular disease, for broader social policy and for the increasing attention paid in public health to the lifecourse approach to NCD prevention.

I. INTRODUCTION: THE DOHaD CONCEPT

This review is concerned with understanding the physiological and pathophysiological basis for how environmental influences acting during early human development influence the risk of later chronic, especially noncommunicable, disease (NCD). This field of biomedical science and public health has become recognized as the developmental origins of health and disease (DOHaD) (142, 211). The focus of this review is to consider the extent to which early conditioning **(TABLE 1)** mechanisms in humans may represent the physiological processes of developmental plasticity **(TABLE 1)** operating in early life, but having potential adverse consequences later, or whether they are the result of pathophysiological processes acting in early life but manifesting as disease later in life. We will argue that the evidence supports the former concept. The majority of this evidence comes from animals, but there is increasing evidence from human physiology which suggests that the concepts have wider relevance. In addition, they accord with an emerging understanding of the principles of evolutionary developmental biology (evo-devo) **(TABLE 1)** and evolutionary medicine (196, 423). We will also discuss how disruptive processes during development can also lead to later disease, especially if they are novel from an evolutionary point of view. These concepts have significant implications for understanding the epidemiology of NCDs such as type 2 diabetes and cardiovascular disease and hence for their prevention. While the end result of these processes is disease in the modern world, the understanding of the underlying biology which is necessary if we are to devise preventative measures includes not only proximal pathophysiological mechanisms but also more ultimate **(TABLE 1)** mechanistic physiological considerations. Insights into these can be found in the broader biological fields of evo-devo (196, 646), and more

Table 1. *Definitions of terms used in this review*

Term	Definition
Accommodation (phenotypic)	Adaptive adjustment, without genetic change, of variable aspects of the phenotype following a novel input during development (646)
Adaptive	Response (including an effect on phenotype) to a challenge which confers benefit in terms of Darwinian fitness
Assimilation (genetic)	Process by which environmentally induced phenotype may become genetically fixed and no longer requires the original environmental stimulus for its induction (proposed by Waddington, but see Ref. 468)
Canalization	Processes constraining effect of changes in genotype (or theoretically small genetic variations) on developing phenotype (as per Waddington's epigenetic landscape)
Conditioning	A form of "learning" in which a given stimulus becomes increasingly effective in evoking a response or the response occurs more reliably in a prespecified and stable environment
Disruptive	Interference with the normal path of phenotypic development. Environmentally induced severe disruption is equivalent to teratogenesis; less severe challenges outside the normal range may induce an immediately adaptive response with longer term consequences
Distal	Referring to mechanisms which lead to a condition over a long time period, e.g., related to evolutionary history
Epigenetic	Molecular mechanisms affecting gene expression patterns without alterations in DNA base sequence
Epistasis	An interaction between nonallelic genes, especially when one gene suppresses the expression of another
Evo-devo	The field of science concerned with the interaction between evolutionary and developmental processes
Fitness (Darwinian)	The ability to survive and reproduce; not synonymous with physical "fitness"
Immediately adaptive response (IAR)	Developmental (phenotypic) response to a moderately severe challenge, usually outside the normal range, which promotes immediate survival but may incur longer term disadvantage
Induction	Process by which aspects of the developmental environment (including that provided by the mother) alter the trajectory of phenotypic development of the offspring
Mismatch	Difference in the level of an environmental factor which may affect fitness between that predicted on the basis of developmental cues and that extant later; most commonly applies to nutrition. Developmental mismatch can occur as a result of inappropriate developmental cues or a change in environment between plastic and later phases of life, or both; evolutionary mismatch can occur if there is a difference between the extant environment and that for which the fitness of the species had evolved to be best adapted
Nonadaptive	Response (including an effect on phenotype) to a challenge which does not confer benefit in terms of Darwinian fitness
Parental effect	Processes by which phenotypic attributes of the mother (and, less commonly, the father) influence the development of the offspring. They may confer a fitness advantage, although there is debate over whether it is in the interests of the mother or offspring (conflict theory)
Pathological	Functional changes associated with or resulting from disease or injury; or processes resulting in disease
Physiological	Functional processes in the healthy body
Plasticity (not same as flexibility, low resilience)	At the simplest, the ability of one genotype to produce more than one phenotype. Implies morphing from one form to another, here through development, and should be distinguished from resilience (the ability to withstand challenges with no effect) and flexibility (the ability to "bend" in the face of a challenge, to return to the previous state after the challenge) (see Ref. 377)
Predictive adaptive response (PAR)	Effect of aspects of the developmental environment to induce a phenotype which confers fitness advantage in this environment. Hence, use of developmental cues to predict or forecast later environment. Prediction need not be symmetrical in relation to environment, or theoretically accurate in more than 50% of instances, to have been retained during evolutionary selection (see Ref. 220)
Priming	Process by which exposure to an aspect of the developmental environment induces a phenotype which responds appropriately to a similar environmental challenge later
Programming	Term loosely used to refer to relation between early life and later risk of disease, as per developmental origins of health and disease (DOHaD). Disadvantages of the term are that it implies a predetermined ballistic course of development and later function rather than plasticity, and that it echoes the genetic program of development (285) of which it is the opposite
Proximate	Referring to mechanisms which lead directly to condition, usually operating in recent past
Reaction norm	The range of phenotypes produced from a single genotype in particular environment (654)
Robustness	The ability of a phenotype to resist change without changing its initial stable configuration
Teratogenic	Effect of an abnormal aspect of the environment to induce pathophysiological changes in offspring; usually involves exposure to pathogens, chemicals, radiation, and so on
Transgenerational	Effects induced in one generation passed to subsequent generations; strictly, to exclude effects mediated via germ cells in grandmother being manifest as phenotype in grandoffspring, transgenerational effects should be manifest in great grandoffspring
Ultimate	Referring to mechanisms which lead indirectly to condition, usually operating in distant past, e.g., resulting from evolutionary processes

specifically that of maternal or parental effects (TABLE 1) (382a, 417, 599).

While the concept of "parental effects" is widely accepted for lower animals and some plant species, a wide range of animal models have confirmed that such processes also occur in mammals, and this has allowed exploration of the underlying physiological mechanisms (for reviews, see Refs. 48, 264, 338, 399). Parental effects are generally considered to operate within the normative range of environments for a species and when the effect on the next generation may well have adaptive value (176). Some influences in one generation may however have nonadaptive (TABLE 1) effects on the next, and this is more likely in mammals where exposure of the pregnant mother to an environmental agent may have teratogenic effects on her developing offspring. This distinction between potentially adaptive parental effects, which are common across taxa including mammals, and the clearly nonadaptive consequences of developmentally disruptive conditions, which are primarily a feature of mammals, is important but is often not considered in interpreting the experimental and comparative literature. In focusing on this dimension, the present review both builds on previous reviews that have described the mechanistic insights arising from animal studies, generally with specific reference to the development of obesity, insulin resistance, and cardiovascular disease (223, 369, 398) but also develops concepts related to ultimate causation which emerge from evolutionary considerations and which may be more widely applicable. We do not rehearse in detail the physiological processes discussed in earlier reviews, but focus on recent advances in the elucidation of underlying developmental mechanisms, particularly epigenetic (TABLE 1) processes. This integration of different fields shifts the focus of our understanding of the processes underlying DOHaD away from pathophysiology and towards physiology, and provides the rationale for a greater focus on life-course perspectives in relation to the prevention of NCDs.

NCDs, in particular diabetes, cardiovascular disease, chronic lung disease, and some forms of cancer, account for ~63% of all deaths globally (9, 659). Eighty percent of these NCD-related deaths occur in low and middle income countries (LMICs), particularly as such countries undergo socioeconomic transition following reductions in the prevalence of communicable diseases. The greatest burden of these diseases is currently in Asia, but in the near future, the prevalence will rise in sub-Saharan Africa and parts of Central and South America. The risks of NCDs are exacerbated by Western lifestyle, urbanization, migration, and factors associated with greater economic prosperity such as nutritional changes and sedentary lifestyle, all of which produce a "mismatch" (TABLE 1) between human evolved biology and our contemporary habitat (205, 212). In addition, demographic changes leading to increased longevity and smaller family size are shifting the age distribution of many populations upwards (e.g., Refs. 53, 524), increasing the relative burden of such chronic diseases further. These issues are central to the consideration of public health policies in the post-2015 era (600), which will need to build on the continued efforts aimed at meeting the Millennium Development Goals (662).

The potential economic costs of NCDs are predicted to be greater than those of communicable diseases, perhaps equivalent to those of climate change, and approaching those of a global fiscal meltdown (657). The rising global challenge of NCDs prompted the special high level meeting of the United Nations General Assembly in September 2011, at which the importance of developmental processes was recognized, since ". . .maternal and child health is inextricably linked with NCDs and their risk factors. . ." (clause 26) (601). This statement represented a substantial change in public policy focus from the earlier WHO Global status report on NCDs (659) reflecting the impact of rapid progress in addressing a number of the conceptual and scientific issues discussed below.

One of the most important risk factors for NCDs is obesity or overweight, and the problem of the rising burden of NCDs is often conflated with that of obesity via such neologisms as "globesity" (658) or "diabesity" (146). It is however important to recognize that there are marked population differences in the relationship between body mass index (BMI) and the risk of developing NCDs such as type 2 diabetes mellitus (T2D): people of South Asian ancestry have about three times the risk, and those of Chinese ancestry about twice the risk, of developing T2D at a high BMI compared with people of Caucasian ancestry (94). These differences in risk can be seen even at lower BMI.

The currently dominant scientific and public health model for NCDs assumes that they are a consequence of genetic predisposition, coupled with adult lifestyle choices that are largely under voluntary control. However, attempts to reduce the burden of NCDs by promoting weight loss and changing adult lifestyles have been relatively unsuccessful at a public health level. Beyond cultural, behavioral, and public policy issues, there are physiological reasons why maintenance of weight loss is difficult. For example, neuroendocrine drivers to sustain hunger and promote food intake persist following enforced weight loss (573). While attempts to promote a less obesogenic environment must not be discouraged, it is illogical to ignore the importance of underlying physiological processes.

If the processes producing propensity to obesity and insulin resistance are established early in life, then interventions in adults are likely to come too late to be very effective (209). Indeed, as Taubes (584) has pointed out, the physiological basis for obesity, in terms of the physiological control of metabolism, appetite, etc., has been overlooked in recent years in favor of a simple energy balance concept: viz. that

obesity arises from excessive caloric intake in relation to daily energy expenditure. Again, this is too simple a view.

The DOHaD concept emerged over the last two decades, although there were many historical precedents for it which were overlooked, partly through declining interest in integrative, and especially developmental, physiology during the latter part of the 20th century as molecular biology became dominant (204, 206). There are a range of historical reasons for the slow acceptance of the concept (see **TABLE 2**) and, as they form themes which run through this review, we note them at the outset.

The first issue was a lack of a conceptual framework. The NCDs which first drew the attention of researchers in the field were coronary heart disease, hypertension, and T2D. The dominant paradigm was that these diseases, which develop gradually over many years in adult life, were the result of lifestyle choices which led to cumulative damage to, for example, the blood vessels, as a result of repeated exposure to high levels of glucose, cholesterol, or low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio, nicotine, and carbon monoxide (CO) from tobacco smoke, etc. This model assumed that all individuals start life with the same risk, but diverge only according to their later lifestyle. The physiological basis for individual or population-based differences in susceptibility to lifestyle challenges was little addressed. It was however appreciated that the risk of such disease had a heritable component in the broadest sense, at least in terms of ethnicity or family history of disease (577) but that a substantial part of this was explicable simply as shared environmental risk. There is limited animal data to support this concept, although it has been shown that genetically distinct strains of rodents show different susceptibility to features of the metabolic syndrome induced by maternal dietary restriction in pregnancy (321).

Table 2. *Historical reasons for a delay in accepting the DOHaD concept*

Historical Reasons
Lack of a conceptual framework
Confusion between factors correlated with disease risk and those involved in causation
Assumption of operation of a single pathway
Undue focus on low birth weight
Lack of plausible underlying biological mechanisms
Failure to recognize its importance under normal rather than only under extreme conditions
Lack of evidence of its relative importance in relation to other risk factors
Lack of plausible ways to use the concept clinically and in public health

DOHaD, developmental origins of health and disease.

The rise of human genomics was associated with a widely held conviction that such variation in risk was explicable in terms of genetic predisposition, specifically small mutations producing single nucleotide polymorphisms (SNPs), gene copy number variation, or other fixed genomic variation. Whilst some SNPs associated with risk of NCDs have been found, those associated with large effects in individuals are uncommon in the population as a whole; the search for more common variants with smaller effects continues in larger cohorts and via wider screening across the exome. The "missing heritability" of chronic disease is still widely viewed as mysterious (376), but it is now recognized that the early optimism about finding the genetic basis for chronic disease was misplaced (303). Moreover, SNPs such as those in the FTO gene known to predispose to adiposity show either no (409) or a complex relation with BMI in childhood (559), so they do not easily account for the life-course pattern of risk. As simply summarized by Watson (635), the contributions of inherited alleles, diet, and levels of exercise are hard to determine even in common diseases.

As workers in the DOHaD field moved in the last decade from the study of simple associations between early life events and subsequent pathology to investigation of underlying mechanisms, new concepts that are central to this review emerged. The processes we appreciate to underlie DOHaD are now seen to operate at the interface between genetic and developmental environmental influences, largely through the resurgence of interest in epigenetic processes which provide a proximate **(TABLE 1)** explanation. Even so it required an evo-devo perspective to put this in context (30, 32, 214, 220, 221) and to place the empirical observations within a coherent framework. We explore this further in sections III*C* and VI*A*.

The second reason for the slow acceptance of the DOHaD concept was that the epidemiological observations of an association between early life attributes, in particular birthweight, and later chronic disease (23, 27) (see below for full discussion), led to the erroneous assumption that such disease processes were initiated during development, when in fact epidemiological observations of this nature can only show correlation, not causation. The intense attention given to consideration of how low birth weight might lead to disease (23) was thus misplaced; indeed, it led to consideration of low birth weight as necessarily lying on the causal pathway. The relatively low incidence of low birth weight in many populations showing high prevalence of NCDs is evidence that, if it exists, the role of such a putative pathway is relatively minor.

The epidemiological observations indicated not only that NCD risk in later life was affected by development, but also that this risk was graded across the entire range of early developmental experiences, even when captured by the relatively crude proxy of birthweight or weight at 1 yr of age. Of key importance, but generally overlooked, was the find-

ing that this included infants whose birth size was unequivocally within the normal range. Recent studies confirm the graded nature of the phenomenon, and for a wider set of processes such as neurocognitive development (623). Other studies have clearly shown that the long-term effects associated with more subtle changes in the fetal environment such as variation in maternal nutrition can be independent of birthweight (185, 229).

As research into what was termed until 2003 the "fetal origins of adult disease" proceeded, competing theories arose about the pathways involved (197). While this led to new insights into developmental effects on tissues, organs, and systems, the concept that such effects form part of an integrated physiological response of the organism to developmental signals was not much discussed. For example, a "mismatch" experiment in which pregnant rats were fed a restricted diet and their offspring fed a high-fat diet was shown to affect central nervous components such as appetite control and voluntary exercise capacity as well as peripheral components including body composition, liver metabolism, and cardiovascular function (611, 612). In addition, there is striking consistency in the adult phenotype, involving multiple physiological systems, in a variety of animal models where the prenatal or early postnatal environment was altered by a range of nutritional or hormonal manipulations (397).

The widespread adoption of the term *programming* did not help to gain acceptance of DOHaD, because its deterministic implications of "programming of disease" or "programming of function along a pathway" are reminiscent of the genetic program for development (285). This slowed acceptance of the importance of the normative, holistic nature of developmental plasticity and its role in affecting sensitivity to later environments (204). As the essence of the DOHaD concept lies in the induction **(TABLE 1)** of phenotypic changes, usually within the normal physiological range, which permit altered responses to later challenges, usually also within the normal physiological range, we prefer the use of terms such as "priming" **(TABLE 1)** (68), "induction" (29), or "conditioning": the echo in the latter of the concept of conditioned reflexes (96) or of conditional growth based on predicted later nutritional or other conditions is not unhelpful in this respect.

From the time of early exposition of the "fetal origins of adult disease" concept, the lack of plausible biological mechanisms limited acceptance of the idea (125). The long latency of the effect, from prenatal life to presentation of adult disease over possibly more than 60 years, was challenging from a mechanistic point of view. In many ways, it was not until the advent of developmental epigenetics (see sect. III*E*) that this particular challenge was addressed (219). Even so, this has until very recently limited the application of DOHaD concepts within clinical medicine and public health and led to misinterpretation of the underlying conceptual model: we will return to this point in section VI, *D* and *E*.

In this review, we first discuss the current state of knowledge on the epidemiological and clinical physiological observations that form the basis of DOHaD. Second, to review new understanding of how developmental physiological processes can predispose to the pathophysiology of NCDs, as opposed to inducing pathology in early life as implied by earlier theories, we will consider DOHaD processes from a lifecourse perspective **(FIGURE 1)**. Linked to this is the issue of the ultimate versus the proximate causation of such effects, and this is considered in the context of evolutionary and developmental biology. Based on this, we go on to distinguish between developmental effects that are potentially adaptive (i.e., physiological; sect. IV) versus those that are nonadaptive (pathophysiological; sect. V). We use a strict evolutionary definition of "adaptive"; adaptive attributes are the result of processes that have been selected during evolution since they confer an advantage in terms of survival to reproduce for the individual, more strictly therefore of Darwinian fitness **(TABLE 1)** The adaptationist argument can limit understanding if it becomes merely teleological (319): we aim to avoid this, but do not discuss its limitations in detail here (for more extensive discussion, see Refs. 217, 220).

Adaptive effects of relevance to DOHaD involve the physiological processes of developmental plasticity and broadly include the categories of immediately adaptive and predictive or anticipatory adaptive responses **(TABLE 1)**. They can lead to greater risks of lifestyle-associated disease through the occurrence of "developmental mismatch" later in the lifecourse **(FIGURE 2)**. Nonadaptive processes often involve an element of evolutionary novelty, either because of the nature of the challenge or because it operates at a level which in humans exceeds the experience of the hominin lineage during its evolutionary history; in both instances, defenses have not evolved to meet the challenge completely. Nonadaptive processes can therefore lead to an increased NCD risk even without later mismatch. Examples that we discuss include those associated with maternal obesity, gestational diabetes, Caesarean delivery, infant overfeeding, and exposure to toxins, pollutants, or tobacco smoke. Finally, we discuss the implications of this broader understanding of the role of development and the opportunities which it offers for preventing NCDs and promoting public health (see sect. VI, *D* and *E*).

II. EPIDEMIOLOGICAL AND CLINICAL PHYSIOLOGICAL EVIDENCE FOR DOHaD

A. Conditioning by a "Poor Start to Life"

We cannot date when the concept that early life influences produce long-term effects on health and disease was first appreciated, but the idea is referred to in the writings of the

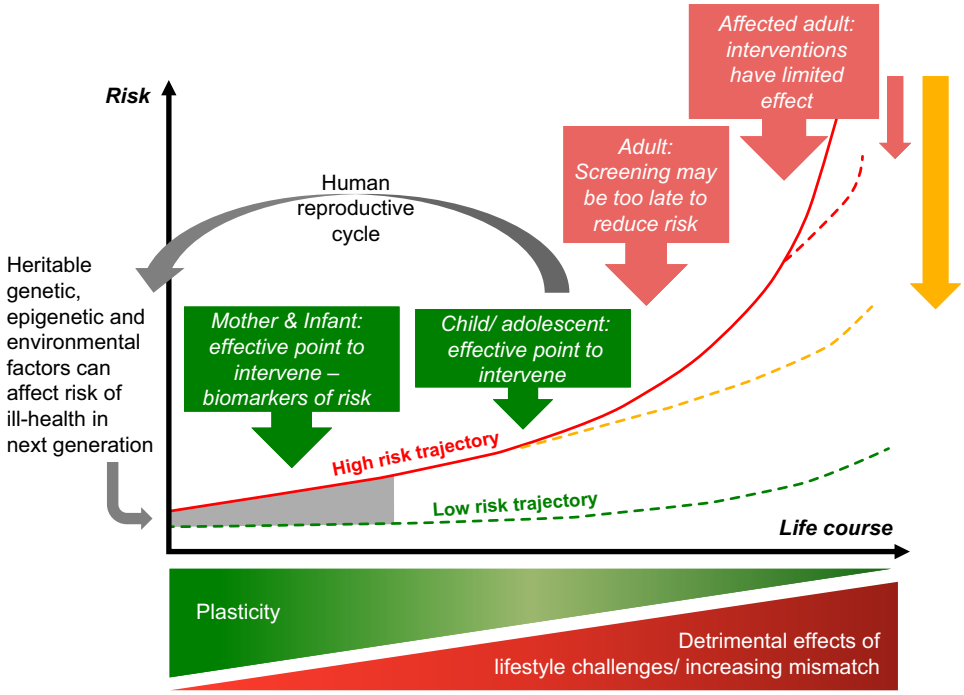

FIGURE 1. Lifecourse view of noncommunicable disease (NCD) risk. Risk increases in a nonlinear way as a result of declining plasticity and accumulative damage from lifestyle-imposed or other challenges. The effect of mismatch between developmentally and evolutionarily influenced phenotype and adult environment also increases through the lifecourse. Interventions in adults, especially those at high risk, can be beneficial, but only to a degree. Screening in middle-aged adults may also be too late to reduce risk substantially. Interventions in adolescents and young adults are likely to be more effective and, importantly, can reduce the risk of NCDs in the next generation. The prenatal period establishes risk through interaction between genetic, epigenetic, and environmental factors. [Based on the author's graph prepared for the World Health Organization (660).]

ancients (e.g., Hippocrates). More recently, Freud (183) noted the importance of early life in his theories of psychosexual development and was aware that even aspects of fetal behavior might set the scene for later mental conditions. Critically, a link between poor living conditions in childhood and later premature mortality was made in 1934 by Kermack et al. (311), and this idea was extended by Forsdahl (171) who reported that a poor childhood environment was associated with adult cardiovascular disease, even when the adult environment was not poor, thus focusing attention on development itself as the initiating period. Dörner and his group (see Refs. 143, 473 for review) studied a range of developmental effects, in particular hormonal influences on sexual behavior, which became controversially applied to issues such as homosexuality, but his work also extended to developmental effects on later obesity, atherosclerosis, and diabetes. Dörner was the first to use the term *programming* ("*programmierung*") to describe these effects (323), a term adopted later by Lucas (370), Barker (22), and many others **(TABLE 1)** (398). Metaphors, while frequently used in biology, can be problematic if they restrict the challenging of preconceptions (32, 177, 416). The metaphor of "programming" implies that the complete instructions to carry out a task, e.g., a developmental strategy, are defined from the outset: this accords more with a computer program than the processes of developmental plasticity. In addition, once running, a program either continues to completion or crashes. This ballistic model, in which development proceeds to a preset destination, is too deterministic to describe the observations accurately. As will be discussed, the effects of different developmental trajectories induced by environmental cues can change the magnitude (222, 611) and, indeed, sometimes the direction (222) of a response to a later environment.

Freinkel (182) introduced the term *fuel-mediated teratogenesis* to describe how prenatal nutrition might produce effects on subsequent development. While this provided an important insight by indicating how nutrition might cue alterations in the development of metabolic homeostasis, as will be discussed in section III*A*, the long-term effects of nutritional exposures within the ecologically normal range during development cannot be viewed as teratogenic, i.e., disruptive to the developmental trajectory. Such terms are not viewed as helpful today.

Experimental studies by van Assche and colleagues in the 1970s (4, 130) first highlighted the long-term consequences for metabolic control in rats which had experienced developmental challenges (264), but there was a delay of more than a decade before the broader importance of this work was appreciated.

The most influential early epidemiological observations in the DOHaD field concerned the cardiovascular system. In 1980, Higgins et al. (260) reported an association between pregnancy complications such as preeclampsia and the blood pressure of the offspring as they grew through adolescence: this effect was only seen in the index pregnancy, it became more exaggerated as the offspring aged, and it persisted after correction for mother's blood pressure. Higgins et al. (260) concluded that prenatal environmental, rather than genetic, effects were therefore involved and suggested that future research should involve the prospective study of

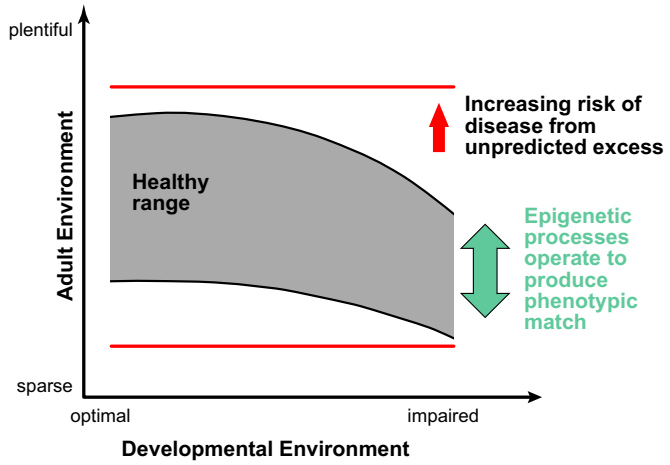

FIGURE 2. The mismatch concept of NCD risk in relation to the nutritional/energy balance in the environment. Humans have evolved to remain healthy over a wide range of adult environments, at least in terms of survival to reproductive age (Darwinian fitness). The level of the environment for health is lower and its range is less following development in an impaired environment, for example, with low or unbalanced nutrient provision. If the adult environment is richer, the risk of NCDs is correspondingly increased. Epigenetic processes are involved in these developmental effects. Note that predictive adaptive responses that confer fitness advantage need operate only for a match between developmental environment and environment up to the time of reproduction. Any further mismatch, for example, as adult lifestyle becomes less healthy, adds to the risk of NCDs in ways against which the developed phenotype may confer little protection. [From Gluckman and Hanson (214), with permission from AAAS.]

women and their children. Interestingly, the effect was more apparent in male children, and sex differences are now commonly seen in both experimental and clinical studies of DOHaD (see sect. IV*B*). This prescient study, which received little recognition, thus predates much later work in the DOHaD field. Wadsworth et al. (621) subsequently reported an inverse association between birth weight, parental social status, and systolic blood pressure in young men and women, and an inverse association between size at birth and later diastolic blood pressure was reported for males by Gennser et al. (192). The effects may appear small, but elevations of blood pressure are known to track from childhood into adulthood and to predict hypertension (20).

The greatest impetus to the emergence of the DOHaD concept came from the series of epidemiological studies by Barker[1] and colleagues from 1986 onwards (25–27, 452) in which links were established between low birthweight, weight at 1 yr of age, and higher prevalence of hypertension, coronary heart disease, stroke, and metabolic syndrome in adulthood. Studies which followed confirmed the association between low birthweight and a range of cardiovascular disease markers or mortality (173, 350, 385, 500, 546). Barker's studies arose from the observations that people born in areas of high perinatal mortality, where poverty, poor diet, overcrowding, and infection led to poor development and early growth, had increased risk of death from coronary heart disease as adults and that, as in Forsdahl's observations, the effect persisted even in those who subsequently moved to more affluent areas. These observations challenged the widely-held belief that conditions such as coronary heart disease are solely the result of affluence although, as discussed below, affluence in adult life may contribute to greater risk of disease through "mismatch."

The relative importance of the developmental component reported by Barker and colleagues was challenged, for example, in a meta-analysis of available data on the relation between birth weight and adult blood pressure (275). This was countered by studies showing that the link is stronger when the outcome is clinical disease rather than a risk factor such as blood pressure (114, 115). Much of this confusion related to the emphasis on birth weight, largely because this was the only proxy available to assess prenatal development. In addition, the older cohorts, such as those which Barker studied initially, came from an era when maternal obesity, gestational diabetes, and fetal macrosomia were uncommon so the low birth weight relationship seemed clear. Similarly, survival following extreme preterm delivery or growth restriction was poor, so conflicting effects at this end of the spectrum from a range of causes were also removed. As younger cohorts were added, the picture became more complex because maternal obesity and gestational diabetes became important influences on NCD risk in the offspring, but these are associated with higher birthweight. As will be discussed in section V, these effects probably involve different mechanisms and have different ultimate explanations.

This early epidemiological work was given support by studies of the consequences of historical events such as war, albeit that they maintained the focus on extreme changes in the developmental environment rather than on more ecologically normal situations. These studies are not always easy to interpret as wartime conditions produce changes not only in nutrition but also in many other factors. Additionally, the timing of the developmental exposure is likely to be important. During the Dutch Hunger Winter of 1944–1945, food supply to the Western part of the Netherlands was cut dramatically (with reported daily intake falling to 400–800 calories). Individuals who were in utero, at least in the later parts of pregnancy during this famine, had a low birth weight and a decreased glucose tolerance at the age of 50 compared with individuals born the year before or after the famine (489). Subsequent studies of this population are inconsistent in relation to whether fetal exposure to famine was associated with elevated blood pressure in adulthood (131, 507, 565). In a study of adults born before, during, or

[1]Since writing this review, sadly David Barker died in August 2013. The authors wish to emphasize the enormous contribution that he made to this field and hope that this review will serve as a tribute to his pioneering work.

after the civil war in Nigeria (1967–1970), an increased risk of hypertension was reported in those exposed to war-time famine during fetal and early postnatal life (273). In contrast, there was no significant difference in blood pressure between adults who were exposed in utero to malnutrition during the siege of Leningrad in World War II versus those who were born at the same time but outside the area under siege (563). A further example is provided by the Great Famine from 1959–1961 in China, where one study showed an association between hypertension following exposure to famine during fetal development (361), whereas another study did not (270). More recently, Wang et al. (628) reported that the risk of hypertension was 1.36-fold higher in those exposed to this famine during only the first trimester of pregnancy. The risks were 1.83- and 1.31-fold higher in those exposed only during infancy and in those exposed during both fetal development and infancy, respectively. One of the problems with such studies is the assumption that the inducing cues are those of malnutrition, when clearly the population was exposed to considerable stress and often had substantial changes in the constitution of their diet as well as its quantity; for example, the Dutch Hunger Winter diet included unusual items such as tulip bulbs which may have contained toxins. A further distinction between these famines is that, whereas the Dutch famine was acutely imposed on a previously well-nourished population and then rapidly relieved, this was not the case in the other recent historical famines, which emerged gradually and took many months to be resolved.

Notwithstanding the debates about the relative roles of early life (as measured by birthweight) and adult lifestyle in the etiology of NCDs, and the rapid increase in the prevalence of NCDs in many populations, the heritable risk of NCDs has continued to be viewed as largely genetic. Substantial differences between populations in the relation between measures such as waist-hip ratio or BMI and prevalence of diabetes are well-known (e.g., Refs. 94, 395). Such variations have been assumed to be due to fixed genetic differences. The original conceptualization of this was Neel's (421) proposition of "thrifty genes," derived from his studies of the Pima native American people living in the states of New Mexico and Arizona, who have a very high incidence of glucose intolerance and T2D even in early adulthood. Until the mid 20th century their lifestyle involved subsistence farming in a harsh environment, so Neel (421) proposed that genes associated with metabolic "thrift," in particular for insulin resistance, had undergone positive selection during presumed historical periods of famine. Confronted with the more abundant and high glycemic index diet of the contemporary United States, such alleles would confer greater risk of glucose intolerance and diabetes. Neel's concept was widely accepted, although more recently it has been subject to considerable critique (e.g., Ref. 333). As will be discussed below, fixed genetic variation which depends on ancestry is not the sole explanation for transgenerational **(TABLE 1)** heritable influences on risk of disease, and there is increasing interest in the potential for both direct and indirect epigenetic inheritance as mediators of such influences.

More widespread acceptance of the DOHaD concept occurred following the plethora of studies which replicated the association between birth size and adult disease, for ischemic heart disease (325), stroke (500), insulin resistance and T2D (425, 504). The adult phenotype associated with lower birthweight includes central adiposity and low skeletal muscle mass (310) reminiscent of the thin/fat neonate found in India, a country with a high prevalence of both low birthweight and T2D (666), and there is now substantial evidence for DOHaD from many populations (223). In addition, very large cohorts have been used to replicate the concept (46, 188, 304, 325, 344, 500, 608). Lastly, whilst most epidemiological studies in the DOHaD field have concerned the metabolic syndrome, or its components of cardiovascular disease or diabetes, and have relied on birth weight or infant size as a proxy index of the developmental exposure, there have been associations found for low birthweight and reduced adult bone density (251), schizophrenia (427), and asthma and atopic conditions (564). Some of these observations, for example, for schizophrenia, have also been linked to the studies of famine (562, 575). There are also however associations between high birthweight and some forms of breast cancer (403).

As we have intimated above, the focus on low birth weight distorted understanding of the underlying phenomena, and it has only been more recently that attention has shifted from extremes of birth weight to considerations of how and why conditioning can operate across all pregnancies and with birth weights across the normal range. While the epidemiological studies of Barker and colleagues (23, 25, 26) showed clear long-term effects on disease risk associated with birthweights within the normal range, the implications of this have often been ignored. In considering the effects of the fetal environment for babies with birth size within the normal range, the processes of maternal constraint, which operates in all pregnancies, are relevant (217, 218, 245). Maternal constraint involves a set of uteroplacental mechanisms by which fetal growth is restricted from reaching its genetic potential, necessary to permit successful passage through the pelvic canal at delivery. Maternal constraint is greater in mothers of short stature, in adolescents, and in primigravida, as the pelvic canal is smaller in such pregnancies (215, 607). Two recent studies have now shown that, in terms of perinatal survival, optimal birthweight is considerably higher than the mean birthweight for the population (180, 607). Mechanistically, even some appropriately grown fetuses show signs from Doppler ultrasonography of being challenged (410), although whether this is the consequence of maternal constraint is not known.

Thus in recent years a shift has been made from the study of the long-term effects of extremes in birthweight to that of cohorts of apparently normal pregnancies. For such studies, accurate measures of gestational age are necessary, as both growth and length of gestation can be influenced by environmental factors that can make the most widely used methods of ultrasound dating inaccurate (295). Effects of maternal diet and body composition within the normal range of fetal growth have been shown on liver blood flow, ductus venosus shunting, and fat deposition in the fetus (313). There are additional effects on hepatic (151), celiac, and splenic (149) arterial hemodynamics and on the portal venous (150) and the intrahepatic circulation (312). There are a few studies (e.g., Ref. 227) on the postnatal sequelae of these fetal patterns of development, but more are needed. Mechanistic studies, for example, those of alterations in vasculogenesis in low birthweight infants (364), need to be extended to cover the normal range.

B. Conditioning by Overnutrition

It has only relatively recently been realized that the DOHaD concept also operates in the context of a prenatally or neonatally excessive or rich nutritional environment (13, 481, 638). Early evidence of this comes from the 1946 United Kingdom birth cohort (247), from the Pima native American population (465) and from the meta-analysis of the Nordic cohorts (188) which show a U-shaped relation between birth weight and blood pressure **(FIGURE 3)**. More recently, both maternal obesity and gestational diabetes mellitus (GDM) have been implicated in leading to a later risk of obesity and cardiometabolic disease risk in the offspring (343, 498). There are also reported associations between excessive weight gain in pregnancy and offspring blood pressure and adiposity (181, 191, 379).

A range of epidemiological studies have shown effects of maternal prepregnancy BMI on offspring's blood pressure or autonomic function (156, 169, 446, 645). Maternal obesity is associated with increased risk of pregnancy complications including hypertension, preeclampsia, and GDM, and a child of an obese mother is also more likely to become obese (85, 649) and to develop asthma and atopic disorders such as dermatitis (248, 349, 470). Offspring's adiposity at age 4 is related to mother's BMI across the entire range from very thin (BMI <18.5) to obese (BMI >40) (649). While the data are less robust, there is the suggestion that infant feeding with formula

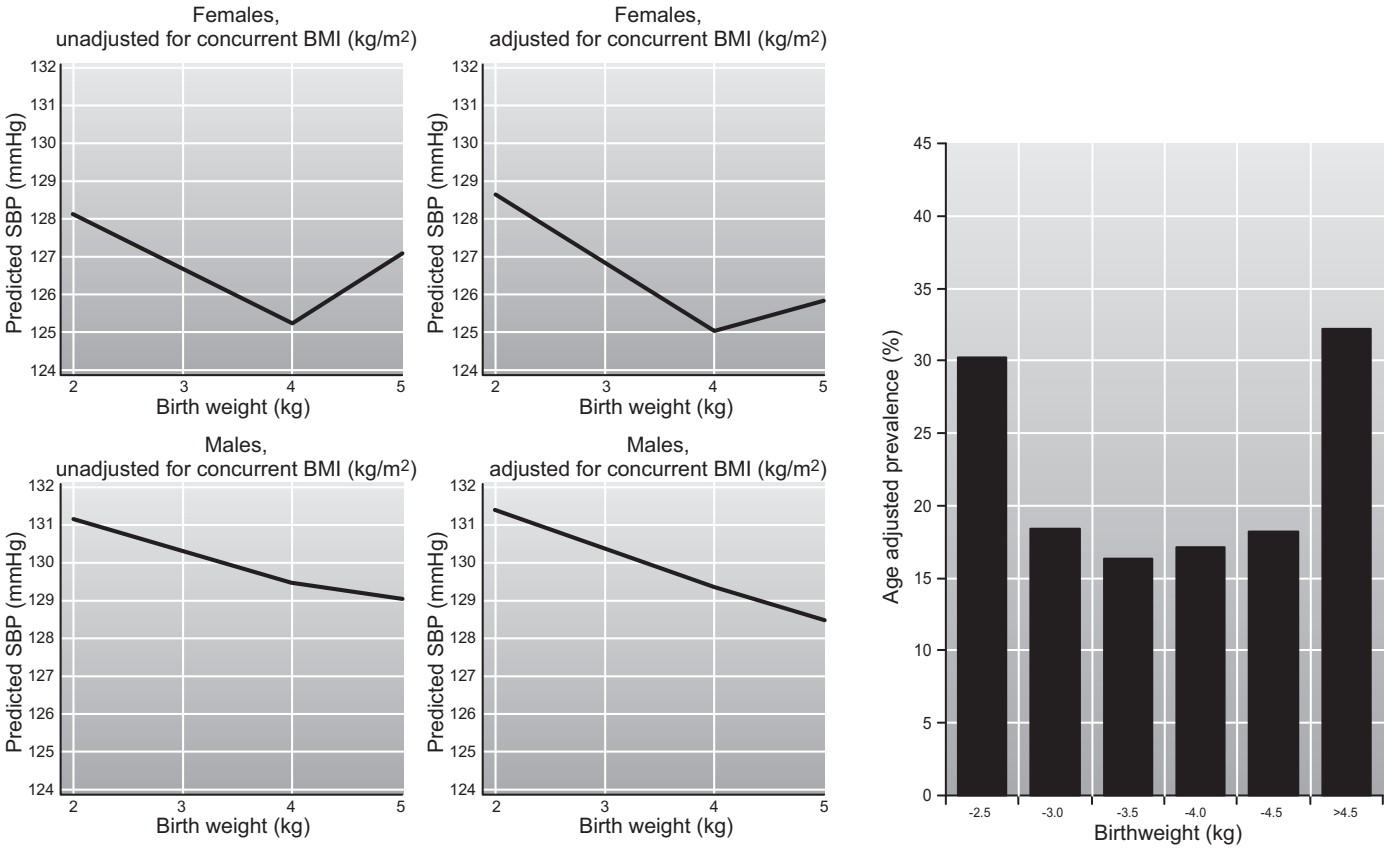

FIGURE 3. *Left*: predicted systolic blood pressure (SBP) as a function of birth weight in 20 Nordic studies, obtained using pooled estimates from spline regressions with a knot point at a birth weight of 4 kg. [From Gamborg et al. (188), by permission of Oxford University Press.] *Right*: prevalence of type 2 diabetes in 1179 Pima Indians aged 20–39 yr in relation to birthweight. [From McCance DR, Pettitt DJ, Hanson RL, Jacobsson LTH, Knowler WC, Bennett PH. BMJ 308: 2000. Reprinted with permission from BMJ Publishing Group, Ltd.]

(which tends to be more calorie-dense and for which intake can be more directly driven by parental behavior than by infant demand) rather than human breast milk also conveys a greater risk of later obesity (12, 568, 616).

An increasing concern is the transmission of risk of diabetes across generations. An increasing number of women develop T2D during their reproductive years (168, 493) and children of type 1 or 2 diabetic mothers are more likely to become obese and to develop diabetes (479, 541). The effect on the offspring is related to intrauterine exposure to hyperglycemia because, among siblings, the risk of diabetes is greater in those born after the mother developed diabetes (116). In turn, the incidence of GDM is rising rapidly in many countries, particularly in Asia (168, 374), and the offspring of gestational diabetics have been shown to have both a greater risk of developing obesity (540) and insulin resistance. While the focus here has been on the clinical condition, again the data show evidence of effects occurring across a range, as even offspring exposed to mild hyperglycemia during pregnancy have increased lean and fat mass and greater risk of diabetes (246, 578). The problem of "diabetes begetting diabetes" is thus of major concern (374, 667).

III. HOW ORGANISMS RESPOND TO THE DEVELOPMENTAL ENVIRONMENT

A. What Is "Normal" Development: Disruption Versus Plasticity

The term *plasticity* **(TABLE 1)** has different connotations in different contexts. We favor Malabou's (377) distinction between plasticity, which involves a change in phenotype from one condition to another, versus resilience in which the phenotype does not change in the face of a certain range of challenges, and flexibility in which a challenge produces some change but a return to the original state when the challenge is removed. The concept of developmental plasticity is based on the understanding that the phenotype and genotype do not have a fixed relationship and that the phenotypic attributes of individuals are affected by developmental processes (32, 646). Such differences exist even between monozygotic twins (560) and in asexually reproducing species isogenic clones can show environmentally induced variation, for example, in crayfish genetically identical individuals show variation in body markings, growth, and reproduction (614). Such developmentally induced phenotypic variations are normative, and the adaptive advantage of the conservation across evolution of the processes of developmental plasticity has been discussed extensively (499, 671). While there may be some stochastic elements, particularly within species with very high reproductive rates such as asexually reproducing bacteria (40), in the context of more slowly reproducing mammalian species such as the human the emphasis needs to be on the relationship between environmental influences and the consequential phenotypic change which, as will be discussed below, has directional components of potential adaptive value. Indeed, the importance of including the life history strategy of the species in considerations of developmental plasticity cannot be overemphasized (382a). The nature of developmental responses to environmental cues is greatly influenced by the reproductive strategy of the species (382a) and, in particular, on the effects on parent or offspring fitness. With this in mind, in the following discussion we focus only on responses relevant to the human.

While environmentally induced developmental plasticity is an evolved and normative process, many external environmental influences can be said also to "disrupt" development (30, 193, 221). Such use of the word *disrupt* is appropriate when the agent produces a somatic mutation with phenotypic consequences, or leads to a toxic effect that disrupts the normal pattern of development. Many teratogens are known: most are evolutionarily novel substances such as thalidomide or synthetic steroids, others are infective agents such as rubella, and still other disruptions involve gross deficiencies of micronutrients such as folate or gross excesses such as of vitamin A. For each of these examples we can assume that they were sufficiently uncommon in the evolutionary past for the hominin lineage not to have evolved effective defenses against the developmental disruption they can cause. Likewise, the loss of the ability to synthesize vitamin C in primates is not associated with detrimental antioxidant effects when the micronutrient is plentiful in the diet (44). It can however be argued that phenotypic accommodation **(TABLE 1)**, i.e., phenotypic responses to the disruption, can allow survival and thus have some adaptive **(TABLE 1)** potential (32).

The distinction between developmental plasticity and developmental disruption is not just semantic (207). It has important conceptual and mechanistic implications, viz. that plasticity is an evolved response aimed at enhancing fitness, while disruption is a passive response that in general impairs fitness. However, some cues can exert either a plastic or a disruptive influence depending on their magnitude (30) in a dose-dependent manner. For example, mild hyperglycemia in utero changes the rate of growth and has adaptive potential (see below), but more severe hyperglycemia can disrupt cardiac development leading to congenital heart anomalies (510), and derangement of maternal lipid profile can also lead to increased risk of congenital heart disease (552).

B. Development in Individuals and Populations: Inheritance and Heritability

In moving from consideration of individuals to populations, the concept of variation in phenotype becomes important, because this is one of the necessary prerequisites

for Darwinian (both natural and sexual) selection. It was soon realized that the variation in most characteristics does not follow Mendelian rules of inheritance (see Provine 1971 referred to in Ref. 468), so the underlying processes must be more complicated than simply random allocation of genetically determined characteristics. Selection operates on the phenotype, not the genotype, but it is the latter that changes through evolution. The range of phenotypes which a particular genotype can produce in a particular environment is termed the "reaction norm" **(TABLE 1)** (654).

It is important to remember that inheritance is a much broader concept than genetic inheritance. The traditional breeder's equation of population genetics assumes independent genetic and environmental factors (39), and measures of heritability attempt to describe how much variation in a particular trait in a population is accounted for by genetic variation. But such measures depend on the environment in which the population resides **(FIGURE 4)** (357). For example, height has a lower heritability in populations where childhood nutrition is variable, leading to environmentally induced stunting in some children who are not well nourished. If the genetic determinants of heritability are low, then classical models of selection have less explanatory power with respect to the evolution of the phenotype. These arguments and others have led to the concept that the multiple processes of plasticity itself may be subject to the processes of evolution (337) and that they evolved because they confer a fitness advantage (32). While beyond the focus of this review, there are also some data showing that, under some conditions, plastic changes in the phenotype can become genotypically fixed (assimilated) and thus incorporated into evolutionary processes (32, 646).

For much of the past 100 years it has been assumed that there are only two kinds of inheritance: genomic and cultural. However, in recent years there has been an explosion of interest in three other forms of inheritance. The first concerns maternal (or paternal) effects, the subject of much of this review, by which the environment in one generation can condition the phenotype of the next, and possibility subsequent, generations. The second, related concept concerns indirect epigenetic inheritance whereby maternal effects induce epigenetic changes in the offspring of the next generation and in turn these epigenetic effects recapitulate the maternal phenotype which induced them; thus the offspring themselves induce the same maternal effects in the next generation, and so on (218). This scenario is most well demonstrated in studies of female rats with high versus low grooming behavior towards their offspring (637) where the indirect nature of the inheritance has been demonstrated from cross-rearing experiments. Third, recently a body of evidence has suggested the potential for trans-meiotic epigenetic inheritance (see Ref. 283 for review) including that from experimental studies in rodents (239, 240, 428) and compatible human observations (462, 463).

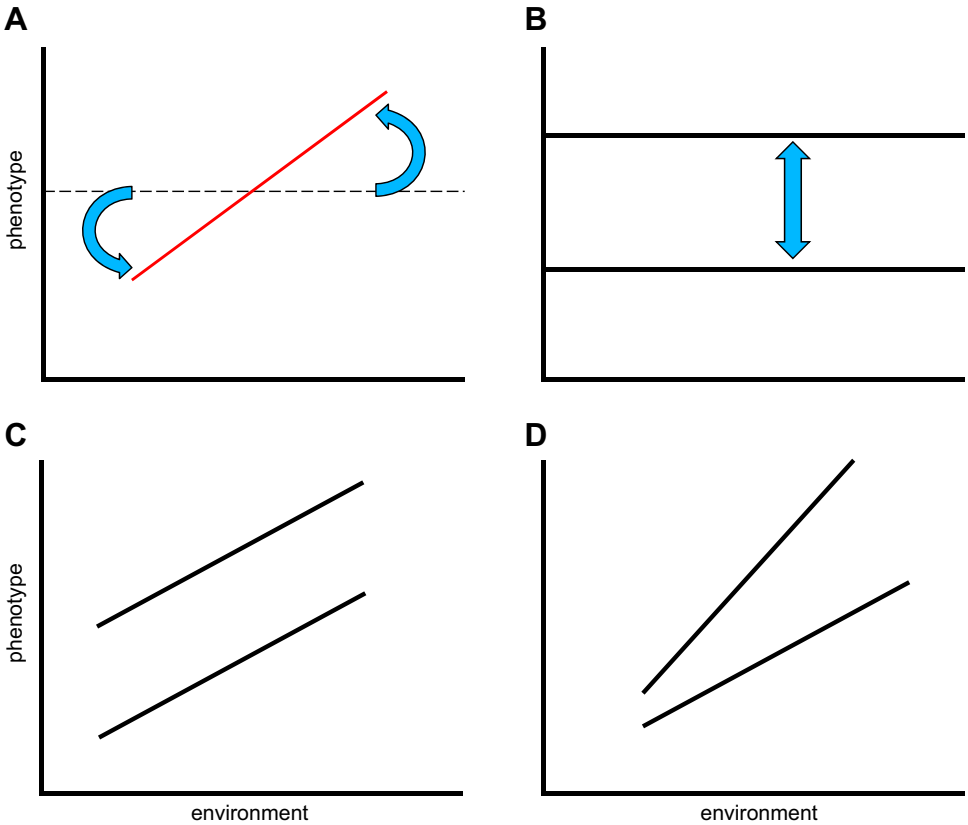

FIGURE 4. Characteristics of linear reaction norms. In *A*, the vertical displacement represents the degree of a particular phenotypic attribute, or the level of the genotype-specific relation between environment and phenotype. The broken line represents the average phenotypic value of the genotype across environments. The slope represents the degree of plasticity in relation to the environment. In *B*, there is genetic variation in the reaction norm of the phenotype (arrows), but no plasticity (slope = 0) and no variation for plasticity (slope does not change with environment). In *C*, there is both genetic variation and plasticity but no variation of plasticity (slope > 0 but is constant across environment). In *D*, there is genetic variation, plasticity, and variation for plasticity. In addition, in *D*, the heritability (extent of variation of phenotype in a particular environment accounted for by genetic variation) of the trait is lower at the left than at the right end of the environmental axis. [Modified from Pigliucci (468). Reprinted with permission of Johns Hopkins University Press.]

In the context of this review, the transgenerational transfer of the gut microbiome and its potential longer term consequences illustrate the importance of taking a broader view of inheritance. Mice reared in a germ-free environment are protected from dietary-induced obesity (18). Breast-fed and formula-fed infants have different patterns of gut microbiota, and while the data has been challenged (326), there is a body of evidence suggesting that breast feeding is associated with a lower risk of obesity. There is also a relation between how the gut is colonized depending on the mode of delivery (vaginal/caesarean) (598) and different disease risks in children. Those born by caesarean section have a higher rate of types 1 and 2 diabetes (81) and allergy.

C. Developmental Plasticity and Canalization: Developmental Constraints Versus Sources of Phenotypic Variation

There are multiple processes of developmental plasticity acting at various levels of organization to produce phenotypic variation. Equally there are multiple mechanisms restricting developmental variation, and so inducing robustness **(TABLE 1)** in the phenotype. These should not necessarily be seen as opposing processes as they reflect integrated mechanisms to optimize the outcomes of development from an adaptive perspective (for review, see Ref. 32).

There are two important points regarding how these processes work together to enhance fitness. The first is the relative robustness of the developmental "program," such that individuals with phenotypic traits of proven evolutionary fitness reproduce this reliably in each generation despite variations in the individual developmental conditions. The second is the ability to respond to changes in such conditions within the normal range, to produce a degree of phenotypic variation through developmental plasticity. Just as for the first process, the second confers a fitness advantage and has thus been preserved through evolution. As the fitness advantage is reflected in the ability to survive to reproduce, it can be manifest at any stage of the lifecourse up to peak reproductive potential, starting from early development. Whyte (650) coined the term *internal selection* to explain how effects on the early embryo would be more likely to have dramatic effects than later challenges and so some might be deselected, although at that time the idea was couched in terms of the lethal effects of mutations.

Of the mechanisms seen as conferring robustness, the best recognized is that of canalization, which permits maintenance of a phenotype in the face of variations in the environment or genotype. Canalization is often associated with the theoretical and empirical work of Conrad Waddington, who coined the term *epigenetics* in about 1942. His well-known epigenetic landscape **(FIGURE 5)** shows not only how developmental processes are canalized to buffer against variations in genotype and certain developmental exposures (the steepness of the walls of the valleys representing the degree of canalization) but also that epigenetic processes can induce switches in a developmental pathway, for example, to induce different cell types from a pluripotent stem cell line, or at the organism level to induce a different morph in a polymorphic species.

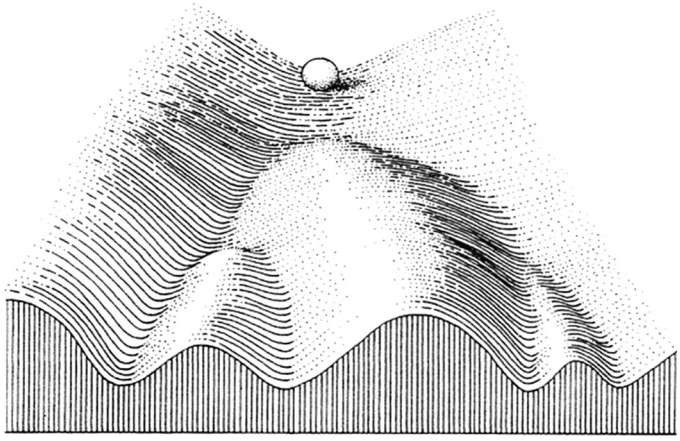

FIGURE 5. Waddington's "epigenetic landscape." In contemporary terms, the ball may be viewed as a group of pluripotent stem cells, for which the final destination in terms of final committed cell line depends on the path selected at a series of bifurcations. In Waddington's model, phenotypic development is "canalized" by processes which restrict its variability in the face of variation in genotype. Such processes are essential for replication of the lineage. Processes that reduce the steepness of the walls of the valley therefore increase plasticity. [From Waddington (619). Reprinted by permission from Macmillan Publishers Ltd.]

From a physiological point of view, it has been proposed that canalization **(TABLE 1)** utilizes processes controlled by factors including heat shock protein (HSP) 90, at least in some species (407), and HSP90 has been suggested to act as a "capacitor" to alter the degree of buffering of phenotypic effects (483). In rodents, the transgenerational passage of changes in the expression of the metabolic genes phosphoenolpyruvate carboxykinase (PEPCK) and increased PPARα and carnitine palmitoyltransferase-1 expression, induced by a sustained switch to a higher energy diet, were accompanied by changes in HSP90 expression and epigenetic changes (70). HSP90 acts a chaperone for a wide range of genes and can modulate effects of steroid hormones (512) that are known to be involved in developmental conditioning.

The term *genetic accommodation* is sometimes used to reflect the processes of phenotypic canalization that act to reduce the impact of randomly occurring genetic mutations (646). Such buffering may prevent their affecting the phenotype, but they can remain in the genotype as cryptic genetic variations (195) that may become manifest in later generations under different circumstances. For example, in the classic experiments of Belyaev using the wild silver fox, where animals were selected artificially on the basis of reduced fear of humans, cryptic variation in a number of

phenotypic features appearing early in development, such as coat color as well as head and ear shape, was exposed (596). Presumably the selection on aspects of familiarity with humans had epistatic **(TABLE 1)** effects reducing the degree of canalization of coat color and other morphology in the offspring.

D. The Temporal Dimension of Developmental Responses to Environmental Change

Developmental plasticity can also be placed in the context of different time scales of environmental change (measured with respect to the intergenerational period of a species) (332) (see **FIGURE 6**). The most rapid response of an adult organism to a change in its environment constitutes physiological homeostasis, operating to achieve constancy of the milieu interieur (235). This operates over a time scale of seconds to hours and involves changes in metabolism, cell signaling, and neuroendocrine responses. At the other temporal extreme, natural selection acts to change the genotype of a lineage in response to a sustained shift in the environment acting over many generations. Developmental plasticity occupies an intermediate position between these two extremes. It allows an organism to change its phenotypic development from that of its evolved lineage in response to an experienced or anticipated environmental change, but where the change is neither consistent over generations nor sufficiently prolonged to induce evolutionary change. The presence of maternal effects allows such plastic responses to persist over more than one generation but not to be sustained indefinitely in subsequent generations if the environmental shift is not permanent. The fitness advantages of such an intermediate response to environments which fluctuate over a longer time base than the generation time is apparent (334).

E. Nature Versus Nurture: The Rebirth of Epigenetics

The dichotomy of distinct influences inherent in the "nature versus nurture" phrase was first put in place by Charles

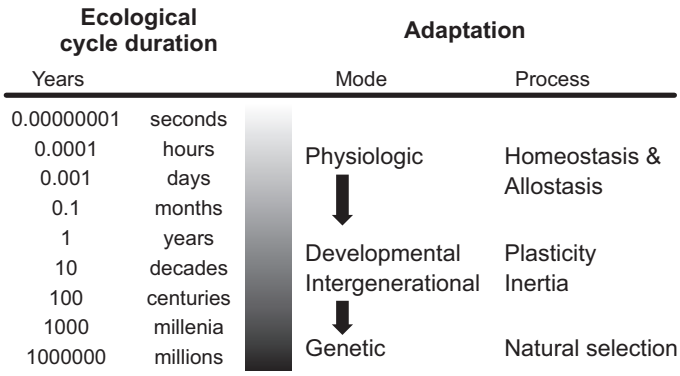

FIGURE 6. The time scales of adaptive processes. [From Kuzawa and Bragg (332), with permission from University of Chicago Press.]

Darwin's cousin Francis Galton (187). It was such concepts that paved the way for the eugenics movement in the first part of the 20th century and which continued into the postwar years (243). Following the rise in the science of genetics, "nature" became associated with heritable genetic traits and "nurture" with environmental or cultural influences, especially those operating during childhood. Unfortunately, the debate persists even today, with widespread belief that it is possible to separate the genetic from the developmental environment component of many traits, including disease susceptibility (308). Increasingly, our understanding of development shows the artificial nature of the distinction and the limitations of attempting to separate genetic and environmental influences, because they interact continuously across the lifecourse.

Furthermore, the concept of the gene as a physical entity in the process of the Central Dogma (111) is now seen to be flawed; indeed, "gene" now has varied and quite different definitions (415). Genes can be defined as segments of DNA, that is as structural elements, or alternatively as functional entities, although this depends on what definition of function is used (32, 416). The problem has become evident most recently in the current debate over the interpretation of the ENCODE data (152), in the sense that "intergenic" regions formerly thought to be "junk" DNA with little functional importance were shown to be potentially expressed, even if their functions remain unknown. In turn, the functional operation of a gene, and indeed its definition according to some interpretations, involves considerable input and influence from the environment. As Fox Keller has pointed out (308), the idea that the two processes of nature and nurture are distinct is neither helpful nor correct. The ways in which integrative physiological thinking is challenging the fundamental tenets of neo-Darwinism as enshrined in the Modern Synthesis (274) has recently been elegantly described (433). In some respects, this indicates a return to Bateson's definition of genetics as "the physiology of descent" (35).

The essential role of development in phenotypic variation was widely recognized by the early 20th century Russian school of biologists, as exemplified by the writings of Schmalhausen (523). Unfortunately, these were appropriated, misapplied, and then suppressed by Lysenko. In the Western world it was the work of Waddington (619), perhaps influenced by Schmalhausen, that placed similar emphasis on this concept. Waddington introduced the term *epigenetics* at a time when the underlying molecular mechanisms were unknown. It was only with the more recent understanding of the molecular basis of epigenetics that the importance of these early scholars' work was recognized.

There is now a plethora of reviews on the part played by epigenetics in phenotypic development (228). The majority of studies have focused on DNA methylation acting at CpG

base pairs although there is growing interest, especially in cancer biology, in effects on the covalent modification of histone protein tails, which affects DNA compaction (74), and on the role of noncoding RNAs (400). One source of confusion is the very different biological roles which epigenetic mechanisms play, even leaving aside their role in the pathological **(TABLE 1)** processes of cancer; for example, during evolution the epigenetic mechanisms which control gene expression under normal circumstances appear to have been coopted to regulate gene dosage (497). Thus the term *epigenetics* can encompass very distinct biological processes including transposon silencing, cellular differentiation (essential for the evolution of metazoa), chromosomal silencing in sex determination, and the imprinting of alleles depending on parental origin which evolved in marsupials (496) but is also found in plants (389). Epigenetic inheritance has been shown over eight generations in *Arabidopsis* (293). Between the appearance of metazoa and marsupials, the same biochemical pathway has been coopted to serve several quite disparate functions. Adaptive developmental plasticity, which is present in species as widely different as *Daphnia* and humans, and is the physiological mechanism of central interest for this review, is another distinct class of epigenetic function (216).

DNA methylation and hydroxymethylation affect gene expression by altering the access of transcription factors, which may then either augment or repress transcription, or through promoting the binding of the methyl CpG-binding proteins to methylated cytosines which recruit histone-modifying complexes to the DNA. These include histone acetyltransferases (HATs), which add acetyl groups to the histone tails and make the chromatin transcriptionally active, and histone methyltransferases (HMTs) such as Suv39H, which methylates lysine 9 on H3, and produces a closed chromatin structure and silencing of transcription. Most studies have examined such methylation across large regions of the genome, sometimes called differentially methylated regions (DMRs) (167), or at major clusters of CpGs called CpG islands and shores. However, these different patterns of CpG distribution have distinct biological roles that are only now being elucidated (570), an example being the role of DMRs in determining cell differentiation (318).

Recent evidence however stresses the importance of examining methylation at individual CpGs and patterns of methylation in small genomic regions (229). Methylation of CpGs de novo is catalyzed by DNA methyltransferases (Dnmts) 3a and 3b, which remethylate parts of the genome after the widespread demethylation that occurs following fertilisation (412). The pattern of DNA methylation is then maintained through mitosis by methylation of hemimethylated DNA by Dnmts. DNA methylation patterns induced during development were originally thought not to change greatly later, except in epimutations associated with cancer (138), but are now known to be fundamental to the processes of developmental plasticity. In monozygotic (MZ) twins, epigenetic variability increases with age (655), and this change is affected by lifestyle (178). DNA methylation differences are apparent even at age 5 yr in MZ twins (655). Thus, while the epigenome is most flexible from the perspective of developmental plasticity in early life, some degree of flexibility extends well after birth.

There is now evidence that environmental cues can alter patterns of DNA methylation in the embryo (316), and this is of relevance to the observations of an apparent increased incidence of imprinting disorders in children conceived using assisted reproductive technology (ART) (110, 133, 316, 451; for review, see Ref. 604). There is also evidence that ART can lead to long-term phenotypic effects in the offspring including greater risks of obesity, insulin resistance, and hypertension (250).

In addition to the processes of methylation which produce 5-methylcytosine (5mC), there are also well-regulated demethylation processes, for example, TET (ten-eleven-translocation) which catalyzes conversion of 5mC to 5-hydroxymethylcytosine (5hmC) (279, 663, 664) which may be an intermediate in the removal of 5mC. As 5hmC levels across the genome are low, it may be short-lived, or it may act as another epigenetic modification, inducing chromatin and transcriptional modifications. The distribution of 5hmC relative to 5mC (664), and its presence at exons strengthens the idea that it is associated with gene expression.

There is a high degree of specificity in the processes of DNA methylation despite the small number of methylation-related enzymes involved. It is assumed that specificity is conferred by microRNAs acting in concert with these enzymatic processes, but this is poorly elucidated. A further complication is the phenomenon of allele specific methylation whereby a SNP may impact on the pattern of methylation in a CpG *cis* to that SNP (538). The underlying mechanism may relate to the capacity for that SNP to affect small RNA production. It is thus important to use advanced bioinformatic techniques to identify methylation changes that are responsive to the environment and additionally those that are secondary to a fixed genetic mutation.

Some epigenetic processes, and particularly those related to developmental plasticity, are susceptible to nutritional influences, in part because processes such as DNA or histone methylation require a source of methyl groups from 1-carbon metabolism. These are not usually in short supply in the diet and can be derived from the nonessential amino acid glycine. However, the demands for this in the late gestation human fetus are such that glycine becomes a conditionally essential amino acid. Animal studies show that the phenotypic effects on the offspring of a maternal low-protein diet

can be prevented by supplementation with glycine (64, 284). Folate is also required for the provision of methyl groups, and this is largely derived from the maternal diet. Folate plays a major role in many aspects of fetal developmental (606) pathways via epigenetic mechanisms (238), and imbalance can lead to the accumulation of homocysteine, which has damaging effects on many organs including the kidney and cardiovascular system and which can act via increased oxidative stress (641).

In rodents, folic acid supplementation of the low-protein diet fed to the dam prevents epigenetic and phenotypic effects on her offspring (365), and paternal dietary folate level produces epigenetic effects in sperm and affects pregnancy outcome (336). Provision of methyl group donors in the diet also prevents the induction of epigenetic effects via retrotransposons in the agouti mouse (630). In humans, dietary supplementation with folic acid is known to reduce the risk of neural tube and other "congenital" defects (127), and the balance between folate and vitamin B_{12} status is linked to diabetes risk (668). The critical period when epigenetic changes can be reversed by folic acid supplementation is not known, although in rodents it may extend into the postweaning prepubertal period (72).

Nutritional influences on the developmental epigenetic state are however broader than specific influences on one-carbon metabolism. Taurine has long been considered to be an important factor (5), and recent studies implicate its deficiency in endoplasmic reticular (ER) stress (36a), which can have a range of downstream effects, including on sirtuins and ageing (92). Given that epigenetic mechanisms underpin developmental plasticity and that nutritional cues are important with respect to adaptive developmental plasticity, it is to be expected that a variety of nutritional cues in development will have specific epigenetic consequences. Most experimental studies of nutritional effects on the offspring have used an unbalanced maternal diet with a low protein-to-carbohydrate ratio or a global dietary restriction during pregnancy. However, unbalanced diets with high levels of dietary fat or cafeteria diets simulating the Western "junk food" diet have also been explored (38, 39).

Epigenetic effects on the developing offspring can also be induced by altered maternal behavior. Offspring of rat dams that exhibit high levels of licking and grooming were shown to have lower levels of methylation at specific CpG dinucleotides within the hippocampal *GR* promoter, concomitant with higher expression of the gene product which regulates hypothalamic-pituitary-adrenal activity (636). These offspring were better able to cope with stressors in adulthood, demonstrating a functional link. Maternal care-dependent gene expression changes in the hippocampus could be reversed by intracranial administration of the histone deacetylase inhibitor Trichostatin A and L-methionine, which acts as a methyl donor (637).

As Ozanne has pointed out (e.g., Ref. 147), the regulation of transcription factors by epigenetic processes is an effective way of altering the developing phenotype via manipulation of physiological control processes: examples include effects on RXRA (229), Pdx1 (458), and Hnf4α (518).

Prenatal epigenetic effects are not confined to the developing fetus. Some effects are mediated by epigenetic processes in the placenta, for example, at the level of amino acid transporters (352) and imprinted genes that in some species affect fetal growth (177, 294). There may also be effects on glucose transporters (298). The interaction between fetal growth and placental vascular function via the NO system appears also to be mediated in part by epigenetic processes (328).

From a physiological point of view, it is now important that a range of processes have been discovered which affect gene expression and thus phenotype beyond structural mutations such as SNPs. In addition to the processes discussed above, we should note gene copy number variations, the occurrence of which in the offspring can also be affected by maternal diet (75). Evidence that epigenetic processes can affect the probability of mutations through the hypermutability of CpG sites should promote greater acceptance of the previously heretical notion that physiological processes can affect the genotype; this idea has implications not only for developmental but for evolutionary biology (434). Finally, it is now becoming clear that studies of developmental conditioning will require measurement of the interaction between genetic and epigenetic processes.

F. Developmental Strategies

As Hertzman has summarized (259), there are several ways of thinking about DOHaD phenomena. In practice, they are hard to separate. One, which accords with the concept of critical periods in development (see also Ref. 330), proposes latent effects whereby early life environment produces effects on later health and disease risk independently of intervening environmental influences. This has similarities with aspects of neural development, such as the visual system, but less so with cardiometabolic control. The second involves pathway effects, whereby the response to a cue at a particular point in time depends on the developmental pathway leading to that time, and this is currently the most favored explanation. The third possibility uses a cumulative effects model for the detrimental consequences on health of repeated and graded exposure to adverse environmental conditions. While this concept is incorporated into current DOHaD thinking (see **FIGURE 1**), on its own it does not differ from the damage accumulation/adult lifestyle model that does not account for the demographic patterns of disease. For example, although the prevalence of obesity has continued to rise in most countries over the last years, there has been a steady decline in global mean blood pressure,

and interventions to reduce blood pressure, glucose, and cholesterol account for only 50% of the excess risk of coronary heart disease (201).

The phenotype emerging from the interaction between genetic and environmental factors, and mediated via epigenetic processes, will be adaptive if aspects of the phenotype induced affect either the individual's survival until reproductive age, or reproductive capacity and fecundity. Strictly, fitness is measured in terms of the number of viable offspring which themselves reach reproductive age, or better the number of resulting grand-offspring. Simple examples can be found in egg-laying species including fish, birds, and insects, where environmental factors such as nutrient availability or number of predators affect both the number of eggs laid and their size, which in turn influences the survival chances of the offspring (155). We can see that there may be a potential conflict here between maternal use of food resources for metabolism and investment in the fitness of the next generation (this concept of maternal-offspring conflict is discussed in sect. IV*D*). In addition, mechanisms which evolved to confer fitness may not have the same effects in contemporary conditions (34, 591).

The role of maternal effects or, where there is also an influence of the father, parental effects and their evolutionary significance has been reviewed (382a, 599). They can be quite dramatic in terms of the offspring phenotype induced. East African grasshoppers that are normally green develop into a black morph after a grassland fire (509). Another excellent example is the desert locust (*Schistocerca gregaria*). This species has two distinct phenotypes (or morphs): solitary and migratory. They differ dramatically in terms of behavior, with the shy, nocturnal, solitary form contrasting with the gregarious, diurnal, migratory form; in nutritional physiology, with the solitary form having a restricted range of food plant species whilst the migratory form is far more omnivorous; and in metabolism, with only the migratory form being capable of long flight. The morph that forms following larval hatching is influenced by the environmental conditions. A high population density affects the composition of the secretion produced by the mother around the eggs, and it is this chemical stimulus which influences the phenotype, inducing the migratory morph which is more likely to move to a less well-populated area (392). An equivalent mammalian phenomenon has been reported in the red squirrel, in which high population density and low food abundance produces a glucocorticoid response in the mother which is associated with accelerated growth in the offspring (120), permitting them to reach reproductive age more quickly.

The direct role of nutrition as an inducer of phenotype in the developing offspring is exemplified by the honey bee (*Apis mellifera*) where the maturation of the female larva into a queen versus a worker can be produced by feeding it exclusively on royal jelly for a longer period: the active component in the royal jelly responsible for this induction is not known, but the polyphenism is mediated by epigenetic mechanisms as it can be altered by use of an siRNA to suppress Dnmt3 activity (329).

It is not known whether such polyphenisms are relevant to mammals. We have argued that there is some evidence in the rodent for developmental bifurcations in response to maternal nutrition which might suggest an echo of distinct morphs (222). Furthermore, the distinct forms of response of children to severe undernutrition, which have different adaptive consequences and which appear to originate prenatally, suggest that some aspects of human physiology do not follow a continuous reaction norm but may be discontinuous, reminiscent of polyphenism (170). However, in mammals, most developmental plastic responses do produce a continuous reaction norm (522), for example, in linear growth, birth weight, gestational length, or metabolic function. The upper and lower limits of that reaction norm are limited by various tradeoffs; for example, gestational length is limited by viability of the offspring at one extreme and by placental senescence and the ability of the fetus to pass through the pelvic canal at the other.

G. Predicting the Future

The concept that phenotypic traits formed during development, and which confer fitness advantage in some way will, if they have a heritable component, be selected during evolution is uncontentious. Similarly the concept that plasticity itself is an evolved and conserved process is generally accepted. But a relatively new concept concerns the role of developmental anticipation, i.e., that the developing organism can detect critical aspects of the current environment and use these as cues for the induction of a developmental path which can potentially confer adaptive benefit later. For example, frog larvae exposed to chemical signals suggesting the presence of a predator will develop into tadpoles with tail morphology allowing greater swimming speed and thus greater chance of survival (393). That this might confer a later life disadvantage is traded-off against the adaptive advantage of the changes to tadpole morphology because they provide a greater chance of survival to reproduce.

Such anticipatory responses are common across all biological taxa and can span generations. Other well-known examples are the helmet in *Daphnia*, the shell morphology of the whelk, and the thicker body of the crucian carp that form in response to signals of predation (66, 141). Studies in *Daphnia* show the critical importance of the developmental stage in determining the phenotypic outcome (408). The example given earlier of the desert locust indicates the use of an early cue to predict later overcrowding and thus the development of a morph able to migrate to a more favorable environment. The examples differ in that in

Daphnia the cue is passed directly from the environment to the developing individual; in the locust, it is mediated by the mother when she lays her eggs. For mammals, the role of the mother both before birth and in infancy is even more important as a transducer of the current environment. Licking and grooming behavior of the rat dam, which may convey information about her stress level, has prolonged effects on the stress responses of her pups (95). Belding's ground squirrels developing in open grassland habitats, where the risk of predation is higher, develop into more anxious adults than do those developing in woodland habitats (386). Similar effects of parental stress levels on the offspring are seen in arctic species such as the lemming and snowshoe hare (535, 536). A mammalian example that resembles the responses of the desert locust is reported in the North American red squirrel, where greater population density leads to an offspring phenotype characterized by faster growth and earlier puberty. That the effect is induced by population density detected by the mother is shown by its occurrence when recorded calls of squirrels in dense populations are played (120). The effect may be mediated by maternal glucocorticoids (see sect. IVC) as their metabolite levels in feces are increased. Maternal effects may integrate a range of environmental aspects, as well as affecting a range of phenotypic characteristics in the offspring (134).

We have termed the class of developmental response that underpins these adaptive anticipatory traits predictive adaptive responses (PARs) **(TABLE 1)** (210, 220). There is growing support for the concept from a range of species, (e.g., Ref. 513; see also Ref. 33). The prediction does not need to be perfectly accurate for the capacity to respond in anticipation to have evolved: provided the prediction is more often correct than incorrect, the capacity to predict will have adaptive potential (204, 282). Several studies have modeled the adaptive advantage of a predictive response in early development and shown that, despite the considerable potential for error in the prediction, it confers advantage as long as there is some inertia in the cue, i.e., that the environmental change is interpreted as persisting over a significant portion of the lifecourse (411, 572). Nettle et al. (424) have recently subdivided PARs into external, based on environmental cues, and internal, based on an organism's functional phenotype. We argue that this is an artificial distinction and that "internal PARs" are equivalent to immediately adaptive responses (IARs). The suggestion that PARs are only effective when the environment is relatively stable is countered by the model of del Giudice et al. (134), which takes account of shorter and longer term environmental effects with varying levels of autocorrelation. However, detailed analysis of the stability of the epigenetic processes underlying PARs requires consideration of their costs (256), following Nishimura's (431) discussion of the optimal delay between an environmental cue and the induction of a phenotype.

There is likely to be a directional bias in the maladaptive effects of an inaccurate prediction. Prediction of condition A but being exposed later to condition B need not have the same consequences as the reverse, and thus there may be an advantage in evolving mechanisms which favor one set of predictions over another. As we will discuss below, a good example is that there is a greater fitness disadvantage in humans predicting a plentiful nutritional environment but ending up in a famine than the reverse: the former leads to an individual who is poorly adapted to restricted nutrition and reproductive function, at least in the female, is likely to be compromised. On the other hand, even though a woman who is better adapted to a low nutrition environment may become obese if she lives in a high nutrition environment, her fertility will be compromised only at extreme levels of such obesity (297).

We recognize that the use of the term *predictive* may seem teleological; however, as with the terms *forecasting* or *anticipatory*, it is not intended to imply a conscious decision but it does capture the importance of the response, hence why it may have evolved.

PARs differ from the thrifty phenotype model of Hales and Barker (241) in several ways. First, the thrifty phenotype concept rested on the immediate advantage to the developing individual of economizing on nutrient consumption by reducing growth: this is more akin to an IAR. If there were unintended detrimental health consequences later, this was unfortunate. In contrast, PARs do not necessarily need to have any IAR nature and, indeed, can be induced by stimuli that do not of themselves necessitate a developmental response and that are not necessarily accompanied by a reduction in growth: PARs are induced to gain a fitness advantage in the postnatal period until the time of reproductive competence. Furthermore, some attributes of a PAR can be the opposite of "thrifty," for example, a greater initial insulin sensitivity in early postnatal life (401) which may promote adipose deposition, greater postnatal muscle deposition especially in males, greater appetite, and accelerated body growth. In addition, a range of behavioral attributes may be affected, which confer advantage in the predicted environment, including appetite (611) and physical activity. Just as larvae of the butterfly *Bicyclus anynana* develop stronger thoracic muscles if poorly nourished, enabling them to fly to potentially better habitats (513), so offspring of undernourished rat dams will be more sedentary when kept in standard cages (612) but will run greater distances than offspring of well-nourished dams if given a wheel in the cage (406). These induced responses are not easily viewed as thrifty.

It is important to note that not all responses of a mammalian fetus which have phenotypic consequences are predictive in nature: where the developmental cue is evolutionarily novel or extreme, it may induce a disruptive response

(see above); where it is severe but not disruptive, it may induce an immediate "coping" or adaptive response (IAR), usually a reduction in growth which allows the fetus to survive (221); and lastly, the effect on the fetus may be neutral in terms of both fetal survival and longer term effects, depending on the circumstances. Intrauterine growth retardation in response to maternal undernutrition or impaired placental function is a good example of an IAR because, unless the fetus slows its somatic growth, the high energetic demands of the fetal heart and brain cannot be met. The effects of reduced nutrition or an environmental cue mediated by glucocorticoids to reduce nephron number is however an example of a PAR. In humans and sheep, complete complement of nephrons is established before birth, and the relatively low metabolic requirements of the kidney may not confer a great survival advantage from reducing this number before birth. Postnatally, however, the kidneys receive 25% of the cardiac output, so reduced nephron number may be adaptive in a poor nutritional environment. The longer term deleterious effects on cardiovascular function of reduced number are not manifest until later (19). PARs can occur independently of IARs or both may be induced, and this is why fetal size often correlates with longer term phenotypic outcomes that are associated with disease risk, even though the processes which set the risk may differ from those which restricted growth and growth may not be only the causal pathway to later risk.

The distinction between IARs and PARs may seem somewhat semantic but is important because some critics of the PARs concept (643) have failed to appreciate the conceptual significance of the clinical observations which show that long-term consequences for the fetus can occur in the absence of IARs (i.e., in the absence of reduced birth weight). If the long-term phenotypic changes associated with later disease risk in the offspring were simply a by-product of a maternal adaptive response, then an IAR would be expected always to be demonstrable: this is not the case for such effects occurring in the absence of an effect on birth weight (185).

Two questions become important in considering the role of adaptive plasticity in the pathways to altered disease risk in humans: the first is when in the lifecourse the adaptive advantage is demonstrated, and the second concerns the causes and consequences of faulty prediction. Both of these have been subject to some confusion from some commentators.

Williams (651) recognized that the pressure generated by natural selection declines with age; survival to reproductive age and fecundity are particularly important in defining human fitness (299). Indeed, the well-accepted evolutionary concept of antagonistic pleiotropy (652) is based on the selection for traits that have value early in life even if they have postreproductive deleterious consequences. Thus, in seeking the adaptive advantage of putative PARs, one would expect to see any advantage manifest in childhood and/or adolescence, not necessarily in adulthood. Indeed, PARs only have to give survival advantage into the next stage of the lifecourse after they are induced to have adaptive value; for example, if they are induced early in fetal life, their potential impact may be on infant and child survival. This key point was not emphasized in the earliest expositions of the PARs hypothesis (204).

A range of studies in humans has shown that maternal body composition affects a range of characteristics in the offspring, including body composition, neurocognitive behavior, kidney size, and reproductive function (223, 413, 551). However, a striking example of a PAR in human comes from a comparison of Jamaican children who develop marasmus or kwashiorkor in childhood famine. Kwashiorkor is more metabolically wasteful, and such children have a higher mortality (169a); they have a higher birthweight than children who develop marasmus in the same community (170), suggesting that their prenatal conditions were better, leaving them less well prepared to meet famine. The more economical metabolic phenotype in the marasmic children was not only associated with greater chance of survival, but was manifest as insulin resistance and glucose intolerance in adulthood (179).

Misleading predictions can occur either because the environment changes over the lifecourse or because cues are inaccurate or misinterpreted. Considering the nutritional environment as an example, maternal ill health, placental dysfunction, or unbalanced maternal diets affecting nutrient transfer can all signal a poor nutritional environment, when in fact the nutritional environment for the population as a whole is adequate or even abundant. Conversely, infant overfeeding with formula can signal a rich environment when in reality it is more nutritionally constrained.

We have already introduced the concept of maternal constraint, and this has important implications for how nutritionally induced PARs operate in humans. In humans, maternal constraint mechanisms generally limit fetal growth to match maternal (i.e., pelvic) size and their evolutionary significance has been discussed elsewhere (215). In polytocous species, the operation of maternal constraint may be linked to the limits imposed by multiple fetuses. One important component may be the saturable nature of placental amino acid transporters (100), another the clearance of insulin-like growth factors by the placenta (28, 104). But, in contrast to nutrients such as amino acids and fatty acids, there is no limit to the capacity of glucose to cross the human placenta to the fetus, where it drives insulin release and in turn promotes both somatic, and particularly adipose, tissue growth. Hence, in untreated gestational diabetes mellitus, fetal overgrowth leading to potential obstructed labor may occur. That humans did not evolve a limit on placental

glucose transfer suggests that maternal obesity and GDM were uncommon in our evolutionary past (375). Type 1 diabetes and GDM can be associated with changes in placental glucose transporters, although this appears not to be so in late gestation (289).

Thus we can see two distinct kinds of "mismatch" operating with respect to developmental conditioning, one based on postnatal evolutionary novelty (evolutionary mismatch) and one a consequence of the qualitatively different nutritional signals operating between fetal and postnatal life (developmental mismatch). The modern diet of high glycemic index and energy-dense processed foods is qualitatively very different from the range of diets that humans consumed until recently (478). The modern diet exceeds the range that can be predicted in terms of developmental conditioning because of its evolutionary novelty, and thus a mismatch is likely between the diet predicted in utero or in infancy and that which the individual is likely to consume later. Such evolutionary mismatch can also have consequences for the development of the next generation as for maternal obesity and gestational diabetes. There is some evidence for the operation of a PAR induced by abundant nutrition in utero, which may make the individual less able to cope with a poor environment later. There is anecdotal evidence for lower survival rates in larger individuals in concentration camps (29), and in Ethiopia higher birthweight was associated with greater risk of rickets (88).

H. Transgenerational Effects

The evolutionary significance of the adaptive pathways by which environmental information is passed across generations via the phenotype has been discussed above. We and others have emphasized nutrition as the most obvious example, and examined how epigenetic changes are amplified or modified across generations in the face of a sustained nutritional challenge (70, 358). But there are also a range of other cues that can induce transgenerational effects.

One may be the parental influences on the developing offspring produced by behavior. Animal data for this come from research showing that the licking and grooming behavior of rats produces effects on the behavior of their offspring, an effect mediated via epigenetic changes in the hippocampus of the pups (368) involving the GABA system (677). As cross-fostering in infancy abolished the effect, this can be considered an example of indirect epigenetic inheritance (218). In the wider context, the effect has similarities with niche construction (445). In humans, a range of behavioral attributes are passed between generations and, while it has been generally considered that these are culturally transmitted, the animal observations also raise the possibility of epigenetic effects. Indeed, a recent and somewhat controversial study has suggested that suicide victims who had been abused as children have the same epigenetic changes in their hippocampus as the low groomed rats (394). Such epigenetic dysregulation has also been observed in cord blood from neonates born to mothers who experienced depression late in pregnancy (443). At age 3 mo, assessment of salivary cortisol levels following exposure to a stressor showed that these infants had heightened HPA stress responses. This is an area requiring careful research across generations to resolve the extent to which human behavior may be conditioned by prior generations or by biological processes in utero or infancy.

Female-line transmission from F_0 to F_2 generations could be produced by an effect on the primordial ovarian follicles developing in the fetus, as they contain the maternal genetic information which will pass to the grand-offspring at the time of fertilization. There is growing evidence that such effects can be mediated by epigenetic processes (672). When such a process operates, a stimulus to the F_0 generation may produce effects on the F_2 offspring phenotype but should not affect F_3 or subsequent generations unless the environmental cue is repeated during the development of these generations. There are several examples of such transmission (70, 144). For the process to be termed truly transgenerational as opposed to intergenerational therefore, it should be manifest in the F_3 generation without the environmental cue persisting into the F_1 generation (547).

There is growing interest in the intergenerational transmission of effects via the male line (236, 272, 670), although it is unclear how prevalent such effects might be. However, it is now clear that some DNA methylation and chromatin marks can persist in the sperm (84) and that the small amount of cytoplasm remaining in the sperm contains microRNAs that have been shown experimentally to have phenotypic effects (488). For example, injection of RNA from sperm of mice heterozygotic for the Kit paramutation which results in a white spotted phenotype into wild-type embryos led to their developing the spotted phenotype (487). Injection of a miRNA associated with cardiac hypertrophy into embryos led to transmission of the effect to the F_3 generation (622). Additionally such transmission appears to involve DNA methylation (317). Dramatic male line transmission effects have been shown for chemical exposures, in particular to endocrine disruptor chemicals such as vinclozolin which have anti-estrogenic and pro-testosteronic properties. Administration of these chemicals to male rats can produce effects on sperm counts and markers of testicular cancer up to the fifth generation, mediated by the male line (11). Manikkam et al. (380) recently showed that endocrine disruptors such as BPA, DEHP, and DBP derived from plastics can induce epigenetic transgenerational inheritance of conditions such as obesity and reproductive disorders and that these are accompanied by sperm epimutations. In mice, fear responses to a chemical stimulus, conditioned by an electric shock, are passed from male rats to their offspring even when the dam was unexposed (136). In

rats, dexamethasone prenatally administered to males leads to metabolic effects in offspring (144), and paternal obesity induces pancreatic dysfunction in female offspring (426). In the latter study, myriad gene expression changes were detected in offspring islets; the largest change was seen for a gene encoding a component of the Jak-Stat signal transduction pathway and was coincident with hypomethylation at its putative regulatory region. Paternal prediabetes in mice leads to disrupted glucose metabolism in offspring that persists to at least the F_2 generation, and induces an array of methylome alterations in offspring pancreatic islets (639). Most interestingly, many of these epigenomic changes were reflected in paternal sperm. In humans, fathers of low-birthweight infants are more likely to have metabolic disease (262), while a poorer lipid profile in childhood has been linked to advanced paternal age (519). In an historial study of a Swedish rural population, poor nutrition before puberty in men was associated with lower incidence of diabetes or cardiovascular disease in their grandsons (302). Smoking in fathers in adolescence is associated with increased risk of obesity in their sons (463). Recent evidence (382) shows that smoking can affect miRNAs in sperm, raising the prospect that aspects of paternal behavior can have epigenetic effects on the next generation. Other mechanisms of transgenerational transmission via the male line may include changes in the packaging of DNA around protamine, a cue in the semen, because offspring of male mice lacking seminal vesicles are fatter (65), or even prions, which can induce heritable traits in yeast (242).

IV. PHYSIOLOGICAL (ADAPTIVE) PATHWAYS IN DOHaD

The discussion above distinguishes between ultimate and proximate mechanisms that are encompassed within the study of DOHaD-related phenomena. Lack of clarity over the multiple underlying mechanisms and pathways has slowed progress in this field.

A. Mismatch

The acceptance of the DOHaD concept was delayed to an extent by the lack of physiological insights into underlying mechanisms: this necessitated detailed animal investigations (360, 398, 479, 480, 495, 576) in which it is possible to define and control the stimulus used to induce the response, and to measure that response in a range of tissues and at various stages during development and throughout the lifecourse. The animal models used included the rat, mouse, guinea pig, sheep, pig, and non-human primate, and in each the DOHaD concept has been confirmed. However, while much of the early work focused on the physiological mechanisms, it was both the development of conceptual models based on evolutionary principles (221, 241) and the recognition of the role of developmental plasticity (30, 32) and the associated epigenetic processes (214) that gave the field a solid mechanistic basis and led to the acceptance of the concept of "mismatch" (469) **(FIGURE 2)**. We emphasize that it is important to distinguish between mechanisms operating within the normal range of developmental exposure, which are likely to operate via adaptive mechanisms, and those associated with evolutionary novelty that are likely to be nonadaptive in origin.

Adaptive responses operate at multiple levels in the organism to produce an integrated phenotype (217). The levels are summarized in **FIGURE 7**. If the stimulus occurs during early development, the responses include effects on stem cell lineages that will in turn affect the growth of individual organs and tissues. They produce effects on mitochondria (3, 543, 586, 674) which affect metabolic function. Subsequent interactions between metabolic demands of tissues, the levels of growth hormones, and the interaction between blood supply and organ function then affect the relative growth of organs. Finally, they affect control systems such as stress responses involving the HPA axis and the sympathetic nervous system (474), hypothalamic function, and appetite (61, 480, 495, 501, 571). These effects can be viewed as changes in the speed of maturation of organs and systems in addition to changes in growth. The effectors operate on multiple pathways, for example, atrial natriuretic peptide has been shown to play a role in vascular and renal effects, possibly via alterations in placental perfusion (290), hormone production (418), cytokines (117), endothelin-1 (139), and the RAS following changes in AT_1R expression (673). For many of these processes, changes in placental function are responsible for mediating the effects (418, 526). Because the physiological processes operating in such responses interact, effects on one system can be compensated for by another. This makes measurement of the phenotype complex, especially where there are multiple processes involved in regulating a function. It can also explain why some apparently straightforward interventions do not achieve the desired result, as noted earlier for energy balance considerations with respect to obesity (584).

Where the effects concern behavior, they may also have consequences for relatives or other members of the population. Where there are commensal species, such as the gut microbiota, these may be affected too, and this may then have further reciprocal consequences for the individual (7). The mechanisms thought to operate at these different levels are discussed in detail below.

B. Physiological Mechanisms: Effects

These are summarized in **FIGURE 7**.

Initially most animal studies involved investigation of effects of unbalanced or poor maternal diet and body composition on cardiovascular and metabolic function in the

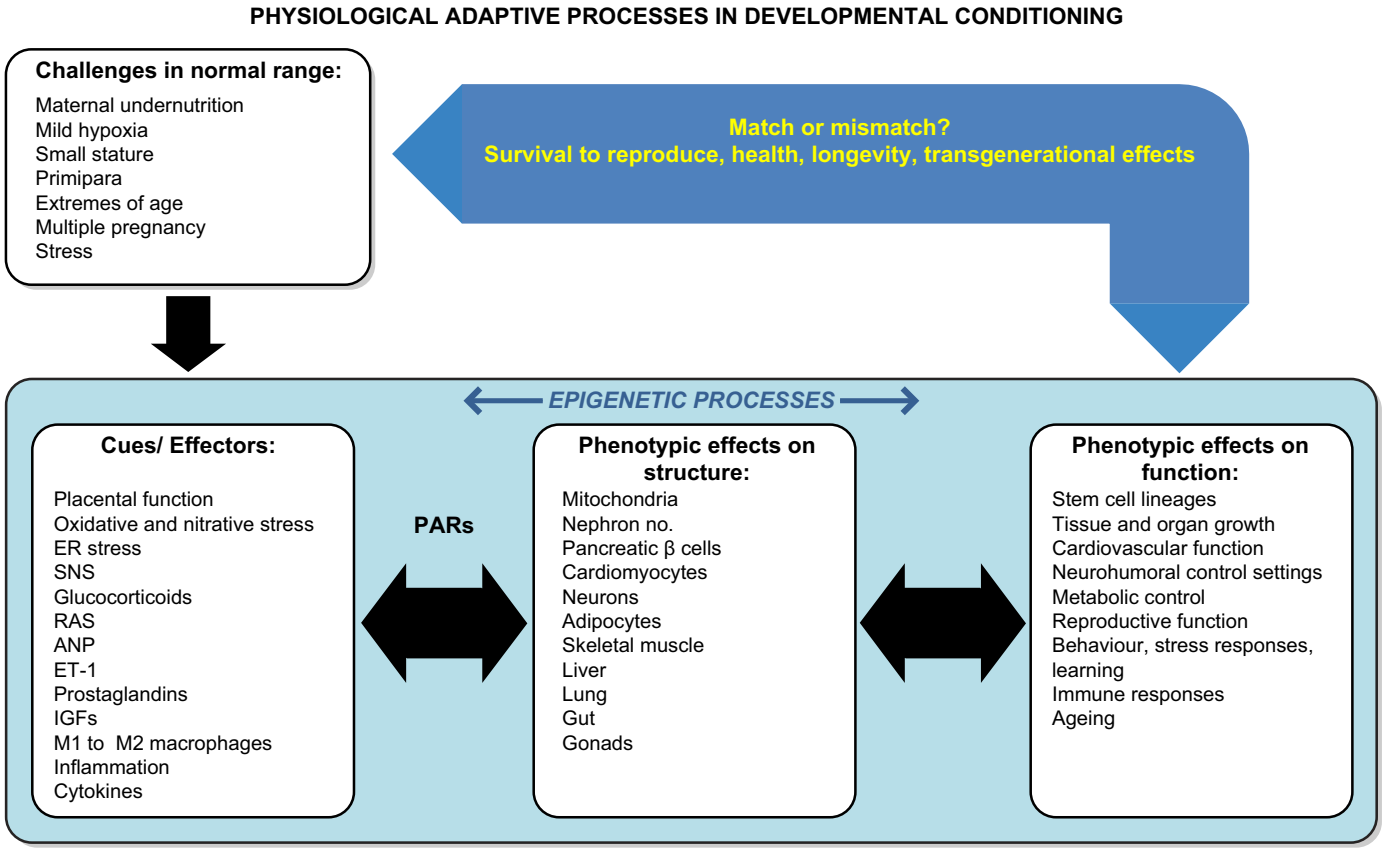

FIGURE 7. Physiological adaptive processes in developmental conditioning.

offspring (69, 481, 592). The most commonly used challenge was a low-protein diet fed to the mother during pregnancy (554). This produced low birth weight and later growth (unless the animals were cross-fostered) and produced effects on offspring blood pressure (6, 48, 429, 453), the heart (91, 162), and blood vessel structure and function (50, 64, 593, 669). There are also studies using global dietary restriction (253, 430, 611, 656) and low-salt diet (36). The effects on blood vessels differ between beds (595). They can be viewed as changes in the maturation of control of vascular tone which involve a shift in the balance between NO and endothelial hyperpolarizing factor (56) and which can be affected by a high-salt (55) or high-fat diet and which interacts with oxidative stress (438).

Dietary manipulation of postnatal growth in the offspring provided data that led to the mismatch hypothesis, since accelerated growth is associated with shortened lifespan (292, 454–456), accompanied by shorter telomere length in the kidney, pancreas, and aorta (580, 581) and reduced antioxidant protection (582). Unbalanced nutrition in utero affects a range of organs and systems, including brain metabolism and function (186, 612), appetite (38), the sympathetic nervous system (517), HPA axis (476), circadian rhythms (78), kidney (59, 398), pancreas (267, 583), liver (68, 441), skeletal muscle (108, 109), brown and white adipose tissue (372), and bone (340). Vascular effects on the offspring include endothelial dysfunction and effects on intraventricular wall thickness in the heart. There is considerable information about the processes involved in cardiomyocyte development because of its relevance to heart failure in adults. The maturation of the fetal heart in late gestation, triggered by glucocorticoids and thyroid hormone, changes the balance of the α and β isoforms of the myosin heavy chain (MyHC), the former being faster acting and therefore capable of greater force development (640); maturing cardiomyocytes become binucleated and no longer divide. Subsequent changes in afterload, as systemic arterial pressure increases at birth and with vascular disease in later life, produce hypertrophic thickening of cardiomyocytes. In heart failure, reexpression of fetal genes, mediated by epigenetic processes involving a cardiac-specific microRNA (605), can produce temporary compensatory processes.

In humans it is becoming increasingly apparent that long-term effects on health are induced in early gestation, measurable for example in terms of fetal growth in the first trimester and cardiovascular risk in childhood (286). Similar considerations apply to the preconception period (603).

Adaptive processes can be induced experimentally in the preconception and peri-implantation period via manipulation of maternal diet or body composition (76, 101, 102, 112, 595). In both rodents and sheep, such short-duration dietary manipulation preimplantation produces sustained

cardiometabolic effects on the adult offspring (631). These effects can be induced in the embryo in vitro, subsequently implanted into the uterus of a recipient dam which is fed a balanced diet (632). The effects are manifest even if the dietary challenge is induced during oocyte maturation (634). The results in both large and small animals again support the PARs model (102, 633). The metabolic effects on the offspring are sex dependent (73) and influence postnatal growth (71). Similarly conditioning effects can be induced postnatally in rodents, for example, by changing litter size (620), and conditioning can be reversed by neonatal intervention (613). Distinguishing between the effects of unbalanced nutrition in early versus later pregnancy is not easy in the rat or mouse; however, in the guinea pig such effects have been shown (47) on both cardiovascular and stress responses in a manner reminiscent of the trimester-dependent effects of famine on those exposed in utero to the Dutch Hunger Winter (507).

As these developmental effects are part of an adaptive strategy **(FIGURE 8)** rather than the early inception of a pathological process, they reflect lifecourse biology theory and generate an integrated and somewhat stereotypic phenotype (218). From a physiological point of view, this phenotype has reductions in the size of metabolically active organs such as the kidney, giving the individual a reduced reserve capacity to cope with the naturally occurring detrimental processes of ageing and unhealthy lifestyle. The trade-off includes faster postnatal growth in the face of abundant nutrition and earlier puberty, (102, 213, 551). In line with many evolved traits, such effects show sexual dimorphism, for example, in relation to body composition and metabolic control (475). This is consistent with the concept of PARs as Darwinian fitness traits are often sexually dimorphic. Such effects, especially in relation to the timing of menarche, growth in height, and adiposity have been known in humans for many years (see seminal studies of Tanner and colleagues, e.g., Ref. 579).

How long after birth conditioning effects can be induced in humans is an open question, but it is clear that they can persist through infancy. It has been argued that it is the catch-up growth in infancy rather than the environment of the fetus that induces metabolic conditioning (545), but this ignores the fact that by definition catch-up growth follows impaired fetal growth. The issue is rather whether reversal of the changed later disease risk is possible by postnatal manipulation of growth, a matter yet to be resolved although there is some evidence to support the concept (544). Most data on postnatal growth relate to postnatal overnutrition (see sect. V*B*), which is likely to involve a nonadaptive pathway, or to behavior where the distinction between biologically conditioned and behaviorally learned mechanisms is complex.

There are a number of maternal and demographic factors that can influence the risk of the mismatch pathway being induced. Godfrey and co-workers confirmed the relation between maternal BMI and fat mass reported in the child (649) in adult offspring aged 28–32 yr (499). Interestingly,

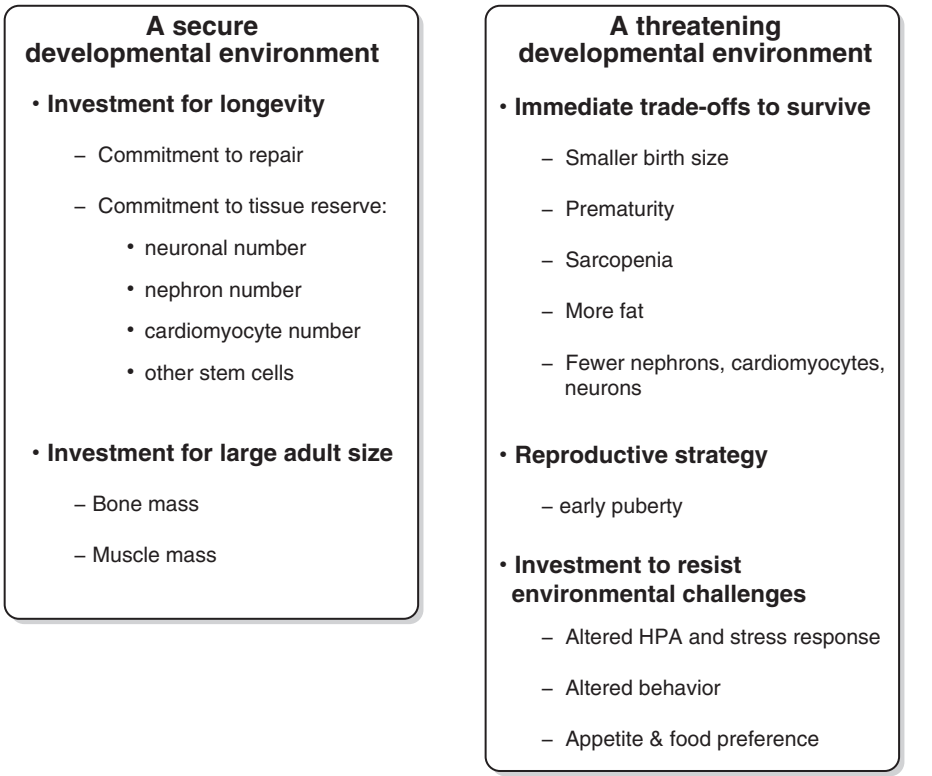

FIGURE 8. Components of lifecourse strategies induced during development, derived from a range of animal species in relation to integrated adaptive responses that increase Darwinian fitness, but argued to be applicable to humans. [Modified from Gluckman et al. (217). Copyright 2007 John Wiley and Sons.]

however, the effect was greatly magnified in primi- versus multiparous pregnancies. Other studies have also shown both greater obesity, impaired insulin sensitivity, and higher blood pressure (16) in first-born children. This accords with the mismatch theory as the processes of maternal constraint would be expected to be greater in first-born children and therefore the potential for an inappropriate PAR is larger. Similar considerations may apply to twins and multiple conceptions (291) and to preterm infants (265). They may also apply in a complex way to maternal age (567). Evidence is now accumulating for a greater NCD risk in offspring born post-term (43). It is possible that this also represents the consequence of the fetus outgrowing its placenta or that function declines in the post-term placenta (617) as apoptosis is reported in such placentas (553).

In many high-income countries, maternal age at first pregnancy is increasing as couples have access to contraception and wish to establish careers or have a range of experience before starting a family. The relation between increasing maternal age and adverse pregnancy outcomes has been investigated (342). Older women are more likely to have declining fertility and to seek ART (see sect. VG). There is also some evidence that risk of diabetes in the offspring increases with maternal age (567), but this has not been examined extensively.

C. Role of the Placenta

Human placental function differs in some respects from that of the more extensively studied animal species such as the sheep or mouse, e.g., with respect to amino acid transport (63, 354) and the operation of novel exchange mechanisms (98, 99) or specific gene transcripts (104). The functional capacity of the placenta, affected by its size (24), surface area for exchange (e.g., Ref. 539), and perfusion (87) are major determinants of fetal nutrient provision, and this varies across the normal range. From a gross anatomical point of view, the placenta is fully formed before the peak in fetal growth and nutrient demand (508). A range of factors affect placental development from early in gestation, the concept of the placental exposome (353). As for fetal development, the role of oxidative and nitrosative stress in early placental development, particularly after the rise in intervillous space perfusion at about 12 wk gestation in the human, may be critical to subsequent structure and function (77). In late gestation, there is currently interest in whether increasing placental perfusion may promote fetal growth in growth-restricted fetuses; in animal models, the administration of an NO donor promotes such growth (137), and increased VEGF expression using an adenovirus vector promotes fetal growth, although whether this is via effects on uterine perfusion is not clear (83).

The placenta is sensitive to fetal demands, but its responses are also conditioned by maternal factors. In the mouse, the paternally imprinted insulin-like growth factor 2 (IGF2) P0 transcript is responsible for upregulating placental nutrient transport and thus fetal growth, a process limited by maternally driven IGF clearance (104). Placentas deficient in the placental specific IGF2 P0 transcript produce effects on the responses to nutritional challenges in pregnancy, for example, in being less able than wild-type placentas to upregulate amino acid transport (532). Thus a mismatch between fetal nutrient demand and placental supply, for example, in the capacity of the small *Igf2P0* placenta to supply nutrients at a sufficient rate to meet the demands for nutrients for growth by the normal fetus, can have long-term effects on the offspring; this has recently been shown for increased anxiety behavior responses (404).

Recent studies have shown that placental function is affected by caloric restriction (93), obesogenic diet (533), and dexamethasone administration (609), all factors known to produce a range of effects on the offspring.

Although the majority of work has been conducted on amino acid transport, studies are now ongoing for the placental handling of fatty acids (356) and calcium transport in relation to bone mineral accrual in the fetus (383) and its later consequences for risks of osteoporosis and fracture (105, 106), again with links to maternal nutrition.

Small increases in maternal and thus fetal glucose would be expected to increase fetal growth if this situation represented the relaxation of maternal constraint, and mild hyperglycemia produces a small increase in lean body as well as fat mass (132, 153, 574, 644). This may be viewed as potentially adaptive, as in infancy relative adiposity provides metabolic reserves for thermogenesis, critical organ function, and growth in the event of inadequate maternal care (331). In addition, it appears that epigenetic control of glucose transport (436) and adiponectin expression in the placenta is related to maternal blood glucose across the range from normal to pathological (60), indicating a role in regulating placental transport and growth of the fetus in relation to maternal nutrient status. Changes in the placental epigenome are now being studied systematically in relation to gestational age as well as maternal and environmental factors (437) and in twins (449).

The placenta plays a role in regulating the response of the fetus to glucocorticoids and in integrating the nutritional response with a hormonal response (418), initially as an adaptive response (**FIGURE 9**; Ref. 418).

The balance of enzymes that convert glucocorticoids to the active form cortisol (corticosterone in the rat), i.e., 11βHSD1, or which inactivate it, 11βHSD2, controls the fetal exposure to glucocorticoids of maternal origin (527). There are parallels here with the role of these enzymes in protecting the mineralocorticoid receptor of the kidney and

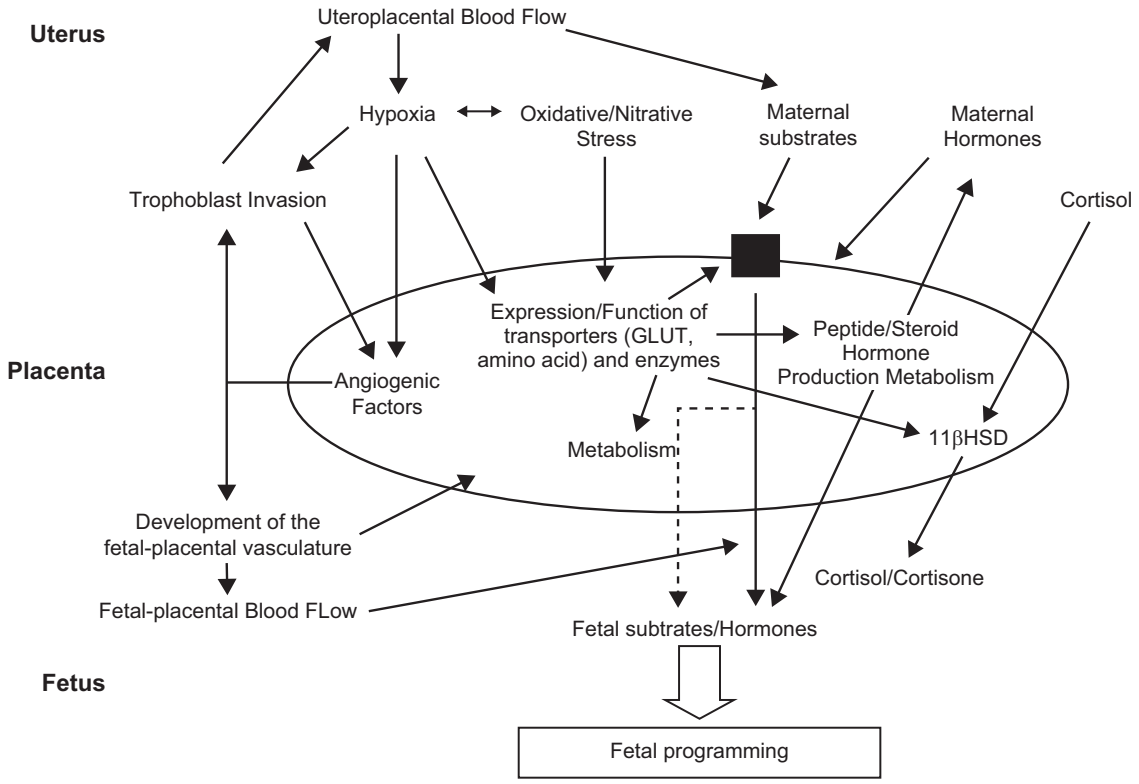

FIGURE 9. Placental adaptive responses. [From Myatt (418). Copyright 2006 John Wiley and Sons.]

other tissues from activation by glucocorticoids (529). In rodents, experimental inactivation of the 11βHSD2 enzyme by carbonoxalone produces effects on the offspring including elevated blood pressure and hyperglycemia (367). Interestingly, glycorrhizin is a natural product in licorice with similar properties, and studies in Finland, where licorice is widely consumed, have shown that eating it in large amounts in pregnancy produces effects on the timing of labor and offspring HPA axis function (485). Poor maternal nutrition in rats affects the concentrations of placental 11βHSD2, thus potentially exposing the fetus to higher glucocorticoid levels (339).

Within the normal range, the adaptive responses of the placenta will contribute to the PARs of the fetus. Outside the normal range, pregnancy conditions such as preeclampsia or gestational diabetes have pronounced effects on placental function (135, 492). These in turn produce substantial effects on the factors that are likely to operate in the nonadaptive range. The mechanisms involved include oxidative stress and inflammatory pathways (484). There are now a range of studies reporting the epigenetic effects of gestational diabetes on specific gene pathways including those controlling growth and metabolism (511). Ongoing studies are examining the extent to which maternal body composition, including obesity, muscle mass, and diet, affects placental development and function (89, 355, 440). There are some data showing altered methylation of a cardiovascular disease-associated gene, *ABCA1*, in placenta and cord blood samples from women diagnosed with impaired glucose tolerance during pregnancy (268).

D. Conflicting Demands

It has been argued that effects of environment on the mother-offspring dyad have more adaptive significance for the mother than for her offspring (643) because, in the face of conflict for resources such as nutrition, it makes more sense teleologically for the mother to prevail; she has passed a Darwinian fitness test in reproducing, whilst the fitness of her offspring is untested, and her survival will allow her to capitalize on her fitness by reproducing again. While this argument may apply in rapidly reproducing species which produce large numbers of offspring (382a), there is no evidence for it in the human. Indeed, considerations of life history theory make it an unlikely strategy for a slow reproducing species where there is large maternal investment in each pregnancy (207), all of which will be wasted if the offspring does not survive.

Moreover, available data for human populations do not support the suggestion from conflict theory that maternal interests should be prioritized over those of her offspring at times when resources are limited. Fecundity in humans is only modestly reduced during famine (566), and under conditions of severe undernutrition, there is only a small reduction in fetal growth (506). Even lactation, which places

substantial nutritional demands on the mother, continues during severe famine. Conversely, as discussed earlier, fetal conditioning has long-term effects and occurs in the absence of any obvious fetal compromise (185), and this similarly counters the maternal advantage argument (226). Fitness is not easy to measure in humans, as we have great control over our reproduction and nurture even weaker members of our species; despite this, a model which involves "détente" between mother and offspring seems more appropriate, as it puts into context both maternal needs and the opportunities which an exchange of information between mother and offspring offer for the subsequent fitness of the latter.

E. Transduction of Cues

There are two, not mutually exclusive, ways of looking at the possible cues on which the developing embryo, fetus, and neonate can base their predictions of the future. One is to argue that the most effective cues, or reliable markers, are those aspects of the environment on which survival and fitness depend, i.e., oxygen tension, nutrition, water availability, and so on. There are many examples of how such cues operate, from the fetal responses to hypoxia (234) or hyperoxia (51), micronutrients (390), macronutrients (225), and the responses of species such as amphibians to thermal stress and dehydration (49).

The second way concerns the advantage of signaling indirectly aspects of the environment on which fitness depends, e.g., population density (392), predator numbers (58), or other stress levels. Interest here is focused on the use of endocrine signals that might provide adaptive cues. Species that are seasonal breeders also utilize cues related to day length (348) via transplacental melatonin signaling. Anxiety levels or the need for vigilance in escaping predation are thought to be signaled via glucocorticoids produced by the maternal adrenal gland and crossing the placenta or being present in the milk. In rodents, stress induced in pregnancy or infancy leads to altered behavior, stress responses, and cardiovascular function in adult offspring (129, 277). In humans, there are several studies showing an association between maternal anxiety or stress level in pregnancy and cognitive, behavioral, or emotional problems in the child (249, 602). There are even possible effects on ageing mediated by shortening of telomere length (163). There has been recent discussion of the adaptive significance of such processes in humans (537), and del Giudice et al. (134) have proposed the adaptive calibration model by which the stress system coordinates and encodes, as well as regulates, the offspring's response to a variety of physical and psychosocial challenges and conditions, with implications for later adolescent behavior (161), for example.

At the level of tissue and organ growth, physiological control is exerted through the action of growth factors, particularly the insulin-like growth factors (IGFs) (208). Their actions can be modulated in turn by levels of IGF binding proteins in the plasma (37), which also convey them to the cell surface to interact with IGF receptors. Fetal development is much less dependent on growth hormone than on IGF. The mechanisms of action of all these agents are complex, however, including effects not only on mitosis but on blood flow, glucose uptake, carbohydrate and lipid metabolism, and oxidative stress.

Moving down the physiological chain of mechanistic effects, there is a large body of work concerning oxidative and nitrosative stress. The balance between pro- and antioxidant species at any site depends on the level of oxygenation (in turn dependent on blood flow and capillary Po_2), tissue metabolism, and the provision of antioxidant protective mechanisms (122, 199). Because of its pivotal role in integrating stimulus and response at the cellular level, oxidative stress is a fundamental regulator of development and has been proposed as a process which "sculpts" development. $O_2^{\cdot -}$ and nitric oxide (NO) interact to modulate peripheral vascular responses to hypoxia in the fetus (414, 588), effects which can be altered by antioxidant treatment (257, 305, 587) or statins (160, 594). In addition to hypoxia, under- and overnutrition, infection, and exposure to exogenous glucocorticoids all produce an increased level of oxidative stress (122, 199, 461, 542, 589). There are a range of studies which show effects on tissues, especially the vasculature (280, 502, 593, 624, 678), but there are also effects on the heart (2, 258, 432, 627) and on brain development (590). The mechanism by which oxidative stress operates at the cellular level in these organs is now beginning to be elucidated. In the heart, the reduced expression of the cardioprotective gene protein kinase C (PKC)-epsilon in hypoxia is prevented by inhibition of DNA methylation (460, 461) or by *N*-acetyl-cysteine. The process may be initiated by norepinephrine via activation of Nox1-dependent reactive oxygen species generation (665).

Circadian rhythms and metabolic control processes interact in both physiological and pathophysiological states, as shown by the perturbations in feeding and activity patterns in rodents whose dams were fed unbalanced diets (66) and the role of clock genes in diabetes (381). There may be links with oxidative stress here, as the role of Rev-erb in adipogenesis is affected by heme, which in turn is modulated by oxidative stress (322). The role of oxidative stress in conditions such as diabetes is not clear however; for example, it has been hypothesized that the beneficial role of exercise is to promote oxidative stress that stabilizes protein structure (635).

Obesity is associated with inflammation; higher levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP); and oxidative stress (128, 486), and this can have adverse effects on the placenta (448) and

cardiovascular system of the offspring (627). The inflammatory process in a range of tissues, including adipose tissue, may involve infiltration and polarization of macrophages from M1 to M2 forms (373) which are associated with a proinflammatory state and the secretion of inflammatory cytokines (642).

As for the effects of hypoxia, the role of oxidative stress associated with obesity is shown by the protective effects on the offspring of maternal treatment with quercetin (362), vitamin E (420), or a combination of antioxidants (531).

Oxidative stress is also linked to sirtuin-mediated ageing processes such as telomere shortening, which can be conditioned by the developmental environment (292). SIRT-1 is a histone deacetylase that senses cellular energy levels via the NAD/NADH ratio (52), so it can mediate epigenetic effects of nutrient provision and also metabolism. This pathway, leading to changes in peroxisomal proliferator-γ coactivator (PGC) 1α, is linked to fat deposition in the liver of offspring of rat dams globally undernourished during pregnancy (653). Changes in PGC-1α, ER-α, ERR-α, and HNF-4α can also be induced in rat offspring by feeding their dams a methyl donor-deficient diet in pregnancy (477). This condition resembles nonalcoholic fatty liver disease (NAFLD) in humans and can also be produced in rodents by feeding a high-fat diet in pregnancy or postnatally (68). A high-fat/high-sugar diet fed to dams produces epigenetic changes in the regulation of the glycerol-3-phosphate acyltransferase 1 gene, which is activated by sterol regulatory element-binding protein-1c (SREBP-1c), a transcription factor that acts as a master regulator of lipogenesis (154). Further evidence for the role of epigenetic processes in this pathway in humans is that methylation of specific CpGs in the promoter region of PGC-1α in the peripheral blood leukocytes of children aged 5–7 yr predicts their level of adiposity at age 14 yr (97). These processes may remain dynamic throughout life, as PGC-1α levels change rapidly following exercise in skeletal muscle, possibly linked to mitochondrial biogenesis (17).

Other processes by which maternal obesity may induce effects on the offspring can result from the elevated levels of insulin and glucose in the offspring's blood. Insulin is associated with increased growth (261), and hyperglycemia can have effects on the fetal heart (107).

There may also be elevations in RAS activity and in sympathetic activity (517). These interact with leptin to induce changes in appetite. Prolonged sympathetic nervous system activation can desensitize β receptors in the heart, for example, initiating a series of processes leading to cardiomyocyte apoptosis (320). Again epigenetic repression of PKC-ε, induced by NO, may involve Nox1-dependent ROS production (665).

Because the two types of cues referred to above are not mutually exclusive, it is possible that they overlap. The evolution of the glucocorticoid system may have arisen through the advantage of a stereotypical response to an environmental challenge, for example, from a noxious stimulus, predator attack, or overcrowding (422). In mammals, the glucocorticoid system has a role in response to other challenges such as unbalanced maternal nutrition (528), hypoxia (200), or infection (231). Glucocorticoids are involved in the maturation of many fetal organ systems (175), preparation for birth (363), and the control of fetal growth (174). They can induce a very useful set of responses that prepare the offspring for the predicted future and may be induced from early gestation. Thus, in the sheep while mild undernutrition in the periconceptional period and early gestation prolongs the duration of gestation (102), more severe undernutrition shortens gestation (54).

For both of these types of cue, attention has largely been focused on the parents in signaling aspects of their contemporary environment. However, another feature of the signaling may be of environmental history over a longer period, integrating this into a cue that drives the optimal adaptive strategy for the species (331). Indeed, some level of inertia in the system seems inevitable so that the fetus responds to either sustained or repeated stimuli. This has not been extensively investigated. However, in the studies of the effects of intrauterine growth retardation on epigenetic changes in pancreatic β cell Pdx1 (459), it was noted that histone changes occurred first and were later consolidated by more stable DNA methylation changes. It may be that the more labile histone system responds first, and it is only with persistent or repeated cues that a more stable change in epigenetic state is induced.

V. PATHOPHYSIOLOGICAL (NONADAPTIVE) PATHWAYS IN DOHaD

These are summarized in **FIGURE 10**.

A. Maternal Overnutrition, Obesity, and Excessive Gestational Weight Gain

A perspective derived from the principles of evolutionary medicine (202) is useful in that it highlights the importance of evolutionary novelty as a pathway to disease risk. The underlying concept is that humans are unlikely to have evolved protective mechanisms against novel challenges: the modern western diet can be seen as one such challenge.

As for the adaptive processes discussed above, insights into nonadaptive processes have largely come from animal studies and then been applied to humans. Most studies involved overnutrition, especially the use of a high-fat, a cafeteria, or a high-fructose diet (611). There have been some studies

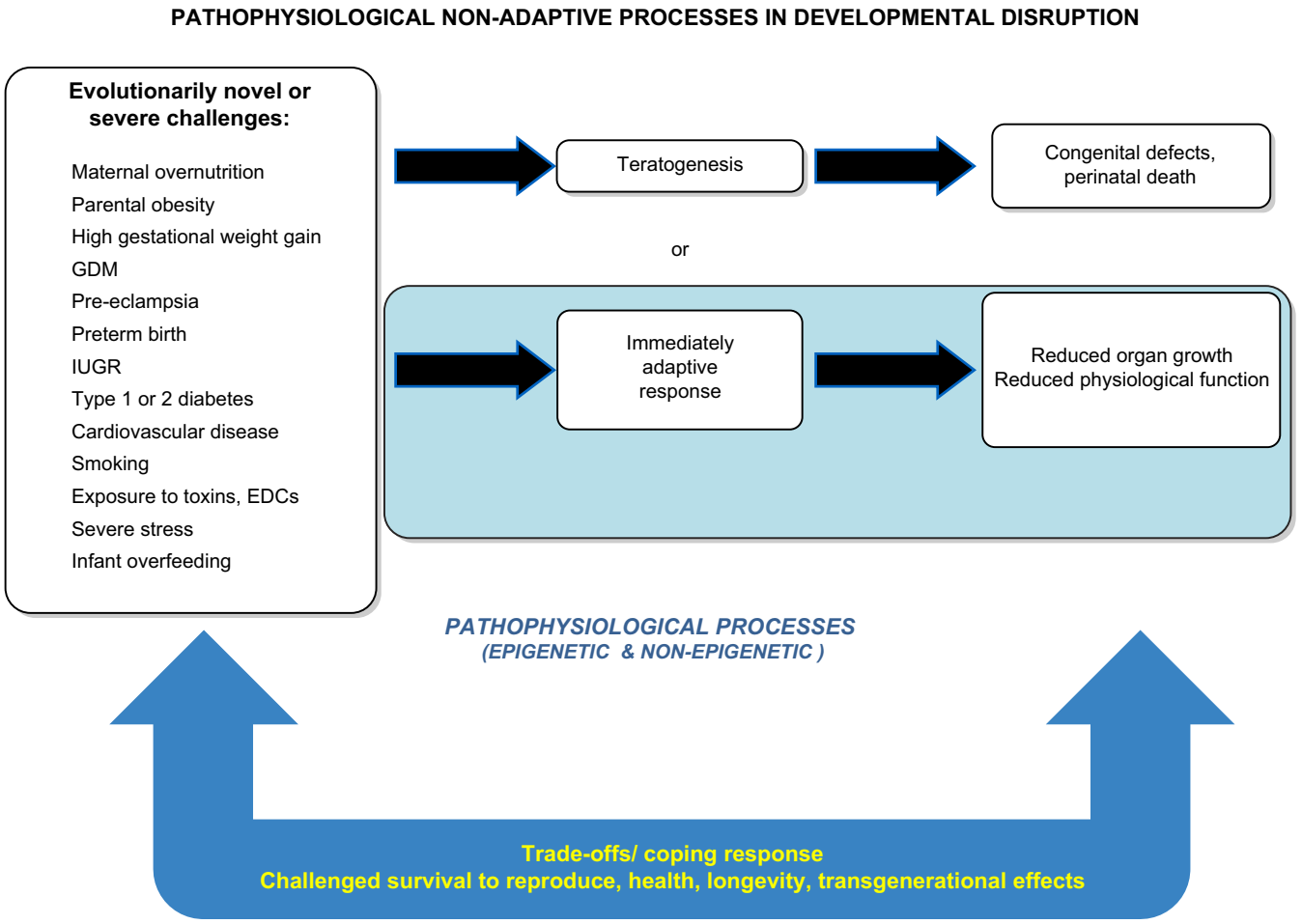

FIGURE 10. Pathophysiological nonadaptive processes involved in developmental disruption.

using non-human primates, in which feeding a highly palatable diet to produce obesity in the mother induces placental effects and changes in fetal growth (166) and differential expression of cardiac microRNAs (378), and feeding a high-fat diet across generations produces aspects of the metabolic syndrome in the offspring (165). Other studies have used sheep given the similarities to humans in degree of maturity at birth. While sheep do not readily consume a cafeteria diet, dietary-induced obesity in the ewe induces detrimental effects on the cardiac function of their lambs (271, 627).

The majority of studies have been performed in rodents. A high-fat diet during pregnancy produces adiposity, metabolic and vascular effects in adult offspring, changes in aortic and cardiac lipid composition (159, 194, 315, 549, 586, 676), and also early signs of fatty liver disease (159, 442), reminiscent of the NAFLD now thought to be an early marker of metabolic syndrome. Changes in mitochondrial function are present (68). There is also evidence for left ventricular hypertrophy in this model and for the disruption of the cyclin signaling pathway (14), which may also include mitochondrial effects and epigenetic changes (145). Although many of these studies involved exposure of the dam to a high-fat diet only during pregnancy/lactation, longer-term exposure which mimics a human nutritional transition produces similar effects (159, 516). Interestingly there is evidence that prenatal undernutrition followed by dietary-induced obesity in rodents advances the timing of puberty in their offspring (550), a feature of transitional human societies, especially migrants (457).

Most recently, it has been demonstrated that, as for folate supplementation of the maternal low-protein diet, methyl donor supplementation blocks the epigenetic effects of a maternal high-fat diet on offspring prefrontal cortex, accompanied by effects on weight gain and food preference (82). In the vasculature the effects of the quantity and the nature of maternal dietary fat on offspring vascular function involve epigenetically mediated changes in FADS1 leading to changes in prostanoid production (309). Ectopic fat accumulation is reported in many sites in the metabolic syndrome, and such deposition even occurs in bone (340). Some effects on offspring are mimicked by exposure of the pregnant dam to endocrine disruptors (79, 230), and there are effects on circadian rhythms as well as stress responses (see Ref. 78).

There is much evidence that maternal obesity and/or excessive weight gain in pregnancy is associated with offspring adiposity. This seems likely to have a nonadaptive basis as extreme maternal body size and nutrition is likely to have been relatively rare in our prehistory (375). Once again it is clear that the transmission of phenotype from mother to offspring occurs across a wide range, both for maternal weight gain in pregnancy and for maternal blood glucose. At the extreme, fetal macrosomia is associated with a greater risk of shoulder dystocia, obstructed labor and, in the absence of modern medicine, stillbirth, genitourinary fistula, and possible maternal death (62). Such problems contribute substantially to maternal and fetal deaths globally. But such processes have not apparently been subject completely to negative selection through evolution, suggesting they have been traded-off against the advantages of bipedalism and large head size in our evolutionary past. Although pregnancy produces relative maternal insulin resistance, which promotes glucose transfer to the fetus (335), incidence of maternal obesity, high pregnancy weight gain, and gestational diabetes would presumably have been low in hominid evolution where high glycemic index foods were not available. In support of this, and as discussed earlier, it appears that there is no transport maximum for glucose in the human placenta, as there is for many other nutrients (126). Maternal obesity is likely to induce fetal hyperinsulinemia (86) leading to greater fetal adipogenesis (see below), although effects via other systems studied in animals as discussed above have yet to be undertaken in humans.

There is now accumulating evidence from several cohort studies that maternal obesity and excessive gestational weight gain are associated with increased risk of asthma and atopic disease in the offspring (248, 349, 469). Because the effect is amplified by infant weight gain (371), it gives another example of the consequences of mismatch (469), so arguably they are not inherently nonadaptive. The role of epigenetic processes in producing effects on immune function (384) provides clues to underlying mechanisms that could be viewed as physiological, in shifting the balance of innate versus acquired immune function. However, the exacerbating effects of unbalanced maternal diet, smoking, or exposure to toxins or pollutants indicate their pathophysiological nature.

B. Infant Overfeeding

Infant overfeeding is essentially an evolutionary novelty made possible by infant formula products. Children showing rapid growth in early infancy or in early childhood are at greater risk of adulthood cardiovascular and metabolic disease, especially if they were small at birth (164, 172). In premature infants who are fed with infant formula, rapid growth is associated with risk factors for cardiovascular disease in adolescence (545). Rapid weight gain in infancy is associated with childhood (447, 450, 569) and adolescent (198) obesity and with childhood cardiovascular dysfunction (184). Formula feeding is widely believed to produce rapid growth in early infancy (13), although the validity of these data has been challenged (327). Meta-analysis shows a reduced incidence of childhood or adulthood obesity in breast- versus formula-fed infants (279). The protective effects of breast feeding may extend to allergy/atopy (444, 525) and cardiorespiratory function (212). However, the protection against obesity afforded by breast feeding remains controversial (520) and may be explained by different effects of breast feeding in normal compared with overweight children (29). A further issue which merits consideration is the composition of the formula, especially its protein content (556).

C. Preeclampsia and Hypertension in Pregnancy

There is a limited amount of evidence that the offspring of preeclamptic pregnancies have elevated blood pressure and BMI (123) and also greater risk of later cardiovascular disease and stroke (124). Such offspring usually have lower birthweight and are often preterm, although there appears to be an effect of preeclampsia on offspring cardiovascular and metabolic risk independent of gestational age. The relative contributions of reduced growth, undernutrition, hypoxia, as well as anti-angiogenic and immune factors to the effects on the offspring are not known. In addition, there may be effects related to maternal hypertension and preterm birth (345) (see below).

D. Preterm Birth

A range of studies have shown an association between preterm birth and higher risk of cardiovascular disease, insulin resistance, and T2D in the offspring as children or adults (265, 278, 351, 387, 471). The assumption has been that this is largely due to the small size of the infant at birth as shown from a large historical cohort (57). We have discussed above why this explanation does not seem adequate. A recent study (626) has, however, separated out these components in a prospective cohort in which births were classified as early preterm (<34 wk), late preterm (34–36 wk), early term (37–38 wk), and full term (=39 wk gestation). Wang et al. (626) confirmed the association between plasma insulin level in children and their size at birth (SGA vs. AGA) but also found an independent association with gestational age in their four categories. This persisted after correcting for ethnicity, maternal smoking, BMI prepregnancy, parity, pre- and gestational diabetes, and also infant's sex and birthweight for gestational age. Moreover, the plasma insulin levels at birth tracked into those in the children in early childhood (up to 6.5 yr old). The study thus provides evidence for prenatal factors conditioning postnatal insulin sensitivity, although as yet it is not known

how this is mediated, or whether it depends on the conditions leading to preterm delivery. It does however raise the question of whether late (and possibly some early) preterm birth should be viewed as part of an adaptive response; the consequences of extremely preterm birth and very low birthweight (269) are likely to be an IAR.

E. Gestational Diabetes Mellitus

Pregnancy is associated with some degree of insulin resistance due to the actions of placental lactogen (306) and growth hormone (21). This is thought to induce a homeorhetic change in maternal physiology to favor glucose transfer to the fetus. But as discussed above, there is no effective barrier to placental glucose transfer and thus, if maternal glucose rises excessively so will fetal glucose, leading to fetal hyperinsulinemia and excess somatic and particularly adipose growth. There are also distinct epigenetic effects (157). The consequences if untreated can be dystocia and fetal and maternal death; thus we have argued that gestational diabetes mellitus (GDM) is an evolutionary novelty and that the consequences for the next generation have nonadaptive origin.

GDM is more common in obese women and in those with a preexisting predisposition to insulin resistance. Women of lower birth weight themselves have a greater risk of developing GDM, reflecting their already conditioned predisposition to insulin resistance (153), whilst genetic variants associated with T2D are also associated with increased risk of GDM (324, 341). The evolutionarily novel situation of abundant nutrition and low levels of physical activity plays an important role in perpetuating a vicious cycle of disease. New criteria for defining GDM (402) have now produced a dramatic upward revision in the number of women suffering from this condition, the prevalence of which is approaching 30% in some parts of the world (244), especially in populations which have gone through rapid socioeconomic and nutritional transition such as parts of Asia (263), the Middle East, and some Pacific islands (629). Indeed, in a Canadian First Nation Peoples population, the proportion of T2D incidence explicable in terms of GDM in the previous generation was 30% (148, 671).

Apart from GDM, the link between maternal diabetes and risk of metabolic syndrome in the offspring is well established (see Ref. 648). Epidemiological studies show greater risk of diabetes in children of type 1 or 2 diabetic mothers (307, 347, 465, 555). This risk of diabetes is greater in children born after the mother is diagnosed with diabetes, presumably due to prenatal exposure to hyperglycemia (116). These offspring are also more likely to develop diabetes at a younger age (466). Recent studies show that even individuals exposed to mild hyperglycemia prenatally have greater adiposity and risk of later diabetes and cardiometabolic disease (237, 578), and there is evidence from a meta-analysis that GDM is associated with higher blood pressure in offspring (1).

F. Caesarean Delivery

There is a small but clear increased risk of diabetes in offspring born by caesarean section (81), which is of course an evolutionary novelty. One possible mechanism concerns the gut microbiota, which colonize the infant gut from the maternal vaginal and gastrointestinal tracts and which differs according to the mode of delivery (7). Interestingly, use of antibiotics in the first six months of life in a large Danish cohort of mother-child dyads is associated with childhood overweight in offspring of normal weight, but not of obese, mothers perhaps as a result of effects on the gut microbiota (7).

G. Assisted Reproductive Technologies

An issue that is now receiving much attention concerns the apparently greater risk of NCDs in offspring conceived by ART (250), also an evolutionary novelty. It is of note that the effects seem to be independent of the medical or other reasons for the couple seeking fertility treatment. Animal studies show that short-term culture of the early embryo can induce NCD risk-related phenotypes (632), and this appears to be the case even for effects of maternal dietary manipulation during the period of oocyte maturation (634). In humans, the hormonal treatments used to induce ovulation prior to ART may have longer-term effects. Some of these effects may be mediated by epigenetic processes (604).

H. Effects of Drugs

Relatively few drugs are prescribed in pregnancy, and the teratogenic **(TABLE 1)** effects of thalidomide, prescribed to control hyperemesis, are well-known (391). There has been considerable research on the effects of antenatal steroids given to women with threatened premature delivery, to accelerate fetal lung maturation. Exogenous glucocortioids such as dexamethasone, given during a critical period of early development, are detrimental to cardiovascular and renal function and to glucose homeostasis in several species (140, 388, 528) and affect neurocognitive function in juvenile non-human primates (503). Most obstetricians now advocate use of only a single dose of glucocorticoid, although even this has been reported to be associated with elevated blood pressure in some children (405). Young adults exposed to a single course of betamethasone in utero showed no psychological or health-related quality of life effects (118), although there were small effects on glucose tolerance (119). The most recent evidence comes from a Cochrane review of 10 trials, which concluded that there is benefit of multiple versus single doses for neonatal outcomes, without any evidence of either significant benefit or

harm at follow-up (396). At present, it appears that the gain from administration of antenatal corticosteroids, preferably as a single dose, outweighs the potential disadvantage.

I. Smoking, Toxins, and Endocrine Disruptor Chemicals

Smoking is well-known to produce a range of effects on the fetus, including overall growth restriction (419) and effects on the development of many organs and systems. There are similar concerns about a range of toxins to which the woman and her fetus or suckling infant may be exposed, including those produced by bacteria (288) or fungi (e.g., Ref. 490) in foodstuffs. The detrimental effects of maternal viral or bacterial infection are also well-known, and possible detrimental effects on the fetus associated with their treatment raise other issues (15, 67) as are those of infestation with parasites such as *Plasmodium falciparum*, *Schistosoma*, or tapeworm (435, 557, 610). There is great concern about alcohol consumption in pregnancy, and although the recommended safe limit is low, only high levels of consumption are associated with fetal alcohol syndrome and permanent effects on the offspring (300). Cocaine and other drugs are well-known to have a range of effects on the fetus (41), with consequences for cardiometabolic, neural, and behavioral development in the child.

In many industrial and heavily populated urban areas, exposure to heavy metals, dyes, and airborne microparticles is of concern (189, 561, 597). A well-known example of detrimental effects is the contamination of rice oil with PCBs in Japan in 1968, leading to the hyperpigmentation of Yusho disease and low birth weight (597). Similar concerns relate to exposure to pesticides and other agrichemicals in some rural settings (255). The concentrations of such compounds build up in the mother's body over time, and this may explain the relation between effects on the offspring and birth order (314).

The most dramatic effects of such agents are teratological or increased risk of cancer, especially of the reproductive system, in the offspring (558). Such effects are clearly disruptive of development. Some of these agents produce effects on endocrine (45) and nuclear receptor (346) function, hence the term *endocrine disruptor chemicals* (EDCs). In some instances they may act via effects on epigenetic control systems regulating endocrine function (548), and this is an area of intense research and debate. By acting in this way, they can induce greater risk of NCDs without producing an overt disruption of development per se. In animals, prenatal exposure to compounds such as bisphenol A can produce effects on offspring adiposity and cardiometabolic control (79, 615). As the effects of an EDC in isolation can be subtle, and as even low environmental levels of several EDCs can act together to affect development, more research on their long-term health effects is needed. A recent report from the Royal College of Obstetricians and Gynaecologists on possible effects during pregnancy (491) seems to demonstrate the importance of the precautionary principle in this regard, but may cause unnecessary anxiety in an area for which evidence is not clear.

VI. BROADER IMPLICATIONS OF THE DOHaD CONCEPT

A. Evolutionary Developmental Biology

For natural selection to produce an evolutionary modification, an environmental change, if sustained, must lead to an alteration in genotype that is both adaptive and heritable. But the principles of developmental plasticity suggest that initially these responses may be transient and induced by epigenetic processes. The issue then is whether such induced epigenetic changes could influence the likelihood of genomic change (296) and how these phenotypic changes get fixed into the genotype by the processes of genetic assimilation **(TABLE 1)** (647). Two models of genetic assimilation were proposed by Waddington: the first was simply the uncovering of covert genetic variation and selection against modifying genes which suppressed the exhibition of the desired gene, and the second was that such "fixation" occurs by random mutation. More recently, the possibility of a bias in the pattern of mutation has been proposed based on the greater mutability of methylated cytosine, which may spontaneously convert to thymine (467). The evidence for this possibility has been reviewed elsewhere (32, 33).

Much has been written on the evolution of adaptive developmental plasticity (32, 196, 282, 468, 647), but its implications have not been fully reconciled with classical evolutionary theory. The concepts described above suggest the possibility that while adaptive developmental variants are induced during transient environmental change, and preserved in fluctuating environments, they might become fixed during sustained environmental change. This would provide a new model by which epigenetically initiated but biased mutation could lead to developmentally driven evolutionary change and reconcile evolutionary developmental biology with classical evolutionary biology. Indeed, evidence for such transition is found in cancer cells (233), which can be seen as a form of evolution occurring at a cellular clone level. There are now a range of reports which suggest the operation of such processes, although they are beyond the scope of this review (80, 103, 218, 296, 301, 359, 505, 675, but see Refs. 276, 625).

These concepts have many attractive, albeit unproven, aspects. First they explain how an adaptive process can occur rapidly enough to meet an environmental challenge. In addition, they allow such a process to be induced in several individuals in a population simultaneously. They allow the process to be "tuned" to relevant parts of the genome where

the probability of mutation is greater at the site of epigenetic change. This is parsimonious and also protects against the potentially harmful effects of merely random mutations. Lastly, they allow the process of genetic assimilation to be related to the environmental change itself. Because the epigenetic effect increases the likelihood of a mutation, such assimilation would be more likely to occur if the environmental change is sustained over several generations. If that change is transient, the reversibility of the epigenetic processes will permit the phenotype to return to a previous state with no genetic modifications.

B. Biomarkers of Risk

The epidemiological studies that focused on lower birth weight raised the issue of whether phenotypic characteristics could be used to predict individuals at particular risk of later NCDs. However, the usefulness of any biomarker depends on its sensitivity and specificity. The association of both low birth weight and high birth weight with greater risk makes the use of this particular characteristic problematic as the adaptive and nonadapative pathways, which are somewhat reflected in birth weight, involve different ultimate and proximate mechanisms that may confer different risks of later disease. In addition, there are multiple pathways to a specific birth weight: a low-birth-weight fetus at term may result from a slow growth trajectory throughout gestation, a rapid trajectory followed by a period of greater constraint, or simply reflect mild prematurity. It is likely that the longer-term consequences of these developmental trajectories may vary.

Even though measurement of the trajectory of fetal growth throughout gestation is feasible, it is not routinely undertaken. Postnatal growth is, however, routinely measured. This allows such growth to be used as a biomarker of later risk, e.g., it has been suggested that crossing of two growth centiles in the first 6 mo after birth is associated with obesity in children aged 3 yr (585). The problem with the use of such measures is that, as with birth weight, growth trajectory is more a measure of the integrated responses of the infant to a complex set of environmental circumstances, an end result of effects on metabolism, appetite, immune function, emotional, and other influences such as parental bonding, etc., so again infants with similar growth trajectories can have different combinations of these processes in operation and so different later risk.

The broader question thus concerns the nature of any biomarker. Is it a component of a mechanistic pathway from challenge to pathological state, or rather a measure of an epiphenomenon that has occurred in parallel? Very often the answer to this question is not known. Surrogate or proxy biomarkers for a process are not necessarily inferior if the effects on them are large and consistent, for example, the use of cholesterol as a marker of cardiovascular disease risk.

Developmental epigenetics may provide new opportunities and certainly provide the capacity to estimate the relative importance of developmental conditioning to disease risk. Epigenetic marks measured at birth cannot only give a measure of the response which the embryo and fetus made to developmental environment, but they can also provide measures of the setting of homeostatic systems, i.e., the conditioning, which will regulate responses to later challenges. For example, the degree of methylation of one CpG associated with the RXRA gene is related both to aspects of maternal diet in early pregnancy and to child's fat mass 6–9 yr later (229). In this example, the effect size is large, with the level of methylation accounting for 25% or more of the variation in fat mass of the child, larger than any other early life marker of lean or fat mass or current estimates of the fixed genomic contribution to obesity. Confirmation of this concept has come from the work of others using cord blood samples (464, 494) and for the Southampton cohort with child's bone density as an outcome (252).

These studies used a combination of array discovery techniques to give a measure of the genomic regions in which epigenetic changes may be manifest, followed by more in-depth analysis of candidate regions. In addition, they examined whether the epigenetic changes occur at sites known to possess SNPs relevant to disease. As this field progresses, the interaction between fixed genetic variants and epigenetic changes is likely to become more apparent (42).

Finally, biomarkers may or may not be useful as measures of the efficacy of an intervention. This may depend on whether they are reversible or not, usually thus on whether they contribute to part of the causative process or are a proxy for it.

C. Possibilities for Interventions: Proof of Principle in Animals, Opportunities for Humans

Several groups have explored the concept that an intervention given during development, either to the mother or her offspring, can reduce or prevent the detrimental effects of dietary mismatch on her offspring. Interventions that have been tested are dietary, endocrine, or pharmacological. A dietary intervention with folic acid or glycine, given to the pregnant dam at the same time as the unbalanced diet, prevented the effects on the epigenome in the offspring (82), with similar effects on growth and metabolic responses of the offspring (71) and on the transcriptome (366). The effects of folate can also be seen during the adolescent period in the rat (72), which is interesting as its protective effects are mediated after administration of the unbalanced diet of the dam which induced the response. This effect has been explored in more detail for the PEPCK gene (266).

Leptin administration to the newborn rat prevents the hyperphagia, adiposity, and other detrimental effects of mismatch produced by global undernourishment of the dam followed by feeding the pups a high-fat diet (613). It also reversed effects of maternal undernutrition on the expression of candidate genes and associated epigenetic processes (222). There are more recent studies on the effects of neonatal leptin (515), exendin-4 (190), including epigenetic effects (472), and growth hormone (232).

Oxidative stress has been shown to play a role in producing effects of maternal low-protein diets on the peripheral vasculature of the offspring and the potential for antioxidants to reverse this has been explored (502, 593). Because effects can be passed to the F_2 generation via effects on the uterine vasculature of the pregnant dam offspring, this gives a further avenue for intervention, explored using an angiotensin receptor antagonist to promote such vascular function (514). Administration of a statin to the offspring can prevent effects on vascular function induced by the maternal low-protein diet, and it restored endothelial function without affecting plasma cholesterol (594), an effect possibly mediated by effects on endothelial progenitor cells. If the statin is given in the second half of pregnancy, it can protect the offspring against the conditioning effects of a maternal high-fat diet (158).

While these experiments only serve as proof of principle, they offer promise that, with the appropriate use of biomarkers of risk, timely interventions during development may have the potential to reduce the effects of developmental environment in priming risk of later cardiovascular and metabolic disease in the offspring.

D. Developmental Conditioning and NCDs: Policy and Preventative Interventions

The developmental component of NCD risk does not conform to the generally accepted model of lifestyle and environmental contributions to the burden of NCDs. These are primarily derived from the relatively effective approaches to reducing the adverse health impacts of smoking, but the interventions that have proven effective in reducing smoking do not easily apply even to changing the high energy nutritional environments that contribute both to evolutionary and developmental mismatch.

Legislation cannot be focused so easily on particular aspects of developmental or adult exposures despite considerable attention to the latter in public health policy. Part of the problem is the assumption that adult obesity and its complications are largely a function of inherited genetic susceptibility plus individual choice in lifestyle (203); at the extreme, this leads to blame culture, even the use of pejorative terms such as "gluttony" and "sloth," two of the biblical deadly sins. Given the impossibility of returning to a premodern diet and lifestyle, a greater focus on creating resilience by obviating the effects of early life influences may be critical.

The science of developmental conditioning thus offers a different perspective. It suggests that a significant component of the risks of obesity and NCDs has a developmental element that is potentially amenable to preventative intervention and monitoring through the use of epigenetic biomarkers. Thus the failure to recognize the lifecourse nature of NCD risk and to incorporate it into public policy may limit capacity to reduce the escalation in the NCD burden. It is now timely to develop an adequate model of this risk and identify points in the lifecourse at which it is most sensitive to strategies to reduce it (660). The epigenetic epidemiological data reviewed above (229) suggest that the developmental component is a major part of the pathway to disease risk. The experimental and epidemiological data on mismatch reviewed above make a point that is often missed, namely, the nature of the response to the modern obesogenic environment is very much influenced by the early environmental exposures even if there is little evidence in early life of a phenotypic effect of that environmental exposure; it may be that the only evidence of the developmental effect at this age lies in an altered epigenetic biomarker.

Public health policy inevitably favors devoting resources to those with current illness over long-term prevention that may not be manifest until the next generation, if only because the former are likely to be voters, taxpayers, and influential citizens. Regrettably, when looked at from a global perspective, the all-too-frequent philosophy of "women and children last" when it comes to issues such as food security appears to operate (530). As will be evident from the science reviewed in this paper, this is not appropriate.

As yet it is hard to put a figure on the cost implications of ignoring a developmental emphasis. For a hypothetical low-income country, an estimate from the World Bank (8) focused only on low birth weight and a limited set of outcomes, in terms of health, education, and economic productivity. More detailed calculations have been made for the early life consequences in terms of cognitive and noncognitive function (254), but this has not as yet been extended to NCDs. The broad range of parental phenotypic characteristics that influence the offspring's future, as well as their lifecourse and even transgenerational influences, suggest that a human capital analogy may be more insightful (121).

Attention is now being given to when in the lifecourse it would be logical for public policy to promote intervention **(FIGURE 11)**. Adolescence is the logical place to start if the state of the parent prior to conception is to be addressed. Diet and other lifestyle factors operating periconceptionally affect the development of the embryo, fetus, and child, and

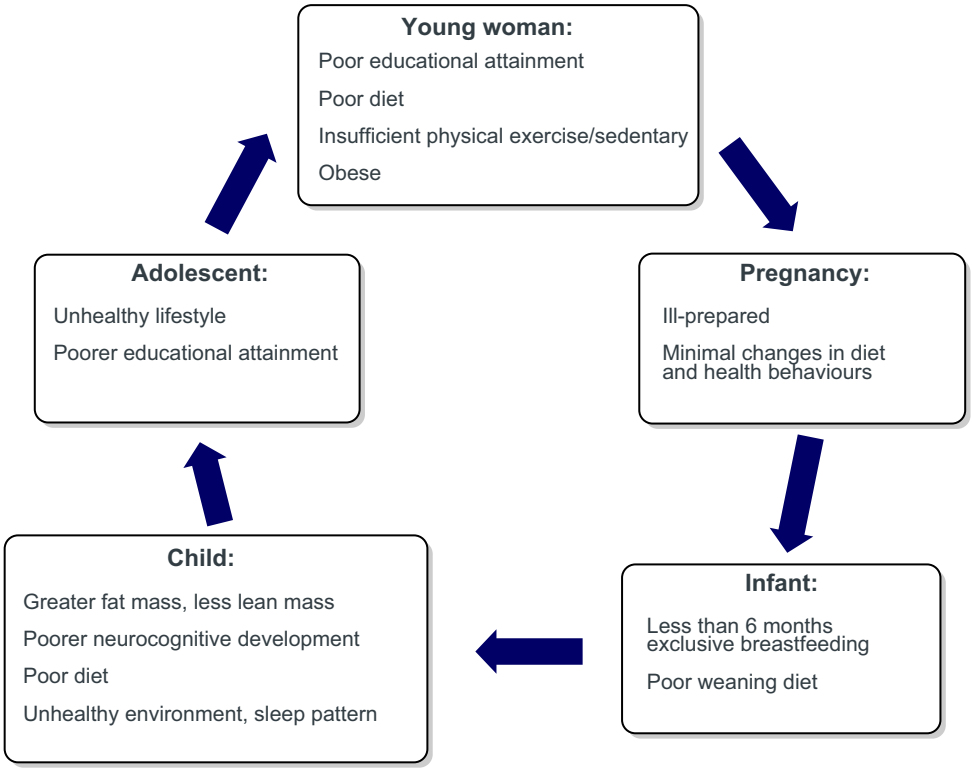

FIGURE 11. Summary of findings from prospective studies in Southampton, illustrating aspects of risk established in mother and affecting her offspring, leading in turn to an intergenerational risk cycle. (Courtesy of Professor Hazel Inskip.)

these processes start to operate even before a couple know that they have conceived. In addition, in many societies a substantial proportion of pregnancies are unplanned, and many women do not change their diet or their lifestyle when they know that they are pregnant (113). Yet adolescents have received less investment in health than younger children in many societies (521). The emphasis needs to extend beyond smoking, alcohol, contraception, and violence to health literacy itself. This is defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (439) and operates at several levels. Increasing health literacy to the highest level in adolescents would allow them to exercise self-efficacy and to make decisions about lifestyle themselves. This may be a particularly important component of addressing behavioral responses conditioned by earlier experience (161).

E. Human Development in the 21st Century: Technology, Social, and Other Issues

Human reproduction has changed dramatically over the last 50 years. On the one hand, the access to effective contraception has enabled many women to choose when to conceive. Many women now opt to have a family later in their lives, to allow greater financial stability and career development as well as freedom from commitments. As fertility declines during the decade before the menopause, this can lead to difficulty in conceiving for some women. In addition, sperm counts are falling in many countries for a variety of reasons including exposure to environmental chemicals, lifestyle, and smoking (534). In parallel with these changes, ART procedures have increased, not only in usage but in complexity. In addition, techniques such as sperm donation and surrogate pregnancy are now more routine.

These benefits do not come without some health costs. As noted above, first-born children may be at greater risk of NCDs and the relative increase in the proportion of the population who is first born has increased dramatically in Western and some Asian countries. Children of older women may be more likely to suffer diabetes in adult life. And ART itself has been reported to be associated with higher levels of cardiometabolic risk markers in the children, an effect which seems to be independent of the current risk factors in the parents and their reasons for seeking fertility treatment. The underlying mechanisms are not known, but animal studies have shown that even embryo transfer produces such effects on the offspring, as does dietary manipulation during oocyte maturation or even the periconceptional period.

Once again, such observations reinforce the importance of an emphasis on parental lifestyle even before conception. In all societies the issues relate to empowerment and self-efficacy particularly in girls and young women. The key issues were raised in a report to World Health Organisation some years ago (661) but have been little acted upon. They included the following: access to secondary education, continued after mar-

riage/childbirth; delaying first pregnancy until at least 4 yr after menarche; diet before and during pregnancy and suckling; reduction of physical exercise levels in pregnancy; and smoking cessation.

These issues are now being reexamined in the context of the post-2015 global health agenda (90, 600).

VII. CONCLUSION

The field of DOHaD has grown rapidly to high prominence in biomedical science, public health, and, to an extent, in public understanding of science. However, many of the fundamental concepts underlying it were articulated in different ways many years ago, and there was much supportive data from early studies that has now resurfaced. In hindsight, it now seems surprising that the DOHaD concept took so long to join mainstream science. There are several reasons for this, related to a slowness to recognize that DOHaD processes operate across the normal range of development and are largely physiological rather than pathophysiological. These processes can influence the risk of later disease and involve multiple pathways. For example, it is now recognized that risk is graded across the range of levels of surrogate markers of development such as size at birth and is not only associated with low birth weight. Moving beyond association studies, insights into developmental epigenetic processes are revealing the mechanisms by which the early life environment can influence phenotypic aspects of the individual. This is indicating the normative nature of the phenomena, revealing underlying mechanisms and providing potential biomarkers of risk. Such markers could be measured in early life and used to indicate the most effective interventions and to monitor their efficacy.

The field of DOHaD has been beset by the problem of the use of metaphor, very often an issue in science when new ground is being broken. We have discussed why the use of the term *programming* has been unhelpful; it implies that a mechanism has been put in place that will inevitably lead to disease, and that the process is ballistic because, once initiated, its outcome is predetermined. This has raised expectations with respect to associations between the environment in early life and later incidence of disease that are unrealistic. We prefer the less deterministic term *conditioning* as it makes clearer the concept that early life environment only conditions an individual to respond physiologically to later environmental challenges in a particular way. Other processes may intercede so that the response may ultimately be different. Moreover, it does not carry the implication that disease processes start during development, as if they are pathophysiological from the outset. Development can affect the future of an individual, but this is always conditional.

We have discussed these issues in the context of evolutionary biology in the sense that, as part of normal development, they could be argued to have been selected during evolution as they confer an adaptive advantage. We stress that such advantage need only be manifest in terms of survival to the age of reproductive competence and until successful reproduction has been achieved. Our concept of predictive adaptive responses encapsulates this, because environmental cues in development will only be adaptive until reproduction is complete. The risk of NCD, which usually increases rapidly in the post-reproductive period, may or may not be influenced by the fidelity of the prediction during development of the nature of the environment in the period up to reproduction. Throughout life, but particularly in the post-reproductive period, disease risk increases due to the accumulative effects of inadequate responses to challenges and to the consequences of changes in lifestyle, behavior, and environment, etc. This latter group we have termed "mismatch" to indicate that they represent challenges with an element of evolutionary novelty, which neither the individual's development nor their evolutionary ancestry may have equipped them to meet completely. The mismatch between an individual's physiological phenotype and their current environment can occur at any point in the lifecourse. During development this is linked to the category of nonadaptive effects which we discuss, many of which have arisen through Westernization, climate change, socioeconomic progress, pollution, etc.

Evolutionary biology applied to medicine can therefore assist in emphasizing the complex interaction between proximate (e.g., an immediate challenge from unbalanced diet) and ultimate (e.g., evolved traits) in the etiology of disease. The recent developments in developmental biology, and in the field of evolutionary developmental biology (evo-devo), contribute to our understanding of this interaction. In particular, substantial work in developmental epigenetics demonstrates how developmental plasticity may be influenced by normal environmental factors to establish phenotype. Moreover, the transgenerational passage of epigenetic marks, at least in animals, the extent of epigenetic processes beyond imprinted genes and beyond only the early embryonic period, and the possibility that environmentally induced epigenetic change can affect the probability of mutation are challenging long-held views about the inherited risk of disease. The nature-nurture divide is now widely recognized not just to be artificial but as meaningless, and the genocentric view of life which underpinned neo-Darwinism is now severely challenged. The Central Dogma of the Modern Synthesis, and the genetic determinism which followed, may have come to the end of their scientific usefulness. In DOHaD, a new era of applied developmental physiology is beginning.

We believe that the implications of such new perspectives will be far-reaching. They will have direct relevance to the initiatives badly needed to address the challenge of NCDs globally, by emphasizing the importance of including development at the start of the lifecourse in interventions, and in moving beyond the emphasis on adult lifestyle and personal choice in NCD prevention. This will have implications for the health

literacy and the empowerment of women of reproductive age and their partners, of children, adolescents, and young adults. It will require wider appreciation of developmental physiology, not only among health professionals but among policy makers and opinion leaders. It will raise many issues concerning the distinction between human biology and our culture, from ethical to philosophical to ideological. And it will underpin the success of interventions to improve health across the lifecourse, operations which will have substantial financial implications across both low and high income societies.

ACKNOWLEDGMENTS

We are grateful to Jane Kitcher for her patient preparation of the manuscript and to Felicia Low for additional research.

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GRANTS

M. A. Hanson is supported by the British Heart Foundation and P. D. Gluckman by Gravida (National Centre for Growth and Development, New Zealand).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES

1. Aceti A, Santhakumaran S, Logan KM, Philipps LH, Prior E, Gale C, Hyde MJ, Modi N. The diabetic pregnancy and offspring blood pressure in childhood: a systematic review and meta-analysis. *Diabetologia* 55: 3114–3127, 2012.

2. Adler A, Camm EJ, Hansell JA, Richter HG, Giussani DA. Investigation of the use of antioxidants to diminish the adverse effects of postnatal glucocorticoid treatment on mortality and cardiac development. *Neonatology* 98: 73–83, 2010.

3. Aerts L, Holemans K, Van Assche FA. Maternal diabetes during pregnancy: consequences for the offspring. *Diabetes Metab Rev* 6: 147–167, 1990.

4. Aerts L, Van Assche FA. Is gestational diabetes an acquired condition? *J Dev Physiol* 1: 219–225, 1979.

5. Aerts L, Van Assche FA. Taurine and taurine-deficiency in the perinatal period. *J Perinatal Med* 30: 281–286, 2002.

6. Aihie Sayer A, Dunn R, Langley-Evans S, Cooper C. Prenatal exposure to a maternal low protein diet shortens life span in rats. *Gerontology* 47: 9–14, 2001.

7. Ajslev TA, Andersen CS, Gamborg M, Sorensen TI, Jess T. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *Int J Obesity* 35: 522–529, 2011.

8. Alderman H, Behrman JR. Reducing the incidence of low birth weight in low-income countries has substantial economic benefits. *World Bank Research Observer* 21: 25–48, 2006.

9. Alwan AD, Galea G, Stuckler D. Development at risk: addressing noncommunicable diseases at the United Nations high-level meeting. *Bull WHO* 89: 546–546a, 2011.

11. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science* 308: 1466–1469, 2005.

12. Arenz S, Ruckerl R, Koletzko B, von Kries R. Breast-feeding and childhood obesity–a systematic review. *Int J Obesity Relat Metab Disorders* 28: 1247–1256, 2004.

13. Armitage JA, Taylor PD, Poston L. Experimental models of developmental programming: consequences of exposure to an energy rich diet during development. *J Physiol* 565: 3–8, 2005.

14. Asopa S, Cagampang FR, Anthony FW, Lanham SA, Schneider JE, Ohri SK, Hanson MA. Effect of a low-protein diet during pregnancy on expression of genes involved in cardiac hypertrophy in fetal and adult mouse offspring. *J Dev Origins Health Dis* 1: 371–375, 2010.

15. Atmar RL, Englund JA, Hammill H. Complications of measles during pregnancy. *Clin Infect Dis* 14: 217–226, 1992.

16. Ayyavoo A, Savage T, Derraik JG, Hofman PL, Cutfield WS. First-born children have reduced insulin sensitivity and higher daytime blood pressure compared to later-born children. *J Clin Endocrinol Metab* 98: 1248–1253, 2013.

17. Baar K, Wende AR, Jones TE, Marison M, Nolte LA, Chen M, Kelly DP, Holloszy JO. Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1. *FASEB J* 16: 1879–1886, 2002.

18. Backhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci USA* 104: 979–984, 2007.

19. Bagby SP. Maternal nutrition, low nephron number, and hypertension in later life: pathways of nutritional programming. *J Nutr* 137: 1066–1072, 2007.

20. Bao WH, Threefoot SA, Srinivasan SR, Berenson GS. Essential-hypertension predicted by tracking of elevated blood-pressure from childhood to adulthood: the Bogalusa Heart-Study. *Am J Hypertens* 8: 657–665, 1995.

21. Barbour LA, Shao J, Qiao L, Pulawa LK, Jensen DR, Bartke A, Garrity M, Draznin B, Friedman JE. Human placental growth hormone causes severe insulin resistance in transgenic mice. *Am J Obstet Gynecol* 186: 512–517, 2002.

22. Barker DJ. The fetal and infant origins of adult disease. *BMJ* 301: 1111, 1990.

23. Barker DJ. Fetal origins of coronary heart disease. *BMJ* 311: 171–174, 1995.

24. Barker DJ, Larsen G, Osmond C, Thornburg KL, Kajantie E, Eriksson JG. The placental origins of sudden cardiac death. *Int J Epidemiol* 41: 1394–1399, 2012.

25. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1: 1077–1081, 1986.

26. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 298: 564–567, 1989.

27. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 2: 577–580, 1989.

28. Bassett NS, Breier BH, Hodgkinson SC, Davis SR, Henderson HV, Gluckman PD. Plasma clearance of radiolabelled IGF-1 in the late gestation ovine fetus. *J Dev Physiol* 14: 73–79, 1990.

29. Bateson P. Fetal experience and good adult design. *Int J Epidemiol* 30: 928–934, 2001.

30. Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, Gluckman P, Godfrey K, Kirkwood T, Lahr MM, McNamara J, Metcalfe NB, Monaghan P, Spencer HG, Sultan SE. Developmental plasticity and human health. *Nature* 430: 419–421, 2004.

32. Bateson P, Gluckman P. *Plasticity, Robustness, Development and Evolution*. Cambridge, UK: Cambridge Univ. Press, 2011.

33. Bateson P, Gluckman P, Hanson M. The biology of developmental plasticity and the predictive adaptive hypothesis. *J Physiol* 592: 2357–2368, 2014.

34. Bateson P, Laland KN. Tinbergen's four questions: an appreciation and an update. *Trends Ecol Evol* 28: 712–718, 2013.

35. Bateson W. The progress of genetic research. In: *Report of the Third International Conference on Genetics 1906*. London: Royal Horticultural Society, 1906, p.90–97

36. Battista MC, Oligny LL, St-Louis J, Brochu M. Intrauterine growth restriction in rats is associated with hypertension and renal dysfunction in adulthood. *Am J Physiol Endocrinol Metab* 283: E124–E131, 2002.

36a. Batista TM, da Silva PM, Amaral AG, Ribeiro RA, Boschero AC, Carneiro EM. Taurine supplementation restores insulin secretion and reduces ER stress markers in protein-malnourished mice. *Adv Exp Med Biol* 776: 129–139, 2013.

37. Baxter RC. Insulin-like growth factor (IGF)-binding proteins: interactions with IGFs and intrinsic bioactivities. *Am J Physiol Endocrinol Metab* 278: E967–E976, 2000.

38. Bayol SA, Farrington SJ, Stickland NC. A maternal "junk food" diet in pregnancy and lactation promotes an exacerbated taste for "junk food" and a greater propensity for obesity in rat offspring. *Br J Nutr* 98: 843–851, 2007.

39. Bayol SA, Simbi BH, Stickland NC. A maternal cafeteria diet during gestation and lactation promotes adiposity and impairs skeletal muscle development and metabolism in rat offspring at weaning. *J Physiol* 567: 951–961, 2005.

40. Beaumont HJ, Gallie J, Kost C, Ferguson GC, Rainey PB. Experimental evolution of bet hedging. *Nature* 462: 90–93, 2009.

41. Behnke M, Smith VC, Committee on Substance Abuse and the Newborn. Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics* 131: e1009–1024, 2013.

42. Bell CG, Finer S, Lindgren CM, Wilson GA, Rakyan VK, Teschendorff AE, Akan P, Stupka E, Down TA, Prokopenko I, Morison IM, Mill J, Pidsley R, International Type 2 Diabetes 1q Committee, Deloukas P, Frayling TM, Hattersley AT, McCarthy MI, Beck S, Hitman GA. Integrated genetic and epigenetic analysis identifies haplotype-specific methylation in the FTO type 2 diabetes and obesity susceptibility locus. *PloS One* 5: e14040, 2010.

43. Beltrand J, Soboleva TK, Shorten PR, Derraik JGB, Hofman P, Albertsson-Wikland K, Hochberg Z, Cutfield WS. Post-term birth is associated with greater risk of obesity in adolescent males. *J Pediatr* 160: 769–773, 2012.

44. Benzie IF. Evolution of dietary antioxidants. *Comp Biochem Physiol A Mol Integr Physiol* 136: 113–126, 2003.

45. Bergman A, Heindel JJ, Jobling S, Kidd KA, Zoeller RT, Jobling SK. State of the science of endocrine disrupting chemicals. Geneva: United Nations Environment Programme and World Health Organization ISBN: 978 92 4 150503 1. 2012.

46. Bergvall N, Iliadou A, Tuvemo T, Cnattingius S. Birth characteristics and risk of high systolic blood pressure in early adulthood: socioeconomic factors and familial effects. *Epidemiology* 16: 635–640, 2005.

47. Bertram C, Khan O, Ohri S, Phillips DI, Matthews SG, Hanson MA. Transgenerational effects of prenatal nutrient restriction on cardiovascular and hypothalamic-pituitary-adrenal function. *J Physiol* 586: 2217–2229, 2008.

48. Bertram CE, Hanson MA. Animal models and programming of the metabolic syndrome. *Br Medical Bull* 60: 103–121, 2001.

49. Beuchat CA, Pough FH, Stewart MM. Response to simultaneous dehydration and thermal-stress in 3 species of Puerto-Rican frogs. *J Comp Physiol* 154: 579–585, 1984.

50. Blackmore HL, Piekarz AV, Fernandez-Twinn DS, Mercer JR, Figg N, Bennett M, Ozanne SE. Poor maternal nutrition programmes a pro-atherosclerotic phenotype in ApoE−/− mice. *Clin Sci* 123: 251–257, 2012.

51. Blanco CE, Chen V, Maertzdorf W, Bamford OS, Hanson M. Effect of hyperoxia (PaO_2 50–90 mmHg) on fetal breathing movements in the unanaesthetized fetal sheep. *J Dev Physiol* 14: 235–241, 1990.

52. Blander G, Guarente L. The Sir2 family of protein deacetylases. *Annu Rev Biochem* 73: 417–435, 2004.

53. Bloom DE. 7 billion and counting. *Science* 333: 562–569, 2011.

54. Bloomfield FH, Oliver MH, Hawkins P, Campbell M, Phillips DJ, Gluckman PD, Challis JR, Harding JE. A periconceptional nutritional origin for noninfectious preterm birth. *Science* 300: 606, 2003.

55. Boegehold MA. The effect of high salt intake on endothelial function: reduced vascular nitric oxide in the absence of hypertension. *J Vasc Res* 50: 458–467, 2013.

56. Boegehold MA. Endothelium-dependent control of vascular tone during early postnatal and juvenile growth. *Microcirculation* 17: 394–406, 2010.

57. Bonamy AK, Norman M, Kaijser M. Being born too small, too early, or both: does it matter for risk of hypertension in the elderly? *Am J Hypertens* 21: 1107–1110, 2008.

58. Boonstra R, Hik D, Singleton GR, Tinnikov A. The impact of predator-induced stress on the snowshoe hare cycle. *Ecol Monogr* 68: 371–394, 1998.

59. Boubred F, Buffat C, Simeoni U. The developing kidney and the fetal origins of adult cardiovascular disease. *Nephrol Fluid/Electrolyte* 139, 2012.

60. Bouchard L, Hivert MF, Guay SP, St-Pierre J, Perron P, Brisson D. Placental adiponectin gene DNA methylation levels are associated with mothers' blood glucose concentration. *Diabetes* 61: 1272–1280, 2012.

61. Bouret SG. Leptin, nutrition, and the programming of hypothalamic feeding circuits. *Nestle Nutrition Workshop Series Paediatric Programme* 65: 25–35, 2010.

62. Boyd ME, Usher RH, McLean FH. Fetal macrosomia: prediction, risks, proposed management. *Obstet Gynecol* 61: 715–722, 1983.

63. Brand AP, Greenwood SL, Glazier JD, Bennett EJ, Godfrey KM, Sibley CP, Hanson MA, Lewis RM. Comparison of L-serine uptake by human placental microvillous membrane vesicles and placental villous fragments. *Placenta* 31: 456–459, 2010.

64. Brawley L, Torrens C, Anthony FW, Itoh S, Wheeler T, Jackson AA, Clough GF, Poston L, Hanson MA. Glycine rectifies vascular dysfunction induced by dietary protein imbalance during pregnancy. *J Physiol* 554: 497–504, 2004.

65. Bromfield JJ, Schjenken JE, Chin PY, Care AS, Jasper MJ, Robertson SA. Maternal tract factors contribute to paternal seminal fluid impact on metabolic phenotype in offspring. *Proc Natl Acad Sci USA* 111: 2200–2205, 2014.

66. Brönmark C, Pettersson L, Nilsson A. Predator-induced defense in crucian carp. *Evol Inducible Defenses* 203–217, 1999.

67. Brost BC, Newman RB. The maternal and fetal effects of tuberculosis therapy. *Obstet Gynecol Clin N Am* 24: 659–673, 1997.

68. Bruce KD, Cagampang FR, Argenton M, Zhang J, Ethirajan PL, Burdge GC, Bateman AC, Clough GF, Poston L, Hanson MA, McConnell JM, Byrne CD. Maternal high-fat feeding primes steatohepatitis in adult mice offspring, involving mitochondrial dysfunction and altered lipogenesis gene expression. *Hepatology* 50: 1796–1808, 2009.

69. Bruce KD, Hanson MA. The developmental origins, mechanisms, and implications of metabolic syndrome. *J Nutr* 140: 648–652, 2010.

70. Burdge GC, Hoile SP, Uller T, Thomas NA, Gluckman PD, Hanson MA, Lillycrop KA. Progressive, transgenerational changes in offspring phenotype and epigenotype following nutritional transition. *PloS One* 6: e28282, 2011.

71. Burdge GC, Lillycrop KA, Jackson AA, Gluckman PD, Hanson MA. The nature of the growth pattern and of the metabolic response to fasting in the rat are dependent upon the dietary protein and folic acid intakes of their pregnant dams and post-weaning fat consumption. *Br J Nutr* 99: 540–549, 2008.

72. Burdge GC, Lillycrop KA, Phillips ES, Slater-Jefferies JL, Jackson AA, Hanson MA. Folic acid supplementation during the juvenile-pubertal period in rats modifies the phenotype and epigenotype induced by prenatal nutrition. *J Nutr* 139: 1054–1060, 2009.

73. Burdge GC, Slater-Jefferies JL, Grant RA, Chung WS, West AL, Lillycrop KA, Hanson MA, Calder PC. Sex, but not maternal protein or folic acid intake, determines the fatty acid composition of hepatic phospholipids, but not of triacylglycerol, in adult rats. *Prostaglandins Leukotrienes Essent Fatty Acids* 78: 73–79, 2008.

74. Burgess DJ. Histone modification at the gene level. *Nature Rev Cancer* 12: 156, 2012.

75. Burgueno AL, Cabrerizo R, Gonzales Mansilla N, Sookoian S, Pirola CJ. Maternal high-fat intake during pregnancy programs metabolic-syndrome-related phenotypes through liver mitochondrial DNA copy number and transcriptional activity of liver PPARGC1A. *J Nutr Biochem* 24: 6–13, 2013.

76. Burrage DM, Braddick L, Cleal JK, Costello P, Noakes DE, Hanson MA, Green LR. The late gestation fetal cardiovascular response to hypoglycaemia is modified by prior peri-implantation undernutrition in sheep. *J Physiol* 587: 611–624, 2009.

77. Burton GJ, Jauniaux E, Watson AL. Maternal arterial connections to the placental intervillous space during the first trimester of human pregnancy: the Boyd collection revisited. *Am J Obstet Gynecol* 181: 718–724, 1999.

78. Cagampang FR, Poore KR, Hanson MA. Developmental origins of the metabolic syndrome: body clocks and stress responses. *Brain Behav Immunity* 25: 214–220, 2011.

79. Cagampang FR, Torrens C, Anthony FW, Hanson M. Developmental exposure to bisphenol A leads to cardiometabolic dysfunction in adult mouse offspring. *J Dev Origins Health Disease* 3: 287–292, 2012.

80. Carbone L, Harris RA, Vessere GM, Mootnick AR, Humphray S, Rogers J, Kim SK, Wall JD, Martin D, Jurka J, Milosavljevic A, de Jong PJ. Evolutionary breakpoints in the gibbon suggest association between cytosine methylation and karyotype evolution. *PLoS Genet* 5: e1000538, 2009.

81. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, Parslow RC, Pozzilli P, Brigis G, Stoyanov D, Urbonaite B, Sipetic S, Schober E, Ionescu-Tirgoviste C, Devoti G, de Beaufort CE, Buschard K, Patterson CC. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia* 51: 726–735, 2008.

82. Carlin J, George R, Reyes TM. Methyl donor supplementation blocks the adverse effects of maternal high fat diet on offspring physiology. *PloS One* 8: e63549, 2013.

83. Carr D, Aitken R, Milne J, Mehta V, Peebles D, Martin J, Zachary I, Wallace J, David AD. Prenatal VEGF gene therapy increases fetal growth velocity and alters uterine artery vascular reactivity in the absence of a measurable effect on uterine blood flow in a sheep model of fetal growth restriction. *Arch Dis Childhood-Fetal Neonatal Edition* 97: A1, 2012.

84. Carrell DT, Hammoud SS. The human sperm epigenome and its potential role in embryonic development. *Mol Hum Reprod* 16: 37–47, 2010.

85. Catalano PM, Ehrenberg HM. The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG* 113: 1126–1133, 2006.

86. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. Fetuses of obese mothers develop insulin resistance in utero. *Diabetes Care* 32: 1076–1080, 2009.

87. Cetin I, Alvino G. Intrauterine growth restriction: implications for placental metabolism and transport. A review. *Placenta* 30 *Suppl* A: S77–82, 2009.

88. Chali D, Enquselassie F, Gesese M. A case-control study on determinants of rickets. *Ethiopian Medical J* 36: 227–234, 1998.

89. Challier JC, Basu S, Bintein T, Minium J, Hotmire K, Catalano PM, Hauguel-de Mouzon S. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta* 29: 274–281, 2008.

90. Chan M. Linking child survival and child development for health, equity, and sustainable development. *Lancet* 381: 1514–1515, 2013.

91. Cheema KK, Dent MR, Saini HK, Aroutiounova N, Tappia PS. Prenatal exposure to maternal undernutrition induces adult cardiac dysfunction. *Br J Nutr* 93: 471–477, 2005.

92. Chen JH, Hales CN, Ozanne SE. DNA damage, cellular senescence and organismal ageing: causal or correlative? *Nucleic Acids Res* 35: 7417–7428, 2007.

93. Chen PY, Ganguly A, Rubbi L, Orozco LD, Morselli M, Ashraf D, Jaroszewicz A, Feng S, Jacobsen SE, Nakano A, Devaskar SU, Pellegrini M. Intrauterine calorie restriction affects placental DNA methylation and gene expression. *Physiol Genomics* 45: 565–576, 2013.

94. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. *Diabetes Care* 34: 1741–1748, 2011.

95. Claessens SE, Daskalakis NP, van der Veen R, Oitzl MS, de Kloet ER, Champagne DL. Development of individual differences in stress responsiveness: an overview of factors mediating the outcome of early life experiences. *Psychopharmacology* 214: 141–154, 2011.

96. Clark RE. The classical origins of Pavlov's conditioning. *Integr Physiol Behav Sci* 39: 279–294, 2004.

97. Clarke-Harris R, Wilkin TJ, Hosking J, Pinkney J, Jeffery A, Metcalf BS, Godfrey KM, Voss L, Lillycrop KA, Burdge G. Peroxisomal proliferator activated receptor-ψ−co-activator-1α promoter methylation in blood at 5–7 years predicts adiposity from 9 to 14 years (EarlyBird 50). *Diabetes*. In press. doi:10.2337/db13-0671.

98. Cleal JK, Brownbill P, Godfrey KM, Jackson JM, Jackson AA, Sibley CP, Hanson MA, Lewis RM. Modification of fetal plasma amino acid composition by placental amino acid exchangers in vitro. *J Physiol* 582: 871–882, 2007.

99. Cleal JK, Glazier JD, Ntani G, Crozier SR, Day PE, Harvey NC, Robinson SM, Cooper C, Godfrey KM, Hanson MA, Lewis RM. Facilitated transporters mediate net efflux of amino acids to the fetus across the basal membrane of the placental syncytiotrophoblast. *J Physiol* 589: 987–997, 2011.

100. Cleal JK, Lewis RM. The mechanisms and regulation of placental amino acid transport to the human foetus. *J Neuroendocrinol* 20: 419–426, 2008.

101. Cleal JK, Poore KR, Boullin JP, Khan O, Chau R, Hambidge O, Torrens C, Newman JP, Poston L, Noakes DE, Hanson MA, Green LR. Mismatched pre- and postnatal nutrition leads to cardiovascular dysfunction and altered renal function in adulthood. *Proc Natl Acad Sci USA* 104: 9529–9533, 2007.

102. Cleal JK, Poore KR, Newman JP, Noakes DE, Hanson MA, Green LR. The effect of maternal undernutrition in early gestation on gestation length and fetal and postnatal growth in sheep. *Pediatr Res* 62: 422–427, 2007.

103. Cocozza S, Akhtar MM, Miele G, Monticelli A. CpG islands undermethylation in human genomic regions under selective pressure. *PloS One* 6: e23156, 2011.

104. Constancia M, Hemberger M, Hughes J, Dean W, Ferguson-Smith A, Fundele R, Stewart F, Kelsey G, Fowden A, Sibley C, Reik W. Placental-specific IGF-II is a major modulator of placental and fetal growth. *Nature* 417: 945–948, 2002.

105. Cooper C, Harvey N, Cole Z, Hanson M, Dennison E. Developmental origins of osteoporosis: the role of maternal nutrition. *Adv Exp Med Biol* 646: 31–39, 2009.

106. Cooper C, Harvey N, Javaid K, Hanson M, Dennison E. Growth and bone development. *Nestle Nutr Workshop Series* 61: 53–68, 2008.

107. Corrigan N, Brazil DP, McAuliffe F. Fetal cardiac effects of maternal hyperglycemia during pregnancy. *Birth Defects Res Part A Clin Mol Teratol* 85: 523–530, 2009.

108. Costello PM, Hollis LJ, Cripps RL, Bearpark N, Patel HP, Sayer AA, Cooper C, Hanson MA, Ozanne SE, Green LR. Lower maternal body condition during pregnancy affects skeletal muscle structure and Glut-4 protein levels but not glucose tolerance in mature adult sheep. *Reprod Sci* 20: 1144–1155, 2013.

109. Costello PM, Rowlerson A, Astaman NA, Anthony FE, Sayer AA, Cooper C, Hanson MA, Green LR. Peri-implantation and late gestation maternal undernutrition differentially affect fetal sheep skeletal muscle development. *J Physiol* 586: 2371–2379, 2008.

110. Cox GF, Burger J, Lip V, Mau UA, Sperling K, Wu BL, Horsthemke B. Intracytoplasmic sperm injection may increase the risk of imprinting defects. *Am J Hum Genet* 71: 162–164, 2002.

111. Crick F. Central dogma of molecular biology. *Nature* 227: 561–563, 1970.

112. Cripps RL, Green LR, Thompson J, Martin-Gronert MS, Monk M, Sheldon IM, Hanson MA, Hales CN, Ozanne SE. The effect of maternal body condition score before and during pregnancy on the glucose tolerance of adult sheep offspring. *Reprod Sci* 15: 448–456, 2008.

113. Crozier SR, Robinson SM, Godfrey KM, Cooper C, Inskip HM. Women's dietary patterns change little from before to during pregnancy. *J Nutr* 139: 1956–1963, 2009.

114. Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, Speizer FE, Stampfer MJ. Birth weight and adult hypertension and obesity in women. *Circulation* 94: 1310–1315, 1996.

115. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation* 94: 3246–3250, 1996.

116. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, Knowler WC. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 49: 2208–2211, 2000.

117. Dahlgren J, Nilsson C, Jennische E, Ho HP, Eriksson E, Niklasson A, Bjorntorp P, Albertsson Wikland K, Holmang A. Prenatal cytokine exposure results in obesity and gender-specific programming. *Am J Physiol Endocrinol Metab* 281: E326–E334, 2001.

118. Dalziel SR, Lim VK, Lambert A, McCarthy D, Parag V, Rodgers A, Harding JE. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. *BMJ* 331: 665, 2005.

119. Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A, Harding JE. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet* 365: 1856–1862, 2005.

120. Dantzer B, Newman AE, Boonstra R, Palme R, Boutin S, Humphries MM, McAdam AG. Density triggers maternal hormones that increase adaptive offspring growth in a wild mammal. *Science* 340: 1215–1217, 2013.

121. Dasgupta P, Serageldin I. Social capital: a multifaceted perspective. *World Bank Publications*, Washington, DC: World Bank ISBN: 0821350048, 2001.

122. Davidge ST, Morton JS, Rueda-Clausen CF. Oxygen and perinatal origins of adulthood diseases: is oxidative stress the unifying element? *Hypertension* 52: 808–810, 2008.

123. Davis EF, Lazdam M, Lewandowski AJ, Worton SA, Kelly B, Kenworthy Y, Adwani S, Wilkinson AR, McCormick K, Sargent I, Redman C, Leeson P. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. *Pediatrics* 129: e1552–e1561, 2012.

124. Davis EF, Newton L, Lewandowski AJ, Lazdam M, Kelly BA, Kyriakou T, Leeson P. Pre-eclampsia and offspring cardiovascular health: mechanistic insights from experimental studies. *Clin Sci* 123: 53–72, 2012.

125. Dawes G. *Fetal Autonomy and Adaptation*. New York: Wiley, 1990.

126. Day PE, Cleal J, Lofthouse EM, Hanson MA, Lewis R. What factors determine placental glucose transfer kinetics? *Placenta* 34: 953–958, 2013.

127. De-Regil LM, Fernandez-Gaxiola AC, Dowswell T, Pena-Rosas JP. Effects and safety of periconceptional folate supplementation for preventing birth defects. *Cochrane Database Syst Rev* CD007950, 2010.

128. De Heredia FP, Gomez-Martinez S, Marcos A. Obesity, inflammation and the immune system. *Proc Nutr Soc* 71: 332–338, 2012.

129. De Kloet ER, Sibug RM, Helmerhorst FM, Schmidt MV. Stress, genes and the mechanism of programming the brain for later life. *Neurosci Biobehav Rev* 29: 271–281, 2005.

130. De Prins FA, Van Assche FA. Intrauterine growth retardation and development of endocrine pancreas in the experimental rat. *Biol Neonate* 41: 16–21, 1982.

131. De Rooij SR, Painter RC, Holleman F, Bossuyt PM, Roseboom TJ. The metabolic syndrome in adults prenatally exposed to the Dutch famine. *Am J Clin Nutr* 86: 1219–1224, 2007.

132. De Santis MS, Taricco E, Radaelli T, Spada E, Rigano S, Ferrazzi E, Milani S, Cetin I. Growth of fetal lean mass and fetal fat mass in gestational diabetes. *Ultrasound Obstet Gynecol* 36: 328–337, 2010.

133. DeBaun MR, Niemitz EL, Feinberg AP. Association of in vitro fertilization with Beckwith-Wiedemann syndrome and epigenetic alterations of LIT1 and H19. *Am J Hum Genet* 72: 156–160, 2003.

134. Del Giudice M, Ellis BJ, Shirtcliff EA. The Adaptive Calibration Model of stress responsivity. *Neurosci Biobehav Rev* 35: 1562–1592, 2011.

135. Desoye G, Hauguel-de Mouzon S. The human placenta in gestational diabetes mellitus. The insulin and cytokine network. *Diabetes Care* 30 *Suppl* 2: S120–126, 2007.

136. Dias BG, Ressler KJ. Parental olfactory experience influences behavior and neural structure in subsequent generations. *Nature Neurosci* 17: 89–96, 2014.

137. Dilworth MR, Andersson I, Renshall LJ, Cowley E, Baker P, Greenwood S, Sibley CP, Wareing M. Sildenafil citrate increases fetal weight in a mouse model of fetal growth restriction with a normal vascular phenotype. *PloS One* 8: e77748, 2013.

138. Dobrovic A, Kristensen LS. DNA methylation, epimutations and cancer predisposition. *Int J Biochem Cell Biol* 41: 34–39, 2009.

139. Docherty CC, Kalmar-Nagy J, Engelen M, Koenen SV, Nijland M, Kuc RE, Davenport AP, Nathanielsz PW. Effect of in vivo fetal infusion of dexamethasone at 0.75 GA on fetal ovine resistance artery responses to ET-1. *Am J Physiol Regul Integr Comp Physiol* 281: R261–R268, 2001.

140. Dodic M, Abouantoun T, O'Connor A, Wintour EM, Moritz KM. Programming effects of short prenatal exposure to dexamethasone in sheep. *Hypertension* 40: 729–734, 2002.

141. Dodson S. Predator-induced reaction norms: cyclic changes in shape and size can be protective. *Bioscience* 39: 447–452, 1989.

142. DOHaD. International Society for Developmental Origins of Health and Disease, http://www.mrc-leu.soton.ac.uk/dohad/index.asp.

143. Dörner G, Rodekamp E, Plagemann A. Maternal deprivation and overnutrition in early postnatal life and their primary prevention: historical reminiscence of an "ecologic experiment" in Germany. *Hum Ontogenet* 2: 51–59, 2008.

144. Drake AJ, Walker BR, Seckl JR. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. *Am J Physiol Regul Integr Comp Physiol* 288: R34–R38, 2005.

145. Dudley KJ, Sloboda DM, Connor KL, Beltrand J, Vickers MH. Offspring of mothers fed a high fat diet display hepatic cell cycle inhibition and associated changes in gene expression and DNA methylation. *PloS One* 6: e21662, 2011.

146. Dunstan D. *Diabesity and Associated Disorders in Australia, 2000: The Accelerating Epidemic: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab)*. Australia: International Diabetes Institute, 2001.

147. Duque-Guimaraes DE, Ozanne SE. Nutritional programming of insulin resistance: causes and consequences. *Trends Endocrinol Metab* 24: 525–535, 2013.

148. Dyck R, Osgood N, Lin TH, Gao A, Stang MR. Epidemiology of diabetes mellitus among First Nations and non-First Nations adults. *CMAJ* 182: 249–256, 2010.

149. Ebbing C, Rasmussen S, Godfrey KM, Hanson MA, Kiserud T. Fetal celiac and splenic artery flow velocity and pulsatility index: longitudinal reference ranges and evidence for vasodilation at a low portocaval pressure gradient. *Ultrasound Obstet Gynecol* 32: 663–672, 2008.

150. Ebbing C, Rasmussen S, Godfrey KM, Hanson MA, Kiserud T. Fetal superior mesenteric artery: longitudinal reference ranges and evidence of regulatory link to portal liver circulation. *Early Hum Dev* 85: 207–213, 2009.

151. Ebbing C, Rasmussen S, Godfrey KM, Hanson MA, Kiserud T. Hepatic artery hemodynamics suggest operation of a buffer response in the human fetus. *Reprod Sci* 15: 166–178, 2008.

152. Ecker JR, Bickmore WA, Barroso I, Pritchard JK, Gilad Y, Segal E. Genomics: ENCODE explained. *Nature* 489: 52–55, 2012.

153. Egeland GM, Skjaerven R, Irgens LM. Birth characteristics of women who develop gestational diabetes: population based study. *BMJ* 321: 546–547, 2000.

154. Ehara T, Kamei Y, Takahashi M, Yuan X, Kanai S, Tamura E, Tanaka M, Yamazaki T, Miura S, Ezaki O, Suganami T, Okano M, Ogawa Y. Role of DNA methylation in the regulation of lipogenic glycerol-3-phosphate acyltransferase 1 gene expression in the mouse neonatal liver. *Diabetes* 61: 2442–2450, 2012.

155. Einum S, Fleming IA. Highly fecund mothers sacrifice offspring survival to maximize fitness. *Nature* 405: 565–567, 2000.

156. Eisenman JC, Sarzynski MA, Tucker J, Heelan KA. Maternal prepregnancy overweight and offspring fatness and blood pressure: role of physical activity. *Pediatr Exercise Sci* 22: 369–378, 2010.

157. El Hajj N, Pliushch G, Schneider E, Dittrich M, Muller T, Korenkov M, Aretz M, Zechner U, Lehnen H, Haaf T. Metabolic programming of MEST DNA methylation by intrauterine exposure to gestational diabetes mellitus. *Diabetes* 62: 1320–1328, 2013.

158. Elahi MM, Cagampang FR, Anthony FW, Curzen N, Ohri SK, Hanson MA. Statin treatment in hypercholesterolemic pregnant mice reduces cardiovascular risk factors in their offspring. *Hypertension* 51: 939–944, 2008.

159. Elahi MM, Cagampang FR, Mukhtar D, Anthony FW, Ohri SK, Hanson MA. Long-term maternal high-fat feeding from weaning through pregnancy and lactation predisposes offspring to hypertension, raised plasma lipids and fatty liver in mice. *Br J Nutr* 102: 514–519, 2009.

160. Elahi MM, Cagampang FR, Ohri SK, Hanson MA. Long-term statin administration to dams on high-fat diet protects not only them but also their offspring from cardiovascular risk. *Ann Nutr Metab* 62: 250–256, 2013.

161. Ellis BJ, Del Giudice M, Dishion TJ, Figueredo AJ, Gray P, Griskevicius V, Hawley PH, Jacobs WJ, James J, Volk AA, Wilson DS. The evolutionary basis of risky adolescent behavior: implications for science, policy, and practice. *Dev Psychol* 48: 598–623, 2012.

162. Elmes MJ, Gardner DS, Langley-Evans SC. Fetal exposure to a maternal low-protein diet is associated with altered left ventricular pressure response to ischaemia-reperfusion injury. *Br J Nutr* 98: 93–100, 2007.

163. Entringer S, Epel ES, Kumsta R, Lin J, Hellhammer DH, Blackburn EH, Wust S, Wadhwa PD. Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood. *Proc Natl Acad Sci USA* 108: E513–E518, 2011.

164. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ* 318: 427–431, 1999.

165. Fan L, Lindsley SR, Comstock SM, Takahashi DL, Evans AE, He GW, Thornburg KL, Grove KL. Maternal high-fat diet impacts endothelial function in nonhuman primate offspring. *Int J Obesity* 37: 254–262, 2013.

166. Farley D, Tejero ME, Comuzzie AG, Higgins PB, Cox L, Werner SL, Jenkins SL, Li C, Choi J, Dick EJ Jr, Hubbard GB, Frost P, Dudley DJ, Ballesteros B, Wu G, Nathanielsz PW, Schlabritz-Loutsevitch NE. Feto-placental adaptations to maternal obesity in the baboon. *Placenta* 30: 752–760, 2009.

167. Feinberg AP. Phenotypic plasticity and the epigenetics of human disease. *Nature* 447: 433–440, 2007.

168. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes Care* 30 *Suppl* 2: S141–146, 2007.

169. Filler G, Yasin A, Kesarwani P, Garg AX, Lindsay R, Sharma AP. Big mother or small baby: which predicts hypertension? *J Clin Hypertens* 13: 35–41, 2011.

169a. Forrester T, Picou D, Walker S (Editors). *The Tropical Metabolism Research Unit. The University of the West Indies, Jamaica: The House That Jack Built*. Kingston: Ian Randle Publishers, 1956-2006, p. 23–60.

170. Forrester TE, Badaloo AV, Boyne MS, Osmond C, Thompson D, Green C, Taylor-Bryan C, Barnett A, Soares-Wynter S, Hanson MA, Beedle AS, Gluckman PD. Prenatal factors contribute to the emergence of kwashiorkor or marasmus in severe undernutrition: evidence for the predictive adaptation model. *PloS One* 7: e35907, 2012.

171. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *Br J Preventive Social Med* 31: 91–95, 1977.

172. Forsen T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D. The fetal and childhood growth of persons who develop type 2 diabetes. *Ann Internal Med* 133: 176–182, 2000.

173. Forsen T, Eriksson JG, Tuomilehto J, Osmond C, Barker DJ. Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study. *BMJ* 319: 1403–1407, 1999.

174. Fowden AL. Endocrine regulation of fetal growth. *Reprod Fertil Dev* 7: 351–363, 1995.

175. Fowden AL, Forhead AJ. Endocrine mechanisms of intrauterine programming. *Reproduction* 127: 515–526, 2004.

176. Fox CW, Mousseau TA. Maternal effects as adaptations for transgenerational phenotypic. *Maternal Effects Adaptations* 159, 1998.

177. Fox Keller E. Elusive locus of control in biological development: genetic versus developmental programs. *J Exp Zool* 285: 283–290, 1999.

178. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suner D, Cigudosa JC, Urioste M, Benitez J, Boix-Chornet M, Sanchez-Aguilera A, Ling C, Carlsson E, Poulsen P, Vaag A, Stephan Z, Spector TD, Wu YZ, Plass C, Esteller M. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci USA* 102: 10604–10609, 2005.

179. Francis-Emmanuel PM, Thompson DS, Barnett AT, Osmond C, Byrne CD, Hanson MA, Gluckman PD, Forrester TE, Boyne MS. Glucose metabolism in adult survivors of severe acute malnutrition. *J Clin Endocrinol Metab* 99: 2233–2240, 2014.

180. Francis JH, Permezel M, Davey MA. Perinatal mortality by birthweight centile. *Aust N Z J Obstet Gynaecol* 2014; doi:10.1111/ajo.12205.

181. Fraser A, Tilling K, Macdonald-Wallis C, Sattar N, Brion MJ, Benfield L, Ness A, Deanfield J, Hingorani A, Nelson SM, Smith GD, Lawlor DA. Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood. *Circulation* 121: 2557–2564, 2010.

182. Freinkel N. Banting Lecture 1980: of pregnancy and progeny. *Diabetes* 29: 1023–1035, 1980.

183. Freud S. *The Standard Edition of the Complete Psychological Works of Sigmund Freud*. London: Vintage, 1999.

184. Gaillard R, Steegers EA, Tiemeier H, Hofman A, Jaddoe VW. Placental vascular dysfunction, fetal and childhood growth, and cardiovascular development: the generation R study. *Circulation* 128: 2202–2210, 2013.

185. Gale CR, Jiang B, Robinson SM, Godfrey KM, Law CM, Martyn CN. Maternal diet during pregnancy and carotid intima-media thickness in children. *Arteriosclerosis Thrombosis Vasc Biol* 26: 1877–1882, 2006.

186. Gallagher EA, Newman JP, Green LR, Hanson MA. The effect of low protein diet in pregnancy on the development of brain metabolism in rat offspring. *J Physiol* 568: 553–558, 2005.

187. Galton F. *English Men of Science: Their Nature and Nurture*. London: Appleton, 1875.

188. Gamborg M, Byberg L, Rasmussen F, Andersen PK, Baker JL, Bengtsson C, Canoy D, Droyvold W, Eriksson JG, Forsen T, Gunnarsdottir I, Jarvelin MR, Koupil I, Lapidus L, Nilsen TI, Olsen SF, Schack-Nielsen L, Thorsdottir I, Tuomainen TP, Sorensen TI, NordNet Study. Birth weight and systolic blood pressure in adolescence and adulthood: meta-regression analysis of sex- and age-specific results from 20 Nordic studies. *Am J Epidemiol* 166: 634–645, 2007.

189. Gardella C. Lead exposure in pregnancy: a review of the literature and argument for routine prenatal screening. *Obstet Gynecol Survey* 56: 231–238, 2001.

190. Gatford KL, Sulaiman SA, Mohammad SN, De Blasio MJ, Harland ML, Simmons RA, Owens JA. Neonatal exendin-4 reduces growth, fat deposition and glucose tolerance during treatment in the intrauterine growth-restricted lamb. *PloS One* 8: e56553, 2013.

191. Geelhoed JJ, LVANOG, Verburg BO, Steegers EA, Hofman A, Helbing W, Witteman JC, Jaddoe VW. Maternal anthropometrics in pregnancy are associated with left ventricular mass in infancy. The generation R study. *Pediatr Res* 63: 62–66, 2008.

192. Gennser G, Rymark P, Isberg PE. Low birth weight and risk of high blood pressure in adulthood. *Br Med J* 296: 1498–1500, 1988.

193. Ghalambor CK, McKay JK, Carroll SP, Reznick DN. Adaptive versus non-adaptive phenotypic plasticity and the potential for contemporary adaptation in new environments. *Funct Ecol* 21: 394–407, 2007.

194. Ghosh P, Bitsanis D, Ghebremeskel K, Crawford MA, Poston L. Abnormal aortic fatty acid composition and small artery function in offspring of rats fed a high fat diet in pregnancy. *J Physiol* 533: 815–822, 2001.

195. Gibson G, Dworkin I. Uncovering cryptic genetic variation. *Nature Rev Genet* 5: 681–690, 2004.

196. Gilbert SF, Epel D. *Ecological Developmental Biology: Integrating Epigenetics, Medicine, and Evolution*. Sunderland, MA: Sinauer, 2009.

197. Gillman MW. Epidemiological challenges in studying the fetal origins of adult chronic disease. *Int J Epidemiol* 31: 294–299, 2002.

198. Gillman MW, Rifas-Shiman SL, Camargo CA Jr, Berkey CS, Frazier AL, Rockett HR, Field AE, Colditz GA. Risk of overweight among adolescents who were breastfed as infants. *JAMA* 285: 2461–2467, 2001.

199. Giussani DA, Camm EJ, Niu Y, Richter HG, Blanco CE, Gottschalk R, Blake EZ, Horder KA, Thakor AS, Hansell JA, Kane AD, Wooding FB, Cross CM, Herrera EA. Developmental programming of cardiovascular dysfunction by prenatal hypoxia and oxidative stress. *PloS One* 7: e31017, 2012.

200. Giussani DA, McGarrigle HH, Moore PJ, Bennet L, Spencer JA, Hanson MA. Carotid sinus nerve section and the increase in plasma cortisol during acute hypoxia in fetal sheep. *J Physiol* 477: 75–80, 1994.

201. Global Burden of Metabolic Risk Factors for Chronic Diseases, Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 18 million participants. *Lancet* 383: 970–983, 2014.

202. Gluckman P, Beedle AS, Hanson MA. *Principles of Evolutionary Medicine*. Oxford, UK: Oxford Univ. Press, 2009.

203. Gluckman P, Hanson M. *Fat, Fate. and Disease.* Oxford, UK: Oxford Univ. Press, 2012.

204. Gluckman P, Hanson M. *The Fetal Matrix: Evolution, Development and Disease*. Cambridge, UK: Cambridge Univ. Press, 2005.

205. Gluckman P, Hanson M. *Mismatch: Why Our World No Longer Fits Our Bodies*. Oxford, UK: Oxford Univ. Press, 2006.

206. Gluckman P, Hanson M, Buklijas T. A conceptual framework for the developmental origins of health and disease. *J Dev Origins Health Dis* 1: 2010.

207. Gluckman P, Hanson M, Spencer HG, Bateson P. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proc Royal Soc* 272: 671–677, 2005.

208. Gluckman PD. Clinical review 68: the endocrine regulation of fetal growth in late gestation: the role of insulin-like growth factors. *J Clin Endocrinol Metab* 80: 1047–1050, 1995.

209. Gluckman PD, Hanson M, Zimmet P, Forrester T. Losing the war against obesity: the need for a developmental perspective. *Sci Transl Med* 3: 93cm19, 2011.

210. Gluckman PD, Hanson MA. Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatr Res* 56: 311–317, 2004.

211. Gluckman PD, Hanson MA. *The Developmental Origins of Health and Disease*. New York: Springer, 2006.

212. Gluckman PD, Hanson MA. The developmental origins of the metabolic syndrome. *Trends Endocrinol Metab* 15: 183–187, 2004.

213. Gluckman PD, Hanson MA. Evolution, development and timing of puberty. *Trends Endocrinol Metab* 17: 7–12, 2006.

214. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science* 305: 1733–1736, 2004.

215. Gluckman PD, Hanson MA. Maternal constraint of fetal growth and its consequences. *Semin Fetal Neonatal Med* 9: 419–425, 2004.

216. Gluckman PD, Hanson MA, Bateson P, Beedle AS, Law CM, Bhutta ZA, Anokhin KV, Bougneres P, Chandak GR, Dasgupta P, Smith GD, Ellison PT, Forrester TE, Gilbert SF, Jablonka E, Kaplan H, Prentice AM, Simpson SJ, Uauy R, West-Eberhard MJ. Towards a new developmental synthesis: adaptive developmental plasticity and human disease. *Lancet* 373: 1654–1657, 2009.

217. Gluckman PD, Hanson MA, Beedle AS. Early life events and their consequences for later disease: a life history and evolutionary perspective. *Am J Hum Biol* 19: 1–19, 2007.

218. Gluckman PD, Hanson MA, Beedle AS. Non-genomic transgenerational inheritance of disease risk. *BioEssays* 29: 145–154, 2007.

219. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 359: 61–73, 2008.

220. Gluckman PD, Hanson MA, Spencer HG. Predictive adaptive responses and human evolution. *Trends Ecol Evol* 20: 527–533, 2005.

221. Gluckman PD, Hanson MA, Spencer HG, Bateson P. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proc Biol Sci* 272: 671–677, 2005.

222. Gluckman PD, Lillycrop KA, Vickers MH, Pleasants AB, Phillips ES, Beedle AS, Burdge GC, Hanson MA. Metabolic plasticity during mammalian development is directionally dependent on early nutritional status. *Proc Natl Acad Sci USA* 104: 12796–12800, 2007.

223. Godfrey K. The "developmental origins" hypothesis: epidemiology. In: *Developmental Origins of Health and Disease*, edited by Gluckman P, Hanson M. Cambridge, UK: Cambridge Univ. Press, 2006, p. .6–32

225. Godfrey K, Robinson S, Barker DJ, Osmond C, Cox V. Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. *BMJ* 312: 410–414, 1996.

226. Godfrey KM, Gluckman PD, Hanson MA. Developmental origins of metabolic disease: life course and intergenerational perspectives. *Trends Endocrinol Metab* 21: 199–205, 2010.

227. Godfrey KM, Haugen G, Kiserud T, Inskip HM, Cooper C, Harvey NC, Crozier SR, Robinson SM, Davies L, Southampton Women's Survey Study, Hanson MA. Fetal liver blood flow distribution: role in human developmental strategy to prioritize fat deposition versus brain development. *PloS One* 7: e41759, 2012.

228. Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD, Hanson MA. Non-imprinted epigenetics in fetal and postnatal development and growth. *Nestle Nutr Inst Workshop Ser* 71: 57–63, 2013.

229. Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, Rodford J, Slater-Jefferies JL, Garratt E, Crozier SR, Emerald BS, Gale CR, Inskip HM, Cooper C, Hanson MA. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. *Diabetes* 60: 1528–1534, 2011.

230. Grandjean P, Bellinger D, Bergman A, Cordier S, Davey-Smith G, Eskenazi B, Gee D, Gray K, Hanson M, van den Hazel P, Heindel JJ, Heinzow B, Hertz-Picciotto I, Hu H, Huang TT, Jensen TK, Landrigan PJ, McMillen IC, Murata K, Ritz B, Schoeters G, Skakkebaek NE, Skerfving S, Weihe P. The faroes statement: human health effects of developmental exposure to chemicals in our environment. *Basic Clin Pharmacol Toxicol* 102: 73–75, 2008.

231. Gravett MG, Hitti J, Hess DL, Eschenbach DA. Intrauterine infection and preterm delivery: evidence for activation of the fetal hypothalamic-pituitary-adrenal axis. *Am J Obstet Gynecol* 182: 1404–1413, 2000.

232. Gray C, Li M, Reynolds CM, Vickers MH. Pre-weaning growth hormone treatment reverses hypertension and endothelial dysfunction in adult male offspring of mothers undernourished during pregnancy. *PloS One* 8: e53505, 2013.

233. Greaves M, Maley CC. Clonal evolution in cancer. *Nature* 481: 306–313, 2012.

234. Green LR, Bennet L, Hanson MA. The role of nitric oxide synthesis in cardiovascular responses to acute hypoxia in the late gestation sheep fetus. *J Physiol* 497: 271–277, 1996.

235. Gross CG. Claude Bernard and the constancy of the internal environment. *Neuroscientist* 4: 380–385, 1998.

236. Grossniklaus U, Kelly B, Ferguson-Smith AC, Pembrey M, Lindquist S. Transgenerational epigenetic inheritance: how important is it? *Nature Rev Genet* 14: 228–235, 2013.

237. Group HSCR. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes* 58: 453–459, 2009.

238. Gueant JL, Namour F, Gueant-Rodriguez RM, Daval JL. Folate and fetal programming: a play in epigenomics? *Trends Endocrinol Metab* 24: 279–289, 2013.

239. Guerrero-Bosagna C, Covert TR, Haque MM, Settles M, Nilsson EE, Anway MD, Skinner MK. Epigenetic transgenerational inheritance of vinclozolin induced mouse adult onset disease and associated sperm epigenome biomarkers. *Reprod Toxicol* 34: 694–707, 2012.

240. Guerrero-Bosagna C, Settles M, Lucker B, Skinner MK. Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome. *PloS One* 5: 2010.

241. Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull* 60: 5–20, 2001.

242. Halfmann R, Jarosz DF, Jones SK, Chang A, Lancaster AK, Lindquist S. Prions are a common mechanism for phenotypic inheritance in wild yeasts. *Nature* 482: 363–368, 2012.

243. Hanson C. *Eugenics, Literature, and Culture in Post-war Britain*. Routledge, 2012.

244. Hanson MA, Gluckman PD, Ma RC, Matzen P, Biesma RG. Early life opportunities for prevention of diabetes in low and middle income countries. *BMC Public Health* 12: 1025, 2012.

245. Hanson MA, Godfrey KM. Commentary: maternal constraint is a pre-eminent regulator of fetal growth. *Int J Epidemiol* 37: 252–254, 2008.

246. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes* 58: 453–459, 2009.

247. Hardy R, Wadsworth ME, Langenberg C, Kuh D. Birthweight, childhood growth, and blood pressure at 43 years in a British birth cohort. *Int J Epidemiol* 33: 121–129, 2004.

248. Harpsoe MC, Basit S, Bager P, Wohlfahrt J, Benn CS, Nohr EA, Linneberg A, Jess T. Maternal obesity, gestational weight gain, and risk of asthma and atopic disease in

offspring: a study within the Danish National Birth Cohort. *J Allergy Clin Immunol* 131: 1033–1040, 2013.

249. Harris A, Seckl J. Glucocorticoids, prenatal stress and the programming of disease. *Horm Behav* 59: 279–289, 2011.

250. Hart R, Norman RJ. The longer-term health outcomes for children born as a result of IVF treatment. Part I: General health outcomes. *Hum Reprod Update* 19: 232–243, 2013.

251. Harvey N, Cooper C. The developmental origins of osteoporotic fracture. *J Br Menopause Soc* 10: 14–15, 29, 2004.

252. Harvey N, Sheppard A, Godfrey K, McLean C, Garratt E, Ntani G, Davies L, Murray R, Inskip H, Gluckman P, Hanson M, Lillycrop KA, Cooper C. Childhood bone mineral content is associated with methylation status of the RXRA promoter at birth. *J Bone Miner Res* 29: 600–607, 2014.

253. Hawkins P, Steyn C, Ozaki T, Saito T, Noakes DE, Hanson MA. Effect of maternal undernutrition in early gestation on ovine fetal blood pressure and cardiovascular reflexes. *Am J Physiol Regul Integr Comp Physiol* 279: R340–R348, 2000.

254. Heckman JJ. The economics, technology, and neuroscience of human capability formation. *Proc Natl Acad Sci USA* 104: 13250–13255, 2007.

255. Heindel JJ, vom Saal FS. Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity. *Mol Cell Endocrinol* 304: 90–96, 2009.

256. Herman JJ, Spencer HG, Donohue K, Sultan SE. How stable "should" epigenetic modifications be? Insights from adaptive plasticity and bet hedging. *Evolution* 68: 632–643, 2014.

257. Herrera EA, Kane AD, Hansell JA, Thakor AS, Allison BJ, Niu Y, Giussani DA. A role for xanthine oxidase in the control of fetal cardiovascular function in late gestation sheep. *J Physiol* 590: 1825–1837, 2012.

258. Herrera EA, Verkerk MM, Derks JB, Giussani DA. Antioxidant treatment alters peripheral vascular dysfunction induced by postnatal glucocorticoid therapy in rats. *PloS One* 5: e9250, 2010.

259. Hertzman C. The biological embedding of early experience and its effects on health in adulthood. *Ann NY Acad Sci* 896: 85–95, 1999.

260. Higgins MW, Keller JB, Metzner HL, Moore FE, Ostrander LD Jr. Studies of blood pressure in Tecumseh, Michigan. II. Antecedents in childhood of high blood pressure in young adults. *Hypertension* 2: 117–123, 1980.

261. Hill DE. Insulin and fetal growth. *Prog Clin Biol Res* 10: 127–139, 1976.

262. Hillman S, Peebles DM, Williams DJ. Paternal metabolic and cardiovascular risk factors for fetal growth restriction: a case-control study. *Diabetes Care* 36: 1675–1680, 2013.

263. Hirst JE, Tran TS, Do MA, Morris JM, Jeffery HE. Consequences of gestational diabetes in an urban hospital in Viet Nam: a prospective cohort study. *PLoS Med* 9: e1001272, 2012.

264. Hoet JJ, Hanson MA. Intrauterine nutrition: its importance during critical periods for cardiovascular and endocrine development. *J Physiol* 514: 617–627, 1999.

265. Hofman PL, Regan F, Jackson WE, Jefferies C, Knight DB, Robinson EM, Cutfield WS. Premature birth and later insulin resistance. *N Engl J Med* 351: 2179–2186, 2004.

266. Hoile SP, Lillycrop KA, Grenfell LR, Hanson MA, Burdge GC. Increasing the folic acid content of maternal or post-weaning diets induces differential changes in phosphoenolpyruvate carboxykinase mRNA expression and promoter methylation in rats. *Br J Nutr* 108: 852–857, 2012.

267. Holness MJ, Langdown ML, Sugden MC. Early-life programming of susceptibility to dysregulation of glucose metabolism and the development of Type 2 diabetes mellitus. *Biochem J* 349: 657–665, 2000.

268. Houde AA, Guay SP, Desgagne V, Hivert MF, Baillargeon JP, St-Pierre J, Perron P, Gaudet D, Brisson D, Bouchard L. Adaptations of placental and cord blood ABCA1 DNA methylation profile to maternal metabolic status. *Epigenetics* 8: 1289–1302, 2013.

269. Hovi P, Andersson S, Eriksson JG, Jarvenpaa AL, Strang-Karlsson S, Makitie O, Kajantie E. Glucose regulation in young adults with very low birth weight. *N Engl J Med* 356: 2053–2063, 2007.

270. Huang C, Li Z, Wang M, Martorell R. Early life exposure to the 1959–1961 Chinese famine has long-term health consequences. *J Nutr* 140: 1874–1878, 2010.

271. Huang Y, Yan X, Zhu MJ, McCormick RJ, Ford SP, Nathanielsz PW, Du M. Enhanced transforming growth factor-beta signaling and fibrogenesis in ovine fetal skeletal muscle of obese dams at late gestation. *Am J Physiol Endocrinol Metab* 298: E1254–E1260, 2010.

272. Hughes V. Epigenetics: the sins of the father. *Nature* 507: 22–24, 2014.

273. Hult M, Tornhammar P, Ueda P, Chima C, Bonamy AK, Ozumba B, Norman M. Hypertension, diabetes and overweight: looming legacies of the Biafran famine. *PloS One* 5: e13582, 2010.

274. Huxley J. *Evolution, The Modern Synthesis*. London: Allen & Unwin1942.

275. Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet* 360: 659–665, 2002.

276. Hwang DG, Green P. Bayesian Markov chain Monte Carlo sequence analysis reveals varying neutral substitution patterns in mammalian evolution. *Proc Natl Acad Sci USA* 101: 13994–14001, 2004.

277. Igosheva N, Klimova O, Anishchenko T, Glover V. Prenatal stress alters cardiovascular responses in adult rats. *J Physiol* 557: 273–285, 2004.

278. Irving RJ, Belton NR, Elton RA, Walker BR. Adult cardiovascular risk factors in premature babies. *Lancet* 355: 2135–2136, 2000.

279. Ito S, D'Alessio AC, Taranova OV, Hong K, Sowers LC, Zhang Y. Role of Tet proteins in 5mC to 5hmC conversion, ES-cell self-renewal and inner cell mass specification. *Nature* 466: 1129–1133, 2010.

280. Iuchi T, Akaike M, Mitsui T, Ohshima Y, Shintani Y, Azuma H, Matsumoto T. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. *Circ Res* 92: 81–87, 2003.

282. Jablonka E, Lachmann M, Lamb MJ. Evidence, mechanisms and models for the inheritance of acquired characters. *J Theor Biol* 158: 245–268, 1992.

283. Jablonka E, Raz G. Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. *Q Rev Biol* 84: 131–176, 2009.

284. Jackson AA, Dunn RL, Marchand MC, Langley-Evans SC. Increased systolic blood pressure in rats induced by a maternal low-protein diet is reversed by dietary supplementation with glycine. *Clin Sci* 103: 633–639, 2002.

285. Jacob F, Monod J. Genetic regulatory mechanisms in the synthesis of proteins. *J Mol Biol* 3: 318–356, 1961.

286. Jaddoe VW, de Jonge LL, Hofman A, Franco OH, Steegers EA, Gaillard R. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. *BMJ* 348: g14, 2014.

288. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. *Emerging Infect Dis* 12: 1638–1643, 2006.

289. Jansson T, Ekstrand Y, Wennergren M, Powell TL. Placental glucose transport in gestational diabetes mellitus. *Am J Obstet Gynecol* 184: 111–116, 2001.

290. Jansson TB. Low-dose infusion of atrial natriuretic peptide in the conscious guinea pig increases blood flow to the placenta of growth-retarded fetuses. *Am J Obstet Gynecol* 166: 213–218, 1992.

291. Jefferies CA, Hofman PL, Knoblauch H, Luft FC, Robinson EM, Cutfield WS. Insulin resistance in healthy prepubertal twins. *J Pediatr* 144: 608–613, 2004.

292. Jennings BJ, Ozanne SE, Dorling MW, Hales CN. Early growth determines longevity in male rats and may be related to telomere shortening in the kidney. *FEBS Lett* 448: 4–8, 1999.

293. Johannes F, Porcher E, Teixeira FK, Saliba-Colombani V, Simon M, Agier N, Bulski A, Albuisson J, Heredia F, Audigier P, Bouchez D, Dillmann C, Guerche P, Hospital F,

Colot V. Assessing the impact of transgenerational epigenetic variation on complex traits. *PLoS Genet* 5: e1000530, 2009.

294. John RM. Epigenetic regulation of placental endocrine lineages and complications of pregnancy. *Biochem Soc Trans* 41: 701–709, 2013.

295. Johnsen SL, Wilsgaard T, Rasmussen S, Hanson MA, Godfrey KM, Kiserud T. Fetal size in the second trimester is associated with the duration of pregnancy, small fetuses having longer pregnancies. *BMC Pregnancy Childbirth* 8: 25, 2008.

296. Johnson LJ, Tricker PJ. Epigenomic plasticity within populations: its evolutionary significance and potential. *Heredity* 105: 113–121, 2010.

297. Jokela M, Elovainio M, Kivimaki M. Lower fertility associated with obesity and underweight: the US National Longitudinal Survey of Youth. *Am J Clin Nutr* 88: 886–893, 2008.

298. Jones HN, Powell TL, Jansson T. Regulation of placental nutrient transport–a review. *Placenta* 28: 763–774, 2007.

299. Jones JH. The force of selection on the human life cycle. *Evol Hum Behav* 30: 305–314, 2009.

300. Jones KL, Hoyme HE, Robinson LK, Del Campo M, Manning MA, Prewitt LM, Chambers CD. Fetal alcohol spectrum disorders: extending the range of structural defects. *Am J Med Genet* 152: 2731–2735, 2010.

301. Jones PA. Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nature Rev Genet* 13: 484–492, 2012.

302. Kaati G, Bygren LO, Edvinsson S. Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. *Eur J Hum Genet* 10: 682–688, 2002.

303. Kaiser J. Human genetics. Genetic influences on disease remain hidden. *Science* 338: 1016–1017, 2012.

304. Kajantie E, Osmond C, Barker DJ, Forsen T, Phillips DI, Eriksson JG. Size at birth as a predictor of mortality in adulthood: a follow-up of 350 000 person-years. *Int J Epidemiol* 34: 655–663, 2005.

305. Kane AD, Herrera EA, Hansell JA, Giussani DA. Statin treatment depresses the fetal defence to acute hypoxia via increasing nitric oxide bioavailability. *J Physiol* 590: 323–334, 2012.

306. Kaplan SL, Grumbach MM. Studies of a human and simian placental hormone with growth hormone-like and prolactin-like activities. *J Clin Endocrinol Metab* 24: 80–100, 1964.

307. Karter AJ, Rowell SE, Ackerson LM, Mitchell BD, Ferrara A, Selby JV, Newman B. Excess maternal transmission of type 2 diabetes. The Northern California Kaiser Permanente Diabetes Registry. *Diabetes Care* 22: 938–943, 1999.

308. Keller EF. *The Mirage of a Space Between Nature and Nurture*. Durham, NC: Duke Univ. Press, 2010.

309. Kelsall CJ, Hoile SP, Irvine NA, Masoodi M, Torrens C, Lillycrop KA, Calder PC, Clough GF, Hanson MA, Burdge GC. Vascular dysfunction induced in offspring by maternal dietary fat involves altered arterial polyunsaturated fatty acid biosynthesis. *PloS One* 7: e34492, 2012.

310. Kensara OA, Wootton SA, Phillips DI, Patel M, Jackson AA, Elia M, Hertfordshire Study. Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. *Am J Clin Nutr* 82: 980–987, 2005.

311. Kermack W, McKendrick A, McKinlay P. Death rates in Great Britain and Sweden: some general regularities and their significance. *Lancet* 223: 1934.

312. Kessler J, Rasmussen S, Godfrey K, Hanson M, Kiserud T. Fetal growth restriction is associated with prioritization of umbilical blood flow to the left hepatic lobe at the expense of the right lobe. *Pediatr Res* 66: 113–117, 2009.

313. Kessler J, Rasmussen S, Godfrey K, Hanson M, Kiserud T. Longitudinal study of umbilical and portal venous blood flow to the fetal liver: low pregnancy weight gain is associated with preferential supply to the fetal left liver lobe. *Pediatr Res* 63: 315–320, 2008.

314. Kessler R. Passing down pollution: calculating intergenerational exposure to PCBs. *Environ Health Perspect* 119: A219, 2011.

315. Khan I, Dekou V, Hanson M, Poston L, Taylor P. Predictive adaptive responses to maternal high-fat diet prevent endothelial dysfunction but not hypertension in adult rat offspring. *Circulation* 110: 1097–1102, 2004.

316. Khosla S, Dean W, Reik W, Feil R. Culture of preimplantation embryos and its long-term effects on gene expression and phenotype. *Hum Reprod Update* 7: 419–427, 2001.

317. Kiani J, Grandjean V, Liebers R, Tuorto F, Ghanbarian H, Lyko F, Cuzin F, Rassoulzadegan M. RNA-mediated epigenetic heredity requires the cytosine methyltransferase Dnmt2. *PLoS Genet* 9: e1003498, 2013.

318. Kim K, Zhao R, Doi A, Ng K, Unternaehrer J, Cahan P, Huo H, Loh YH, Aryee MJ, Lensch MW, Li H, Collins JJ, Feinberg AP, Daley GQ. Donor cell type can influence the epigenome and differentiation potential of human induced pluripotent stem cells. *Nature Biotechnol* 29: 1117–1119, 2011.

319. Kipling R. How the leopard got his spots. In: *Just So Stories for Little Children*. London: Macmillan1902.

320. Kishi T. Heart failure as an autonomic nervous system dysfunction. *J Cardiol* 59: 117–122, 2012.

321. Knight BS, Pennell CE, Adamson SL, Lye SJ. The impact of murine strain and sex on postnatal development after maternal dietary restriction during pregnancy. *J Physiol* 581: 873–881, 2007.

322. Kojetin DJ, Burris TP. A role for rev-erbalpha ligands in regulation of adipogenesis. *Curr Pharm Design* 17: 320–324, 2011.

323. Koletzko B. Developmental origins of adult disease: Barker's or Dorner's hypothesis? *Am J Hum Biol* 17: 381–382, 2005.

324. Konig M, Shuldiner AR. The genetic interface between gestational diabetes and type 2 diabetes. *J Matern Fetal Neonatal Med* 25: 36–40, 2011.

325. Koupilova I, Leon DA, McKeigue PM, Lithell HO. Is the effect of low birth weight on cardiovascular mortality mediated through high blood pressure? *J Hypertens* 17: 19–25, 1999.

326. Kramer MS, Matush L, Vanilovich I, Platt RW, Bogdanovich N, Sevkovskaya Z, Dzikovich I, Shishko G, Collet JP, Martin RM, Smith GD, Gillman MW, Chalmers B, Hodnett E, Shapiro S. A randomized breast-feeding promotion intervention did not reduce child obesity in Belarus. *J Nutr* 139: 417S–421S, 2009.

327. Kramer MS, Moodie EE, Platt RW. Infant feeding and growth: can we answer the causal question? *Epidemiology* 23: 790–794, 2012.

328. Krause BJ, Costello P, Garrat ES, Lillycrop KA, Sobrevia L, Hanson MA, Casanello P. Altered expression of L-arginine/NO-related enzymes in cultured endothelial cells from IUGR placenta is accompanied by specific DNA methylation changes. In: *Journal of Developmental Origins of Health And Disease*. Cambridge, UK: Cambridge Univ. Press, 2011, p. S4.

329. Kucharski R, Maleszka J, Foret S, Maleszka R. Nutritional control of reproductive status in honeybees via DNA methylation. *Science* 319: 1827–1830, 2008.

330. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *J Epidemiol Community Health* 57: 778–783, 2003.

331. Kuzawa CW. Fetal origins of developmental plasticity: are fetal cues reliable predictors of future nutritional environments? *Am J Hum Biol* 17: 5–21, 2005.

332. Kuzawa CW, Bragg JM. Plasticity in human life history strategy: Implications for contemporary human variation and the evolution of genus Homo. *Curr Anthropol* 53: S369–S382, 2012.

333. Kuzawa CW, Gluckman P, Hanson M. Developmental perspectives on the origin of obesity. In: *Adipose Tissue and Adipokines in Health and Disease*, edited by Fantuzzi G, Mazzone T. Totowa, NJ: Humana, 2007, p. 207–219.

334. Lachmann M, Jablonka E. The inheritance of phenotypes: an adaptation to fluctuating environments. *J Theoretical biol* 181: 1–9, 1996.

335. Lain KY, Catalano PM. Metabolic changes in pregnancy. *Clin Obstet Gynecol* 50: 938–948, 2007.

336. Lambrot R, Xu C, Saint-Phar S, Chountalos G, Cohen T, Paquet M, Suderman M, Hallett M, Kimmins S. Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. *Nature Commun* 4: 2889, 2013.

337. Lande R. Adaptation to an extraordinary environment by evolution of phenotypic plasticity and genetic assimilation. *J Evol Biol* 22: 1435–1446, 2009.

338. Langley-Evans SC, Bellinger L, McMullen S. Animal models of programming: early life influences on appetite and feeding behaviour. *Maternal Child Nutr* 1: 142–148, 2005.

339. Langley-Evans SC, Phillips GJ, Benediktsson R, Gardner DS, Edwards CR, Jackson AA, Seckl JR. Protein intake in pregnancy, placental glucocorticoid metabolism and the programming of hypertension in the rat. *Placenta* 17: 169–172, 1996.

340. Lanham SA, Roberts C, Hollingworth T, Sreekumar R, Elahi MM, Cagampang FR, Hanson MA, Oreffo RO. Maternal high-fat diet: effects on offspring bone structure. *Osteoporosis Int* 21: 1703–1714, 2010.

341. Lauenborg J, Grarup N, Damm P, Borch-Johnsen K, Jorgensen T, Pedersen O, Hansen T. Common type 2 diabetes risk gene variants associate with gestational diabetes. *J Clin Endocrinol Metab* 94: 145–150, 2009.

342. Lawlor DA, Mortensen L, Andersen AM. Mechanisms underlying the associations of maternal age with adverse perinatal outcomes: a sibling study of 264 695 Danish women and their firstborn offspring. *Int J Epidemiol* 40: 1205–1214, 2011.

343. Lawlor DA, Najman JM, Sterne J, Williams GM, Ebrahim S, Davey Smith G. Associations of parental, birth, and early life characteristics with systolic blood pressure at 5 years of age: findings from the Mater-University study of pregnancy and its outcomes. *Circulation* 110: 2417–2423, 2004.

344. Lawlor DA, Ronalds G, Clark H, Smith GD, Leon DA. Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s: findings from the Aberdeen Children of the 1950s prospective cohort study. *Circulation* 112: 1414–1418, 2005.

345. Lazdam M, de la Horra A, Pitcher A, Mannie Z, Diesch J, Trevitt C, Kylintireas I, Contractor H, Singhal A, Lucas A, Neubauer S, Kharbanda R, Alp N, Kelly B, Leeson P. Elevated blood pressure in offspring born premature to hypertensive pregnancy: is endothelial dysfunction the underlying vascular mechanism? *Hypertension* 56: 159–165, 2010.

346. Le Maire A, Grimaldi M, Roecklin D, Dagnino S, Vivat-Hannah V, Balaguer P, Bourguet W. Activation of RXR-PPAR heterodimers by organotin environmental endocrine disruptors. *EMBO Rep* 10: 367–373, 2009.

347. Lee SC, Pu YB, Chow CC, Yeung VT, Ko GT, So WY, Li JK, Chan WB, Ma RC, Critchley JA, Cockram CS, Chan JC. Diabetes in Hong Kong Chinese: evidence for familial clustering and parental effects. *Diabetes Care* 23: 1365–1368, 2000.

348. Lee TM, Smale L, Zucker I, Dark J. Influence of daylength experienced by dams on post-natal development of young meadow voles (*Microtus pennsylvanicus*). *J Reprod Fertil* 81: 337–342, 1987.

349. Leermakers ET, Sonnenschein-van der Voort AM, Gaillard R, Hofman A, de Jongste JC, Jaddoe VW, Duijts L. Maternal weight, gestational weight gain and preschool wheezing. *The* Generation R Study. *Eur Respir J* 42: 1234–1243, 2013.

350. Leon DA. Fetal growth and adult disease. *Eur J Clin Nutr* 52 *Suppl* 1: S72–S82, 1998.

351. Lewandowski AJ, Augustine D, Lamata P, Davis EF, Lazdam M, Francis J, McCormick K, Wilkinson AR, Singhal A, Lucas A, Smith NP, Neubauer S, Leeson P. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. *Circulation* 127: 197–206, 2013.

352. Lewis RM, Cleal JK, Hanson MA. Review: placenta, evolution and lifelong health. *Placenta* 33 *Suppl*: S28–S32, 2012.

353. Lewis RM, Demmelmair H, Gaillard R, Godfrey KM, Hauguel-de Mouzon S, Huppertz B, Larque E, Saffery R, Symonds ME, Desoye G. The placental exposome: placental determinants of fetal adiposity and postnatal body composition. *Ann Nutr Metab* 63: 208–215, 2013.

354. Lewis RM, Glazier J, Greenwood SL, Bennett EJ, Godfrey KM, Jackson AA, Sibley CP, Cameron IT, Hanson MA. L-Serine uptake by human placental microvillous membrane vesicles. *Placenta* 28: 445–452, 2007.

355. Lewis RM, Greenwood SL, Cleal JK, Crozier SR, Verrall L, Inskip HM, Cameron IT, Cooper C, Sibley CP, Hanson MA, Godfrey KM. Maternal muscle mass may influence system A activity in human placenta. *Placenta* 31: 418–422, 2010.

356. Lewis RM, Hanson MA, Burdge GC. Umbilical venous-arterial plasma composition differences suggest differential incorporation of fatty acids in NEFA and cholesteryl ester pools. *Br J Nutr* 106: 463–467, 2011.

357. Lewontin RC. Annotation: the analysis of variance and the analysis of causes. *Am J Hum Genet* 26: 400–411, 1974.

358. Li CC, Cropley JE, Cowley MJ, Preiss T, Martin DI, Suter CM. A sustained dietary change increases epigenetic variation in isogenic mice. *PLoS Genet* 7: e1001380, 2011.

359. Li J, Harris RA, Cheung SW, Coarfa C, Jeong M, Goodell MA, White LD, Patel A, Kang SH, Shaw C, Chinault AC, Gambin T, Gambin A, Lupski JR, Milosavljevic A. Genomic hypomethylation in the human germline associates with selective structural mutability in the human genome. *PLoS Genet* 8: e1002692, 2012.

360. Li M, Sloboda DM, Vickers MH. Maternal obesity and developmental programming of metabolic disorders in offspring: evidence from animal models. *Exp Diabetes Res* 2011: 592408, 2011.

361. Li Y, Jaddoe VW, Qi L, He Y, Lai J, Wang J, Zhang J, Hu Y, Ding EL, Yang X, Hu FB, Ma G. Exposure to the Chinese famine in early life and the risk of hypertension in adulthood. *J Hypertens* 29: 1085–1092, 2011.

362. Liang C, Oest ME, Prater MR. Intrauterine exposure to high saturated fat diet elevates risk of adult-onset chronic diseases in C57BL/6 mice. *Birth Defects Research B Dev Reprod Toxicol* 86: 377–384, 2009.

363. Liggins GC. The role of cortisol in preparing the fetus for birth. *Reprod Fertil Dev* 6: 141–150, 1994.

364. Ligi I, Simoncini S, Tellier E, Grandvuillemin I, Marcelli M, Bikfalvi A, Buffat C, Dignat-George F, Anfosso F, Simeoni U. Altered angiogenesis in low birth weight individuals: a role for anti-angiogenic circulating factors. *J Matern Fetal Neonatal Med* 27: 233–238, 2014.

365. Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. *J Nutr* 135: 1382–1386, 2005.

366. Lillycrop KA, Rodford J, Garratt ES, Slater-Jefferies JL, Godfrey KM, Gluckman PD, Hanson MA, Burdge GC. Maternal protein restriction with or without folic acid supplementation during pregnancy alters the hepatic transcriptome in adult male rats. *Br J Nutr* 103: 1711–1719, 2010.

367. Lindsay RS, Lindsay RM, Waddell BJ, Seckl JR. Prenatal glucocorticoid exposure leads to offspring hyperglycaemia in the rat: studies with the 11 beta-hydroxysteroid dehydrogenase inhibitor carbenoxolone. *Diabetologia* 39: 1299–1305, 1996.

368. Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science* 277: 1659–1662, 1997.

369. Low FM, Gluckman PD, Hanson MA. Developmental plasticity and epigenetic mechanisms underpinning metabolic and cardiovascular diseases. *Epigenomics* 3: 279–294, 2011.

370. Lucas A. Programming by early nutrition in man. *Ciba Found Symp* 156: 38–50, 1991.

371. Lucas JS, Inskip HM, Godfrey KM, Foreman CT, Warner JO, Gregson RK, Clough JB. Small size at birth and greater postnatal weight gain: relationships to diminished infant lung function. *Am JRespir Crit Care Med* 170: 534–540, 2004.

372. Lukaszewski MA, Eberle D, Vieau D, Breton C. Nutritional manipulations in the perinatal period program adipose tissue in offspring. *Am J Physiol Endocrinol Metab* 305: E1195–E1207, 2013.

373. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest* 117: 175–184, 2007.

374. Ma RC, Chan JC. Pregnancy and diabetes scenario around the world: China. *Int J Gynaecol Obstet* 5: 529–530, 2009.

375. Ma RCW, Chan JCN, Tam WH, Hanson MA, Gluckman PD. Gestational Diabetes, Maternal Obesity and the NCD Burden. *Clin Obstet Gynecol* 56: 633–641, 2013.

376. Maher B. Personal genomes: the case of the missing heritability. *Nature* 456: 18–21, 2008.

377. Malabou C. *What Should We Do With Our Brain?* Bronx, NY: Fordham Univ Press, 2009.

378. Maloyan A, Muralimanoharan S, Huffman S, Cox LA, Nathanielsz PW, Myatt L, Nijland MJ. Identification and comparative analyses of myocardial miRNAs involved in the fetal response to maternal obesity. *Physiol Gen* 45: 889–900, 2013.

379. Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: evidence from a birth cohort study. *Circulation* 119: 1720–1727, 2009.

380. Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. *PloS One* 8: e55387, 2013.

381. Marcheva B, Ramsey KM, Buhr ED, Kobayashi Y, Su H, Ko CH, Ivanova G, Omura C, Mo S, Vitaterna MH, Lopez JP, Philipson LH, Bradfield CA, Crosby SD, JeBailey L, Wang X, Takahashi JS, Bass J. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature* 466: 627–631, 2010.

382. Marczylo EL, Amoako AA, Konje JC, Gant TW, Marczylo TH. Smoking induces differential miRNA expression in human spermatozoa: a potential transgenerational epigenetic concern? *Epigenetics* 7: 432–439, 2012.

382a. Marshall D, Uller T. When is a maternal effect adaptive? *Oikos* 116: 1957–1963, 2007.

383. Martin R, Harvey NC, Crozier SR, Poole JR, Javaid MK, Dennison EM, Inskip HM, Hanson M, Godfrey KM, Cooper C, Lewis R, Group SWSS. Placental calcium transporter (PMCA3) gene expression predicts intrauterine bone mineral accrual. *Bone* 40: 1203–1208, 2007.

384. Martino D, Prescott S. Epigenetics and prenatal influences on asthma and allergic airways disease. *Chest* 139: 640–647, 2011.

385. Martyn CN, Gale CR, Jespersen S, Sherriff SB. Impaired fetal growth and atherosclerosis of carotid and peripheral arteries. *Lancet* 352: 173–178, 1998.

386. Mateo JM. Ecological and hormonal correlates of antipredator behavior in adult Belding's ground squirrels (*Spermophilus beldingi*). *Behav Ecol Sociobiol* 62: 37–49, 2007.

387. Mathai S, Cutfield WS, Derraik JG, Dalziel SR, Harding JE, Robinson E, Biggs J, Jefferies C, Hofman PL. Insulin sensitivity and beta-cell function in adults born preterm and their children. *Diabetes* 61: 2479–2483, 2012.

388. Matthews SG. Early programming of the hypothalamo-pituitary-adrenal axis. *Trends Endocrinol Metab* 13: 373–380, 2002.

389. Matzke M, Matzke A. Genomic imprinting in plants: parental effects and trans-inactivation phenomena. *Annu Rev Plant Biol* 44: 53–76, 1993.

390. McArdle HJ, Ashworth CJ. Micronutrients in fetal growth and development. *Br Med Bull* 55: 499–510, 1999.

391. McBride WG. Thalidomide and congential abnormalities. *Lancet* 2: 1.499–358, 1961.

392. McCaffery A, Simpson S. A gregarizing factor present in the egg pod foam of the desert locust Schistocerca gregaria. *J Exp Biol* 201: 347–363, 1998.

393. McCollum SA, Leimberger JD. Predator-induced morphological changes in an amphibian: Predation by dragonflies affects tadpole shape and color. *Oecologia* 109: 615–621, 1997.

394. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neurosci* 12: 342–348, 2009.

395. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 337: 382–386, 1991.

396. McKinlay CJ, Crowther CA, Middleton P, Harding JE. Repeat antenatal glucocorticoids for women at risk of preterm birth: a Cochrane Systematic Review. *Am J Obstet Gynecol* 206: 187–194, 2012.

397. McMillen IC, Adam CL, Muhlhausler BS. Early origins of obesity: programming the appetite regulatory system. *J Physiol* 565: 9–17, 2005.

398. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* 85: 571–633, 2005.

399. McMullen S, Mostyn A. Animal models for the study of the developmental origins of health and disease. *Proc Nutr Soc* 68: 306–320, 2009.

400. Mercer TR, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. *Nature Struct Mol Biol* 20: 300–307, 2013.

401. Mericq V, Ong KK, Bazaes R, Pena V, Avila A, Salazar T, Soto N, Iniguez G, Dunger DB. Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for-gestational-age children. *Diabetologia* 48: 2609–2614, 2005.

402. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJN, Persson B, Rogers MS, Sacks DA, Grp HSCR. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 358: 1991–2002, 2008.

403. Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, Colditz GA, Hankinson SE, Speizer FE, Willett WC. Birthweight as a risk factor for breast cancer. *Lancet* 348: 1542–1546, 1996.

404. Mikaelsson MA, Constancia M, Dent CL, Wilkinson LS, Humby T. Placental programming of anxiety in adulthood revealed by Igf2-null models. *Nature Commun* 4: 2311, 2013.

405. Mildenhall LF, Battin MR, Morton SM, Bevan C, Kuschel CA, Harding JE. Exposure to repeat doses of antenatal glucocorticoids is associated with altered cardiovascular status after birth. *Arch Dis Childh Fetal Neonatal Edition* 91: F56–60, 2006.

406. Miles JL, Landon J, Davison M, Krageloh CU, Thompson NM, Triggs CM, Breier BH. Prenatally undernourished rats show increased preference for wheel running v. lever pressing for food in a choice task. *Br J Nutr* 101: 902–908, 2009.

407. Milton CC, Ulane CM, Rutherford S. Control of canalization and evolvability by Hsp90. *PloS One* 1: e75, 2006.

408. Miyakawa H, Imai M, Sugimoto N, Ishikawa Y, Ishikawa A, Ishigaki H, Okada Y, Miyazaki S, Koshikawa S, Cornette R, Miura T. Gene up-regulation in response to predator kairomones in the water flea, *Daphnia pulex*. *BMC Dev Biol* 10: 45, 2010.

409. Mook-Kanamori DO, Ay L, Hofman A, van Duijn CM, Moll HA, Raat H, Hokken-Koelega ACS, Jaddoe VWV. No association of obesity gene FTO with body composition at the age of 6 months. The Generation R Study. *J Endocrinol Invest* 34: 16–20, 2011.

410. Morales-Roselló J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Fetal Doppler changes as a marker of failure to reach growth potential at term. *Ultrasound Obstet Gynecol* 43: 303–310, 2014.

411. Moran NA. The evolutionary maintenance of alternative phenotypes. *Am Naturalist* 139: 971–989, 1992.

412. Morgan HD, Santos F, Green K, Dean W, Reik W. Epigenetic reprogramming in mammals. *Hum Mol Genet* 14: R47–58, 2005.

413. Moritz KM, Cullen-McEwen LA. Kidney development and fetal programming. In: *Early Life Origins of Health and Disease*. New York: Springer, 2006, p. 130–144.

414. Morrison S, Gardner DS, Fletcher AJ, Bloomfield MR, Giussani DA. Enhanced nitric oxide activity offsets peripheral vasoconstriction during acute hypoxaemia via chemoreflex and adrenomedullary actions in the sheep fetus. *J Physiol* 547: 283–291, 2003.

415. Moss L. The meaning of the gene and future of the genotype. *Genet Soc Policy* 4: 38–57, 2008.

416. Moss L. *What Genes Can't Do*. Cambridge, MA: MIT Press, 2002.

417. Mousseau TA, Fox CW. *Maternal Effects as Adaptations*. New York: Oxford Univ. Press, 1998.

418. Myatt L. Placental adaptive responses and fetal programming. *J Physiol* 572: 25–30, 2006.

419. Naeye RL. Effects of maternal cigarette smoking on the fetus and placenta. *Br J Obstet Gynaecol* 85: 732–737, 1978.

420. Napoli C, Witztum JL, Calara F, de Nigris F, Palinski W. Maternal hypercholesterolemia enhances atherogenesis in normocholesterolemic rabbits, which is inhibited by antioxidant or lipid-lowering intervention during pregnancy: an experimental model of atherogenic mechanisms in human fetuses. *Circ Res* 87: 946–952, 2000.

421. Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 14: 353–362, 1962.

422. Nesse RM. Natural selection and the regulation of defenses: a signal detection analysis of the smoke detector principle. *Evol Hum Behav* 26: 88–105, 2005.

423. Nesse RM, Stearns SC, Omenn GS. Medicine needs evolution. *Science* 311: 1071, 2006.

424. Nettle D, Frankenhuis WE, Rickard IJ. The evolution of predictive adaptive responses in human life history. *Proc R Soc Biol Sci* 280: 20131343, 2013.

425. Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. Is birth weight related to later glucose and insulin metabolism? A systematic review. *Diabetic Med* 20: 339–348, 2003.

426. Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ. Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. *Nature* 467: 963–966, 2010.

427. Nilsson E, Stalberg G, Lichtenstein P, Cnattingius S, Olausson PO, Hultman CM. Fetal growth restriction and schizophrenia: a Swedish twin study. *Twin Res Hum Genet* 8: 402–408, 2005.

428. Nilsson EE, Anway MD, Stanfield J, Skinner MK. Transgenerational epigenetic effects of the endocrine disruptor vinclozolin on pregnancies and female adult onset disease. *Reproduction* 135: 713–721, 2008.

429. Nishihara M, Hirooka Y, Kishi T, Sunagawa K. Different role of oxidative stress in paraventricular nucleus and rostral ventrolateral medulla in cardiovascular regulation in awake spontaneously hypertensive rats. *J Hypertens* 30: 1758–1765, 2012.

430. Nishihara M, Hirooka Y, Matsukawa R, Kishi T, Sunagawa K. Oxidative stress in the rostral ventrolateral medulla modulates excitatory and inhibitory inputs in spontaneously hypertensive rats. *J Hypertens* 30: 97–106, 2012.

431. Nishimura K. Inducible plasticity: optimal waiting time for the development of an inducible phenotype. *Evol Ecol Res* 8: 553–559, 2006.

432. Niu Y, Herrera EA, Evans RD, Giussani DA. Antioxidant treatment improves neonatal survival and prevents impaired cardiac function at adulthood following neonatal glucocorticoid therapy. *J Physiol* 591: 5083–5093, 2013.

433. Noble D. Physiology is rocking the foundations of evolutionary biology. *Exp Physiol* 98: 1235–1243, 2013.

434. Noble D, Jablonka E, Joyner M, Muller G, Omholt S. The integration of evolutionary biology with physiological science. *J Physiol* 592: 2237–2438, 2014.

435. Nour NM. Schistosomiasis: health effects on women. *Rev Obstet Gynecol* 3: 28–32, 2010.

436. Novakovic B, Gordon L, Robinson WP, Desoye G, Saffery R. Glucose as a fetal nutrient: dynamic regulation of several glucose transporter genes by DNA methylation in the human placenta across gestation. *J Nutr Biochem* 24: 282–288, 2013.

437. Novakovic B, Yuen RK, Gordon L, Penaherrera MS, Sharkey A, Moffett A, Craig JM, Robinson WP, Saffery R. Evidence for widespread changes in promoter methylation profile in human placenta in response to increasing gestational age and environmental/stochastic factors. *BMC Genomics* 12: 529, 2011.

438. Nurkiewicz TR, Wu G, Li P, Boegehold MA. Decreased arteriolar tetrahydrobiopterin is linked to superoxide generation from nitric oxide synthase in mice fed high salt. *Microcirculation* 17: 147–157, 2010.

439. Nutbeam D. Health literacy as a public health goal: a challenge for contemporary health education and communication strategies into the 21st century. *Health promotion Int* 15: 259–267, 2000.

440. O'Tierney PF, Lewis RM, McWeeney SK, Hanson MA, Inskip HM, Morgan TK, Barker DJ, Bagby G, Cooper C, Godfrey KM, Thornburg KL. Immune response gene profiles in the term placenta depend upon maternal muscle mass. *Reprod Sci* 19: 1041–1056, 2012.

441. Oben JA, Mouralidarane A, Samuelsson AM, Matthews PJ, Morgan ML, McKee C, Soeda J, Fernandez-Twinn DS, Martin-Gronert MS, Ozanne SE, Sigala B, Novelli M, Poston L, Taylor PD. Maternal obesity during pregnancy and lactation programs the development of offspring non-alcoholic fatty liver disease in mice. *J Hepatol* 52: 913–920, 2010.

442. Oben JA, Patel T, Mouralidarane A, Samuelsson AM, Matthews P, Pombo J, Morgan M, McKee C, Soeda J, Novelli M, Poston L, Taylor P. Maternal obesity programmes offspring development of non-alcoholic fatty pancreas disease. *Biochem Biophys Res Commun* 394: 24–28, 2010.

443. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics* 3: 97–106, 2008.

444. Odijk Jv Kull I, Borres M, Brandtzaeg P, Edberg U, Hanson L, Høst A, Kuitunen M, Olsen S, Skerfving S. Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966–2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* 58: 833–843, 2003.

445. Odling-Smee FJ, Laland KN, Feldman MW. Niche construction. *Am Naturalist* 147: 641–648, 1996.

446. Ojala T, Aaltonen J, Siira S, Jalonen J, Ekholm E, Ekblad U, Laitinen K. Fetal cardiac sympathetic activation is linked with maternal body mass index. *Early Hum Dev* 85: 557–560, 2009.

447. Oken E, Gillman MW. Fetal origins of obesity. *Obesity Res* 11: 496–506, 2003.

448. Oliva K, Barker G, Riley C, Bailey MJ, Permezel M, Rice GE, Lappas M. The effect of pre-existing maternal obesity on the placental proteome: two-dimensional difference gel electrophoresis coupled with mass spectrometry. *J Mol Endocrinol* 48: 139–149, 2012.

449. Ollikainen M, Smith KR, Joo EJ, Ng HK, Andronikos R, Novakovic B, Abdul Aziz NK, Carlin JB, Morley R, Saffery R, Craig JM. DNA methylation analysis of multiple tissues from newborn twins reveals both genetic and intrauterine components to variation in the human neonatal epigenome. *Hum Mol Genet* 19: 4176–4188, 2010.

450. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ* 320: 967–971, 2000.

451. Orstavik KH, Eiklid K, van der Hagen CB, Spetalen S, Kierulf K, Skjeldal O, Buiting K. Another case of imprinting defect in a girl with Angelman syndrome who was conceived by intracytoplasmic semen injection. *Am J Hum Genet* 72: 218–219, 2003.

452. Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. *BMJ* 307: 1519–1524, 1993.

453. Ozaki T, Nishina H, Hanson MA, Poston L. Dietary restriction in pregnant rats causes gender-related hypertension and vascular dysfunction in offspring. *J Physiol* 530: 141–152, 2001.

454. Ozanne SE, Hales CN. Lifespan: catch-up growth and obesity in male mice. *Nature* 427: 411–412, 2004.

455. Ozanne SE, Jensen CB, Tingey KJ, Storgaard H, Madsbad S, Vaag AA. Low birthweight is associated with specific changes in muscle insulin-signalling protein expression. *Diabetologia* 48: 547–552, 2005.

456. Ozanne SE, Lewis R, Jennings BJ, Hales CN. Early programming of weight gain in mice prevents the induction of obesity by a highly palatable diet. *Clin Sci* 106: 141–145, 2004.

457. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr Rev* 24: 668–693, 2003.

458. Park JH, Stoffers DA, Nicholls RD, Simmons RA. Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. *J Clin Invest* 118: 2316, 2008.

459. Park JH, Stoffers DA, Nicholls RD, Simmons RA. Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. *J Clin Invest* 118: 2316–2324, 2008.

460. Patterson AJ, Chen M, Xue Q, Xiao D, Zhang L. Chronic prenatal hypoxia induces epigenetic programming of PKCε gene repression in rat hearts. *Circ Res* 107: 365–373, 2010.

461. Patterson AJ, Xiao D, Xiong F, Dixon B, Zhang L. Hypoxia-derived oxidative stress mediates epigenetic repression of PKCepsilon gene in foetal rat hearts. *Cardiovasc Res* 93: 302–310, 2012.

462. Pembrey ME. Male-line transgenerational responses in humans. *Hum Fertil* 13: 268–271, 2010.

463. Pembrey ME, Bygren LO, Kaati G, Edvinsson S, Northstone K, Sjostrom M, Golding J, Team AS. Sex-specific, male-line transgenerational responses in humans. *Eur J Hum Genet* 14: 159–166, 2006.

464. Perkins E, Murphy SK, Murtha AP, Schildkraut J, Jirtle RL, Demark-Wahnefried W, Forman MR, Kurtzberg J, Overcash F, Huang Z, Hoyo C. Insulin-like growth factor 2/H19 methylation at birth and risk of overweight and obesity in children. *J Pediatr* 161: 31–39, 2012.

465. Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC. Congenital susceptibility to NIDDM. Role of intrauterine environment. *Diabetes* 37: 622–628, 1988.

466. Pettitt DJ, Lawrence JM, Beyer J, Hillier TA, Liese AD, Mayer-Davis B, Loots B, Imperatore G, Liu L, Dolan LM, Linder B, Dabelea D. Association between maternal diabetes in utero and age at offspring's diagnosis of type 2 diabetes. *Diabetes Care* 31: 2126–2130, 2008.

467. Pfeifer GP. Mutagenesis at methylated CpG sequences. *Curr Top Microbiol Immunol* 301: 259–281, 2006.

468. Pigliucci M. *Phenotypic Plasticity: Beyond Nature and Nurture*. Baltimore, MD: Johns Hopkins Univ. Press, 2001.

469. Pike KC, Hanson MA, Godfrey KM. Developmental mismatch: consequences for later cardiorespiratory health. *BJOG* 115: 149–157, 2008.

470. Pike KC, Inskip HM, Robinson SM, Cooper C, Godfrey KM, Roberts G, Lucas JS, Southampton Women's Survey Study. The relationship between maternal adiposity and infant weight gain, and childhood wheeze and atopy. *Thorax* 68: 372–379, 2013.

471. Pilgaard K, Faerch K, Carstensen B, Poulsen P, Pisinger C, Pedersen O, Witte DR, Hansen T, Jorgensen T, Vaag A. Low birthweight and premature birth are both associated with type 2 diabetes in a random sample of middle-aged Danes. *Diabetologia* 53: 2526–2530, 2010.

472. Pinney SE, Jaeckle Santos LJ, Han Y, Stoffers DA, Simmons RA. Exendin-4 increases histone acetylase activity and reverses epigenetic modifications that silence Pdx1 in the intrauterine growth retarded rat. *Diabetologia* 54: 2606–2614, 2011.

473. Plagemann A. "Fetal programming" and "functional teratogenesis": on epigenetic mechanisms and prevention of perinatally acquired lasting health risks. *J Perinatal Med* 32: 297–305, 2004.

474. Poore KR, Boullin JP, Cleal JK, Newman JP, Noakes DE, Hanson MA, Green LR. Sex- and age-specific effects of nutrition in early gestation and early postnatal life on hypothalamo-pituitary-adrenal axis and sympathoadrenal function in adult sheep. *J Physiol* 588: 2219–2237, 2010.

475. Poore KR, Cleal JK, Newman JP, Boullin JP, Noakes DE, Hanson MA, Green LR. Nutritional challenges during development induce sex-specific changes in glucose homeostasis in the adult sheep. *Am J Physiol Endocrinol Metab* 292: E32–E39, 2007.

476. Poore KR, Fowden AL. The effect of birth weight on hypothalamo-pituitary-adrenal axis function in juvenile and adult pigs. *J Physiol* 547: 107–116, 2003.

477. Pooya S, Blaise S, Moreno Garcia M, Giudicelli J, Alberto JM, Gueant-Rodriguez RM, Jeannesson E, Gueguen N, Bressenot A, Nicolas B, Malthiery Y, Daval JL, Peyrin-Biroulet L, Bronowicki JP, Gueant JL. Methyl donor deficiency impairs fatty acid oxidation through PGC-1alpha hypomethylation and decreased ER-alpha, ERR-alpha, and HNF-4alpha in the rat liver. *J Hepatol* 57: 344–351, 2012.

478. Popkin BM. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. *Am J Clin Nutr* 84: 289–298, 2006.

479. Poston L. Developmental programming and diabetes: the human experience and insight from animal models. *Best Pract Res Clin Endocrinol Metab* 24: 541–552, 2010.

480. Poston L. Intergenerational transmission of insulin resistance and type 2 diabetes. *Prog Biophys Mol Biol* 106: 315–322, 2011.

481. Poston L, Hanson M. Developmental Origins of Health and Disease. In: *Maternal-Fetal Medicine, Principles and Practice*, edited by Creasy, Resnick. Philadelphia, PA: Saunders Elsevier, 2013.

483. Queitsch C, Sangster TA, Lindquist S. Hsp90 as a capacitor of phenotypic variation. *Nature* 417: 618–624, 2002.

484. Radaelli T, Varastehpour A, Catalano P, Hauguel-de Mouzon S. Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. *Diabetes* 52: 2951–2958, 2003.

485. Raikkonen K, Seckl JR, Heinonen K, Pyhala R, Feldt K, Jones A, Pesonen AK, Phillips DI, Lahti J, Jarvenpaa AL, Eriksson JG, Matthews KA, Strandberg TE, Kajantie E. Maternal prenatal licorice consumption alters hypothalamic-pituitary-adrenocortical axis function in children. *Psychoneuroendocrinology* 35: 1587–1593, 2010.

486. Rajasingam D, Seed PT, Briley AL, Shennan AH, Poston L. A prospective study of pregnancy outcome and biomarkers of oxidative stress in nulliparous obese women. *Am J Obstet Gynecol* 200: 395 e391–399, 2009.

487. Rassoulzadegan M. An evolutionary role for RNA-mediated epigenetic variation. *Transformation of Lamarckism: From Subtle Fluids to Molecular Biology* Cambridge, MA: MIT Press, 2011, p. 227–235.

488. Rassoulzadegan M, Grandjean V, Gounon P, Vincent S, Gillot I, Cuzin F. RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse. *Nature* 441: 469–474, 2006.

489. Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN, Bleker OP. Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 351: 173–177, 1998.

490. Raymond GV. Teratogen update: ergot and ergotamine. *Teratology* 51: 344–347, 1995.

491. RCOG. Chemical exposures during pregnancy: dealing with potential, but unproven, risks to child health. *Scientific Impact Paper* No. 37, RCOG, 2013.

492. Redman CW. Preeclampsia: a multi-stress disorder. *Rev Med Intern* 32 *Suppl* 1: S41–44, 2011.

493. Reece EA, Leguizamon G, Wiznitzer A. Gestational diabetes: the need for a common ground. *Lancet* 373: 1789–1797, 2009.

494. Relton CL, Groom A, St Pourcain B, Sayers AE, Swan DC, Embleton ND, Pearce MS, Ring SM, Northstone K, Tobias JH, Trakalo J, Ness AR, Shaheen SO, Davey Smith G. DNA methylation patterns in cord blood DNA and body size in childhood. *PloS One* 7: e31821, 2012.

495. Remmers F, Delemarre-van de Waal HA. Developmental programming of energy balance and its hypothalamic regulation. *Endocr Rev* 32: 272–311, 2011.

496. Renfree MB, Hore TA, Shaw G, Graves JA, Pask AJ. Evolution of genomic imprinting: insights from marsupials and monotremes. *Annu Rev Genomics Hum Genet* 10: 241–262, 2009.

497. Rens W, Wallduck MS, Lovell FL, Ferguson-Smith MA, Ferguson-Smith AC. Epigenetic modifications on X chromosomes in marsupial and monotreme mammals and implications for evolution of dosage compensation. *Proc Natl Acad Sci USA* 107: 17657–17662, 2010.

498. Reynolds RM, Allan KM, Raja EA, Bhattacharya S, McNeill G, Hannaford PC, Sarwar N, Lee AJ, Bhattacharya S, Norman JE. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ* 347: f4539, 2013.

499. Reynolds RM, Osmond C, Phillips DI, Godfrey KM. Maternal BMI, parity, and pregnancy weight gain: influences on offspring adiposity in young adulthood. *J Clin Endocrinol Metab* 95: 5365–5369, 2010.

500. Rich-Edwards JW, Stampfer MJ, Manson JE, Rosner B, Hankinson SE, Colditz GA, Willett WC, Hennekens CH. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ* 315: 396–400, 1997.

501. Rinaudo P, Wang E. Fetal programming and metabolic syndrome. *Annu Rev Physiol* 74: 107–130, 2012.

502. Rodford JL, Torrens C, Siow RC, Mann GE, Hanson MA, Clough GF. Endothelial dysfunction and reduced antioxidant protection in an animal model of the developmental origins of cardiovascular disease. *J Physiol* 586: 4709–4720, 2008.

503. Rodriguez JS, Zurcher NR, Keenan KE, Bartlett TQ, Nathanielsz PW, Nijland MJ. Prenatal betamethasone exposure has sex specific effects in reversal learning and attention in juvenile baboons. *Am J Obstet Gynecol* 204: 545 e541–510, 2011.

504. Rogers I. Birth weight and obesity and fat distribution in later life. *Birth Defects Res A Clin Mol Teratol* 73: 485–486, 2005.

505. Romero IG, Ruvinsky I, Gilad Y. Comparative studies of gene expression and the evolution of gene regulation. *Nature Rev Genet* 13: 505–516, 2012.

506. Roseboom TJ, van der Meulen JH, Ravelli AC, Osmond C, Barker DJ, Bleker OP. Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. *Twin Res* 4: 293–298, 2001.

507. Roseboom TJ, van der Meulen JH, Ravelli AC, van Montfrans GA, Osmond C, Barker DJ, Bleker OP. Blood pressure in adults after prenatal exposure to famine. *J Hypertens* 17: 325–330, 1999.

508. Rossant J, Cross JC. Placental development: lessons from mouse mutants. *Nature Rev Genet* 2: 538–548, 2001.

509. Rowell C. The variable coloration of the acridoid grasshoppers. *Adv Insect Physiol* 8: 145–198, 1972.

510. Rowland TW, Hubbell JP Jr, Nadas AS. Congenital heart disease in infants of diabetic mothers. *J Pediatr* 83: 815–820, 1973.

511. Ruchat SM, Houde AA, Voisin G, St-Pierre J, Perron P, Baillargeon JP, Gaudet D, Hivert MF, Brisson D, Bouchard L. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. *Epigenetics* 8: 935–943, 2013.

512. Ruden DM, Xiao L, Garfinkel MD, Lu X. Hsp90 and environmental impacts on epigenetic states: a model for the trans-generational effects of diethylstibesterol on uterine development and cancer. *Hum Mol Genet* 14: R149–155, 2005.

513. Saastamoinen M, van der Sterren D, Vastenhout N, Zwaan BJ, Brakefield PM. Predictive adaptive responses: Condition-dependent impact of adult nutrition and flight in the tropical butterfly Bicyclus anynana. *Am Naturalist* 176: 686–698, 2010.

514. Saito T, Musha Y, Miyakawa M, Itoh S, Ohtsuji M, Hanson MA, Takeda S. Angiotensin II receptor antagonist reduces subsequent uterine arterial dysfunction in pregnant offspring of protein-restricted rat dams. *J Obstet Gynecol Res* 38: 483–489, 2012.

515. Samuelsson AM, Clark J, Shattock MJ, Rudyk O, Pombo J, Bae SE, South T, Coen CW, Poston L, Taylor PD. Effect of postnatal Leptin on cardiac structure and function. *Acta Obstet Gynecol Scand* 92: 30, 2013.

516. Samuelsson AM, Matthews PA, Argenton M, Christie MR, McConnell JM, Jansen EH, Piersma AH, Ozanne SE, Twinn DF, Remacle C, Rowlerson A, Poston L, Taylor PD. Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: a novel murine model of developmental programming. *Hypertension* 51: 383–392, 2008.

517. Samuelsson AM, Morris A, Igosheva N, Kirk SL, Pombo JM, Coen CW, Poston L, Taylor PD. Evidence for sympathetic origins of hypertension in juvenile offspring of obese rats. *Hypertension* 55: 76–82, 2010.

518. Sandovici I, Smith NH, Nitert MD, Ackers-Johnson M, Uribe-Lewis S, Ito Y, Jones RH, Marquez VE, Cairns W, Tadayyon M, O'Neill LP, Murrell A, Ling C, Constancia M, Ozanne SE. Maternal diet and aging alter the epigenetic control of a promoter-enhancer interaction at the Hnf4a gene in rat pancreatic islets. *Proc Natl Acad Sci USA* 108: 5449–5454, 2011.

519. Savage T, Derraik JG, Miles HL, Mouat F, Hofman PL, Cutfield WS. Increasing paternal age at childbirth is associated with taller stature and less favourable lipid profiles in their children. *Clin Endocrinol* 80: 253–260, 2014.

520. Save The Children. Superfood for Babies Save The Children: www.savethechildren.org.uk/resouces/online-library/superfood-babies.

521. Sawyer SM, Afifi RA, Bearinger LH, Blakemore SJ, Dick B, Ezeh AC, Patton GC. Adolescence: a foundation for future health. *Lancet* 379: 1630–1640, 2012.

522. Schlichting CD, Pigliucci M. *Phenotypic Evolution: A Reaction Norm Perspective*. Sunderland, MA: Sinauer, 1998.

523. Schmalhausen I. *Factor of Evolution: The Theory of Stabilizing Selection*, edited by Dobxhansky T. Chicago, IL: Univ. of Chicago Press, 1986.

524. Scully T. Demography: to the limit. *Nature* 492: S2–3, 2012.

525. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Poulton R. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 360: 901–907, 2002.

526. Seckl JR. Glucocorticoid programming of the fetus: adult phenotypes and molecular mechanisms. *Mol Cell Endocrinol* 185: 61–71, 2001.

527. Seckl JR. Glucocorticoids, feto-placental 11 beta-hydroxysteroid dehydrogenase type 2, and the early life origins of adult disease. *Steroids* 62: 89–94, 1997.

528. Seckl JR. Prenatal glucocorticoids and long-term programming. *Eur J Endocrinol* 151 *Suppl* 3: U49–62, 2004.

529. Seckl JR, Walker BR. Minireview: 11beta-hydroxysteroid dehydrogenase type 1, a tissue-specific amplifier of glucocorticoid action. *Endocrinology* 142: 1371–1376, 2001.

530. Sen A. Social access and social protection for food security. *Food Security in Asia* 237, 2012.

531. Sen S, Simmons RA. Maternal antioxidant supplementation prevents adiposity in the offspring of Western diet-fed rats. *Diabetes* 59: 3058–3065, 2010.

532. Sferruzzi-Perri AN, Vaughan OR, Coan PM, Suciu MC, Darbyshire R, Constancia M, Burton GJ, Fowden AL. Placental-specific Igf2 deficiency alters developmental adaptations to undernutrition in mice. *Endocrinology* 152: 3202–3212, 2011.

533. Sferruzzi-Perri AN, Vaughan OR, Haro M, Cooper WN, Musial B, Charalambous M, Pestana D, Ayyar S, Ferguson-Smith AC, Burton GJ, Constancia M, Fowden AL. An obesogenic diet during mouse pregnancy modifies maternal nutrient partitioning and the fetal growth trajectory. *FASEB J* 27: 3928–3937, 2013.

534. Sharpe RM. Sperm counts and fertility in men: a rocky road ahead. Science and Society Series on Sex and Science. *EMBO Reports* 13: 398–403, 2012.

535. Sheriff MJ, Krebs CJ, Boonstra R. The ghosts of predators past: population cycles and the role of maternal programming under fluctuating predation risk. *Ecology* 91: 2983–2994, 2010.

536. Sheriff MJ, Krebs CJ, Boonstra R. The sensitive hare: sublethal effects of predator stress on reproduction in snowshoe hares. *J Anim Ecol* 78: 1249–1258, 2009.

537. Sheriff MJ, Love OP. Determining the adaptive potential of maternal stress. *Ecol Lett* 16: 271–280, 2013.

538. Shoemaker R, Deng J, Wang W, Zhang K. Allele-specific methylation is prevalent and is contributed by CpG-SNPs in the human genome. *Genome Res* 20: 883–889, 2010.

539. Sibley CP, Coan PM, Ferguson-Smith AC, Dean W, Hughes J, Smith P, Reik W, Burton GJ, Fowden AL, Constancia M. Placental-specific insulin-like growth factor 2 (Igf2) regulates the diffusional exchange characteristics of the mouse placenta. *Proc Natl Acad Sci USA* 101: 8204–8208, 2004.

540. Silverman BL, Landsberg L, Metzger BE. Fetal hyperinsulinism in offspring of diabetic mothers. Association with the subsequent development of childhood obesity. *Ann NY Acad Sci* 699: 36–45, 1993.

541. Simeoni U, Barker DJ. Offspring of diabetic pregnancy: long-term outcomes. *Semin Fetal Neonatal Med* 14: 119–124, 2009.

542. Simmons RA. Developmental origins of diabetes: the role of oxidative stress. *Best Pract Res Clin Endocrinol Metab* 26: 701–708, 2012.

543. Simmons RA, Suponitsky-Kroyter I, Selak MA. Progressive accumulation of mitochondrial DNA mutations and decline in mitochondrial function lead to beta-cell failure. *J Biol Chem* 280: 28785–28791, 2005.

544. Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? *Circulation* 109: 1108–1113, 2004.

545. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet* 363: 1642–1645, 2004.

546. Skilton MR, Evans N, Griffiths KA, Harmer JA, Celermajer DS. Aortic wall thickness in newborns with intrauterine growth restriction. *Lancet* 365: 1484–1486, 2005.

547. Skinner MK. What is an epigenetic transgenerational phenotype? F3 or F2. *Reprod Toxicol* 25: 2–6, 2008.

548. Skinner MK, Manikkam M, Guerrero-Bosagna C. Epigenetic transgenerational actions of endocrine disruptors. *Reprod Toxicol* 31: 337–343, 2011.

549. Slater-Jefferies JL, Hoile SP, Lillycrop KA, Townsend PA, Hanson MA, Burdge GC. Effect of sex and dietary fat intake on the fatty acid composition of phospholipids and triacylglycerol in rat heart. *Prostaglandins Leukotrienes Essential Fatty Acids* 83: 219–223, 2010.

550. Sloboda D, Howie G, Vickers M. 4A-6 early-onset puberty in offspring after maternal undernutrition is exaggerated by a post-weaning high fat diet: sex specific evidence of nutritional mismatch. *Early Hum Dev* 83: S65–S66, 2007.

551. Sloboda DM, Hart R, Doherty DA, Pennell CE, Hickey M. Age at menarche: Influences of prenatal and postnatal growth. *J Clin Endocrinol Metab* 92: 46–50, 2007.

552. Smedts HP, van Uitert EM, Valkenburg O, Laven JS, Eijkemans MJ, Lindemans J, Steegers EA, Steegers-Theunissen RP. A derangement of the maternal lipid profile is associated with an elevated risk of congenital heart disease in the offspring. *Nutr Metab Cardiovasc Dis* 22: 477–485, 2012.

553. Smith SC, Baker PN. Placental apoptosis is increased in post-term pregnancies. *Br J Obstet Gynaecol* 106: 861–862, 1999.

554. Snoeck A, Remacle C, Reusens B, Hoet JJ. Effect of a low protein diet during pregnancy on the fetal rat endocrine pancreas. *Biol Neonate* 57: 107–118, 1990.

555. Sobngwi E, Boudou P, Mauvais-Jarvis F, Leblanc H, Velho G, Vexiau P, Porcher R, Hadjadj S, Pratley R, Tataranni PA, Calvo F, Gautier JF. Effect of a diabetic environment in utero on predisposition to type 2 diabetes. *Lancet* 361: 1861–1865, 2003.

556. Socha P, Grote V, Gruszfeld D, Janas R, Demmelmair H, Closa-Monasterolo R, Subias JE, Scaglioni S, Verduci E, Dain E, Langhendries JP, Perrin E, Koletzko B, European Childhood Obesity Trial Study. Milk protein intake, the metabolic-endocrine response, and growth in infancy: data from a randomized clinical trial. *The Am J Clin Nutr* 94: 1776S–1784S, 2011.

557. Soma-Pillay P, Macdonald A. Malaria in pregnancy. *Obstet Med* 5: 2–5, 2012.

558. Soto AM, Sonnenschein C. Environmental causes of cancer: endocrine disruptors as carcinogens. *Nature Rev Endocrinol* 6: 363–370, 2010.

559. Sovio U, Mook-Kanamori DO, Warrington NM, Lawrence R, Briollais L, Palmer CNA, Cecil J, Sandling JK, Syvanen AC, Kaakinen M, Beilin LJ, Millwood IY, Bennett AJ, Laitinen J, Pouta A, Molitor J, Smith GD, Ben-Shlomo Y, Jaddoe VWV, Palmer LJ, Pennell CE, Cole TJ, McCarthy MI, Jarvelin MR, Timpson NJ, Consortium EGG. Association between common variation at the FTO locus and changes in body mass index from infancy to late childhood: the complex nature of genetic association through growth and development. *PLoS Genet* 7: 2011.

560. Spector T. *Identically Different: Why You Can Change Your Genes*. London: Weidenfeld & Nicolson, 2012.

561. Sram RJ, Binkova B, Dejmek J, Bobak M. Ambient air pollution and pregnancy outcomes: a review of the literature. *Environ Health Perspect* 113: 375–382, 2005.

562. St Clair D, Xu M, Wang P, Yu Y, Fang Y, Zhang F, Zheng X, Gu N, Feng G, Sham P, He L. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959–1961. *JAMA* 294: 557–562, 2005.

563. Stanner SA, Bulmer K, Andres C, Lantseva OE, Borodina V, Poteen VV, Yudkin JS. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study. *BMJ* 315: 1342–1348, 1997.

564. Steffensen FH, Sorensen HT, Gillman MW, Rothman KJ, Sabroe S, Fischer P, Olsen J. Low birth weight and preterm delivery as risk factors for asthma and atopic dermatitis in young adult males. *Epidemiology* 11: 185–188, 2000.

565. Stein AD, Zybert PA, van der Pal-de Bruin K, Lumey LH. Exposure to famine during gestation, size at birth, and blood pressure at age 59 y: evidence from the Dutch Famine. *Eur J Epidemiol* 21: 759–765, 2006.

566. Stein Z, Susser M. Fertility, fecundity, famine: food rations in the dutch famine 1944/5 have a causal relation to fertility, and probably to fecundity. *Hum Biol* 47: 131–154, 1975.

567. Stene LC, Magnus P, Lie RT, Sovik O, Joner G. Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study. *BMJ* 323: 369, 2001.

568. Stettler N, Stallings VA, Troxel AB, Zhao J, Schinnar R, Nelson SE, Ziegler EE, Strom BL. Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. *Circulation* 111: 1897–1903, 2005.

569. Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter, cohort study. *Pediatrics* 109: 194–199, 2002.

570. Su J, Yan H, Wei Y, Liu H, Liu H, Wang F, Lv J, Wu Q, Zhang Y. CpG_MPs: identification of CpG methylation patterns of genomic regions from high-throughput bisulfite sequencing data. *Nucleic Acids Res* 41: e4, 2013.

571. Sullivan EL, Smith MS, Grove KL. Perinatal exposure to high-fat diet programs energy balance, metabolism and behavior in adulthood. *Neuroendocrinology* 93: 1–8, 2011.

572. Sultan SE, Spencer HG. Metapopulation structure favors plasticity over local adaptation. *Am Naturalist* 160: 271–283, 2002.

573. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, Proietto J. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med* 365: 1597–1604, 2011.

574. Susa JB, Schwartz R. Effects of hyperinsulinemia in the primate fetus. *Diabetes* 34 Suppl 2: 36–41, 1985.

575. Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D, Gorman JM. Schizophrenia after prenatal famine. Further evidence. *Arch Gen Psychiatry* 53: 25–31, 1996.

576. Symonds ME, Sebert SP, Hyatt MA, Budge H. Nutritional programming of the metabolic syndrome. *Nature Rev Endocrinol* 5: 604–610, 2009.

577. Szathmary EJE, Siervogel RM. Ethnicity and disease. *Am J Hum Biol* 5.4: 1993.

578. Tam WH, Ma RC, Yang X, Li AM, Ko GT, Kong AP, Lao TT, Chan MH, Lam CW, Chan JC. Glucose intolerance and cardiometabolic risk in adolescents exposed to maternal gestational diabetes: a 15-year follow-up study. *Diabetes Care* 33: 1382–1384, 2010.

579. Tanner JM. *Growth at Adolescence*. Oxford, UK: Blackwell, 1962.

580. Tarry-Adkins JL, Chen JH, Smith NS, Jones RH, Cherif H, Ozanne SE. Poor maternal nutrition followed by accelerated postnatal growth leads to telomere shortening and increased markers of cell senescence in rat islets. *FASEB J* 23: 1521–1528, 2009.

581. Tarry-Adkins JL, Martin-Gronert MS, Chen JH, Cripps RL, Ozanne SE. Maternal diet influences DNA damage, aortic telomere length, oxidative stress, and antioxidant defense capacity in rats. *FASEB J* 22: 2037–2044, 2008.

582. Tarry-Adkins JL, Martin-Gronert MS, Fernandez-Twinn DS, Hargreaves I, Alfaradhi MZ, Land JM, Aiken CE, Ozanne SE. Poor maternal nutrition followed by accelerated postnatal growth leads to alterations in DNA damage and repair, oxidative and nitrosative stress, and oxidative defense capacity in rat heart. *FASEB J* 27: 379–390, 2013.

583. Tarry-Adkins JL, Ozanne SE. Mechanisms of early life programming: current knowledge and future directions. *Am J Clin Nutr* 94: 1765S–1771S, 2011.

584. Taubes G. Treat obesity as physiology, not physics. *Nature* 492: 155, 2012.

585. Taveras EM, Rifas-Shiman SL, Sherry B, Oken E, Haines J, Kleinman K, Rich-Edwards JW, Gillman MW. Crossing growth percentiles in infancy and risk of obesity in childhood. *Arch Pediatr Adolescent Med* 165: 993–998, 2011.

586. Taylor PD, McConnell J, Khan IY, Holemans K, Lawrence KM, Asare-Anane H, Persaud SJ, Jones PM, Petrie L, Hanson MA, Poston L. Impaired glucose homeostasis and mitochondrial abnormalities in offspring of rats fed a fat-rich diet in pregnancy. *Am J Physiol Regul Integr Comp Physiol* 288: R134–R139, 2005.

587. Thakor AS, Herrera EA, Seron-Ferre M, Giussani DA. Melatonin and vitamin C increase umbilical blood flow via nitric oxide-dependent mechanisms. *J Pineal Res* 49: 399–406, 2010.

588. Thakor AS, Richter HG, Kane AD, Dunster C, Kelly FJ, Poston L, Giussani DA. Redox modulation of the fetal cardiovascular defence to hypoxaemia. *J Physiol* 588: 4235–4247, 2010.

589. Thompson LP, Al-Hasan Y. Impact of oxidative stress in fetal programming. *J Pregnancy* 2012: 582748, 2012.

590. Tijsseling D, Camm EJ, Richter HG, Herrera EA, Kane AD, Niu Y, Cross CM, de Vries WB, Derks JB, Giussani DA. Statins prevent adverse effects of postnatal glucocorticoid therapy on the developing brain in rats. *Pediatr Res* 74: 639–645, 2013.

591. Tinbergen N. On aims and methods of ethology. *Z Tierpsychol* 20: 410–433, 1963.

592. Torrens C, Clough GF, Hanson M. Developmental origins of endothelial dysfunction: a key step in cardiometabolic disease. In: *The Metabolic Syndrome*, edited by Byrne CD, Wild S. New York: Wiley, 2011.

593. Torrens C, Ethirajan P, Bruce KD, Cagampang FR, Siow RC, Hanson MA, Byrne CD, Mann GE, Clough GF. Interaction between maternal and offspring diet to impair vascular function and oxidative balance in high fat fed male mice. *PloS One* 7: e50671, 2012.

594. Torrens C, Kelsall CJ, Hopkins LA, Anthony FW, Curzen NP, Hanson MA. Atorvastatin restores endothelial function in offspring of protein-restricted rats in a cholesterol-independent manner. *Hypertension* 53: 661–667, 2009.

595. Torrens C, Snelling TH, Chau R, Shanmuganathan M, Cleal JK, Poore KR, Noakes DE, Poston L, Hanson MA, Green LR. Effects of pre- and periconceptional undernutrition on arterial function in adult female sheep are vascular bed dependent. *Exp Physiol* 94: 1024–1033, 2009.

596. Trut L. Early Canid Domestication: The Farm-Fox Experiment Foxes bred for tamability in a 40-year experiment exhibit remarkable transformations that suggest an interplay between behavioral genetics and development. *Am Scientist* 87: 160–169, 1999.

597. Tsukimori K, Uchi H, Mitoma C, Yasukawa F, Chiba T, Todaka T, Kajiwara J, Yoshimura T, Hirata T, Fukushima K, Wake N, Furue M. Maternal exposure to high levels of dioxins in relation to birth weight in women affected by Yusho disease. *Environment Int* 38: 79–86, 2012.

598. Turnbaugh PJ, Gordon JI. The core gut microbiome, energy balance and obesity. *J Physiol* 587: 4153–4158, 2009.

599. Uller T. Developmental plasticity and the evolution of parental effects. *Trends Ecol Evol* 23: 432–438, 2008.

600. United Nations. *A New Global Partnership: Eradicate Poverty and Transform Economies Through Sustainable Development. The Report of the High-Level Panel of Eminent Persons on the Post-2015 Development Agenda*. New York: UN, 2013.

601. United Nations General Assembly. *Resolution Adopted by the General Assembly: 66/2. Political Declaration of the High-Level Meeting of the General Assembly on the Prevention and control of Non-communicable Diseases*. New York: UN, 2012.

602. Van den Bergh BR, Mulder EJ, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev* 29: 237–258, 2005.

603. Van der Zee B, de Beaufort I, Temel S, de Wert G, Denktas S, Steegers E. Preconception care: an essential preventive strategy to improve children's and women's health. *J Public Health Policy* 32: 367–379, 2011.

604. Van Montfoort AP, Hanssen LL, de Sutter P, Viville S, Geraedts JP, de Boer P. Assisted reproduction treatment and epigenetic inheritance. *Hum Reprod Update* 18: 171–197, 2012.

605. Van Rooij E, Sutherland LB, Qi X, Richardson JA, Hill J, Olson EN. Control of stress-dependent cardiac growth and gene expression by a microRNA. *Science* 316: 575–579, 2007.

606. Van Uitert EM, Steegers-Theunissen RP. Influence of maternal folate status on human fetal growth parameters. *Mol Nutr Food Res* 57: 582–595, 2013.

607. Vasak B, Koenen SV, Koster MPH, Hukkelhoven CWPM, Franx A, Hanson MA, Visser GHA. Human fetal growth is constrained below optimal for perinatal survival. *Proc Soc Gynecol Invest*. In press.

608. Vasan RS, Pencina MJ, Cobain M, Freiberg MS, D'Agostino RB. Estimated risks for developing obesity in the Framingham Heart Study. *Ann Internal Med* 143: 473–480, 2005.

609. Vaughan OR, Sferruzzi-Perri AN, Coan PM, Fowden AL. Adaptations in placental phenotype depend on route and timing of maternal dexamethasone administration in mice. *Biol Reprod* 89: 80, 2013.

610. Verma A, Chaudhary H. *Study of Haematological Parameters in Advanced Pregnancy*. 2013.

611. Villar J, Klebanoff M, Kestler E. The effect on fetal growth of protozoan and helminthic infection during pregnancy. *Obstet Gynecol* 74: 915–920, 1989.

612. Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. *Am J Physiol Regul Integr Comp Physiol* 285: R271–R273, 2003.

613. Vickers MH, Gluckman PD, Coveny AH, Hofman PL, Cutfield WS, Gertler A, Breier BH, Harris M. Neonatal leptin treatment reverses developmental programming. *Endocrinology* 146: 4211–4216, 2005.

614. Vogt G, Huber M, Thiemann M, van den Boogaart G, Schmitz OJ, Schubart CD. Production of different phenotypes from the same genotype in the same environment by developmental variation. *J Exp Biol* 211: 510–523, 2008.

615. Vom Saal FS, Nagel SC, Coe BL, Angle BM, Taylor JA. The estrogenic endocrine disrupting chemical bisphenol A (BPA) and obesity. *Mol Cell Endocrinol* 354: 74–84, 2012.

616. Von Kries R, Koletzko B, Sauerwald T, von Mutius E, Barnert D, Grunert V, von Voss H. Breast feeding and obesity: cross sectional study. *BMJ* 319: 147–150, 1999.

617. Vorherr H. Placental insufficiency in relation to postterm pregnancy and fetal postmaturity. Evaluation of fetoplacental function; management of the postterm gravida. *Am J Obstet Gynecol* 123: 67–103, 1975.

619. Waddington CH. Canalization of development and the inheritance of acquired characters. *Nature* 150: 563–565, 1942.

620. Wadley GD, Siebel AL, Cooney GJ, McConell GK, Wlodek ME, Owens JA. Uteroplacental insufficiency and reducing litter size alters skeletal muscle mitochondrial biogenesis in a sex-specific manner in the adult rat. *Am J Physiol Endocrinol Metab* 294: E861–E869, 2008.

621. Wadsworth ME, Cripps HA, Midwinter RE, Colley JR. Blood pressure in a national birth cohort at the age of 36 related to social and familial factors, smoking, and body mass. *Br Med J* 291: 1534–1538, 1985.

622. Wagner GP, Pavlicev M, Cheverud JM. The road to modularity. *Nature Rev Genet* 8: 921–931, 2007.

623. Walhovd KB, Fjell AM, Brown TT, Kuperman JM, Chung Y, Hagler DJ Jr, Roddey JC, Erhart M, McCabe C, Akshoomoff N, Amaral DG, Bloss CS, Libiger O, Schork NJ, Darst BF, Casey BJ, Chang L, Ernst TM, Frazier J, Gruen JR, Kaufmann WE, Murray SS, van Zijl P, Mostofsky S, Dale AM, Pediatric Imaging Genetics. Long-term influence of normal variation in neonatal characteristics on human brain development. *Proc Natl Acad Sci USA* 109: 20089–20094, 2012.

624. Wallwork CJ, Parks DA, Schmid-Schonbein GW. Xanthine oxidase activity in the dexamethasone-induced hypertensive rat. *Microvasc Res* 66: 30–37, 2003.

625. Walser JC, Ponger L, Furano AV. CpG dinucleotides and the mutation rate of non-CpG DNA. *Genome Res* 18: 1403–1414, 2008.

626. Wang G, Divall S, Radovick S, Paige D, Ning Y, Chen Z, Ji Y, Hong X, Walker SO, Caruso D, Pearson P, Wang MC, Zuckerman B, Cheng TL, Wang X. Preterm birth and random plasma insulin levels at birth and in early childhood: a prospective birth cohort study. *JAMA* 311: 587–596, 2014.

627. Wang J, Ma H, Tong C, Zhang H, Lawlis GB, Li Y, Zang M, Ren J, Nijland MJ, Ford SP, Nathanielsz PW, Li J. Overnutrition and maternal obesity in sheep pregnancy alter the JNK-IRS-1 signaling cascades and cardiac function in the fetal heart. *FASEB J* 24: 2066–2076, 2010.

628. Wang PX, Wang JJ, Lei YX, Xiao L, Luo ZC. Impact of fetal and infant exposure to the Chinese Great Famine on the risk of hypertension in adulthood. *PloS One* 7: e49720, 2012.

629. Wang Z, Kanguru L, Hussein J, Fitzmaurice A, Ritchie K. Incidence of adverse outcomes associated with gestational diabetes mellitus in low- and middle-income countries. *Int J Gynaecol Obstet* 121: 14–19, 2013.

630. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol* 23: 5293–5300, 2003.

631. Watkins AJ, Lucas ES, Torrens C, Cleal JK, Green L, Osmond C, Eckert JJ, Gray WP, Hanson MA, Fleming TP. Maternal low-protein diet during mouse pre-implantation development induces vascular dysfunction and altered renin-angiotensin-system homeostasis in the offspring. *Br J Nutr* 103: 1762–1770, 2010.

632. Watkins AJ, Platt D, Papenbrock T, Wilkins A, Eckert JJ, Kwong WY, Osmond C, Hanson M, Fleming TP. Mouse embryo culture induces changes in postnatal phenotype including raised systolic blood pressure. *Proc Natl Acad Sci USA* 104: 5449–5454, 2007.

633. Watkins AJ, Ursell E, Panton R, Papenbrock T, Hollis L, Cunningham C, Wilkins A, Perry VH, Sheth B, Kwong WY, Eckert JJ, Wild AE, Hanson MA, Osmond C, Fleming

TP. Adaptive responses by mouse early embryos to maternal diet protect fetal growth but predispose to adult onset disease. *Biol Reprod* 78: 299–306, 2008.

634. Watkins AJ, Wilkins A, Cunningham C, Perry VH, Seet MJ, Osmond C, Eckert JJ, Torrens C, Cagampang FR, Cleal J, Gray WP, Hanson MA, Fleming TP. Low protein diet fed exclusively during mouse oocyte maturation leads to behavioural and cardiovascular abnormalities in offspring. *J Physiol* 586: 2231–2244, 2008.

635. Watson JD. Type 2 diabetes as a redox disease. *Lancet* 383: 841–843, 2014.

636. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. *Nature Neurosci* 7: 847–854, 2004.

637. 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 USA* 103: 3480–3485, 2006.

638. Wei JN, Li HY, Sung FC, Lin CC, Chiang CC, Li CY, Chuang LM. Birth weight correlates differently with cardiovascular risk factors in youth. *Obesity* 15: 1609–1616, 2007.

639. Wei Y, Yang CR, Wei YP, Zhao ZA, Hou Y, Schatten H, Sun QY. Paternally induced transgenerational inheritance of susceptibility to diabetes in mammals. *Proc Natl Acad Sci USA* 111: 1873–1878, 2014.

640. Weiss A, Leinwand LA. The mammalian myosin heavy chain gene family. *Annu Rev Cell Dev Biol* 12: 417–439, 1996.

641. Welch GN, Upchurch GR Jr, Loscalzo J. Homocysteine, oxidative stress, and vascular disease. *Hosp Pract* 32: 81–82, 85, 88–92, 1997.

642. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. *J Clin Invest* 112: 1785–1788, 2003.

643. Wells JC. Flaws in the theory of predictive adaptive responses. *Trends Endocrinol Metab* 18: 331–337, 2007.

644. Wells JC. The thrifty phenotype as an adaptive maternal effect. *Biol Rev Cambr Philos Soc* 82: 143–172, 2007.

645. Wen X, Triche EW, Hogan JW, Shenassa ED, Buka SL. Prenatal factors for childhood blood pressure mediated by intrauterine and/or childhood growth? *Pediatrics* 127: e713–e721, 2011.

646. West-Eberhard MJ. *Developmental Plasticity and Evolution*. Oxford, UK: Oxford Univ. Press, 2003.

647. West-Eberhard MJ. Phenotypic accommodation: adaptive innovation due to developmental plasticity, with or without genetic change. *Integr Comp Biol* 43: 970, 2003.

648. West NA, Crume TL, Maligie MA, Dabelea D. Cardiovascular risk factors in children exposed to maternal diabetes in utero. *Diabetologia* 54: 504–507, 2011.

649. Whitaker RC. Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. *Pediatrics* 114: e29–36, 2004.

650. Whyte L. Internal factors in evolution. *Acta Biotheor* 17: 33, 1965.

651. Williams GC. Pleitropy, natural selection and the evolution of senescence. *Evolution* 11: 398–411, 1957.

652. Williams PD, Day T. Antagonistic pleiotropy, mortality source interactions, and the evolutionary theory of senescence. *Evolution* 57: 1478–1488, 2003.

653. Wolfe D, Gong M, Han G, Magee TR, Ross MG, Desai M. Nutrient sensor-mediated programmed nonalcoholic fatty liver disease in low birthweight offspring. *Am J Obstet Gynecol* 207: 308 e301–306, 2012.

654. Woltereck R. Weitere experimentelle untersuchungen uber artveranderung speziell uber das wesen quantitativer artunterschiede bei daphniden. *Verh Dtsch Zool Gesellschaft* 19: 1909.

655. Wong CC, Caspi A, Williams B, Craig IW, Houts R, Ambler A, Moffitt TE, Mill J. A longitudinal study of epigenetic variation in twins. *Epigenetics* 5: 516–526, 2010.

656. Woodall SM, Johnston BM, Breier BH, Gluckman PD. Chronic maternal undernutrition in the rat leads to delayed postnatal growth and elevated blood pressure of offspring. *Pediatr Res* 40: 438–443, 1996.

657. World Economic Forum. *Global risks 2010 a Global Risk Network Report*, 2010.

658. World Health Organisation, http://www.whoint/nutrition/topics/obesity/en/.

659. World Health Organisation. *Global Status Report on Non-communicable Diseases 2010*. Geneva: World Health Organisation, 2011.

660. World Health Organisation. *Nurturing Human Captial Along The Lifecourse: Investing In Early Child Development*. Geneva: World Health Organisation, 2013.

661. World Health Organisation. *Promoting Optimal Fetal Development Report of a Technical Consultation*. Geneva: World Health Organisation, 2006.

662. World Health Organisation. *Revised Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020*. Geneva: World Health Organisation, 2013.

663. Wu H, D'Alessio AC, Ito S, Xia K, Wang Z, Cui K, Zhao K, Sun YE, Zhang Y. Dual functions of Tet1 in transcriptional regulation in mouse embryonic stem cells. *Nature* 473: 389–393, 2011.

664. Wu H, Zhang Y. Tet1 and 5-hydroxymethylation: a genome-wide view in mouse embryonic stem cells. *Cell Cycle* 10: 2428–2436, 2011.

665. Xiong F, Xiao D, Zhang L. Norepinephrine causes epigenetic repression of PKCepsilon gene in rodent hearts by activating Nox1-dependent reactive oxygen species production. *FASEB J* 26: 2753–2763, 2012.

666. Yajnik CS. Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. *J Nutr* 134: 205–210, 2004.

667. Yajnik CS. Fetal programming of diabetes: still so much to learn! *Diabetes Care* 33: 1146–1148.

668. Yajnik CS, Deshpande SS, Jackson AA, Refsum H, Rao S, Fisher DJ, Bhat DS, Naik SS, Coyaji KJ, Joglekar CV, Joshi N, Lubree HG, Deshpande VU, Rege SS, Fall CH. Vitamin B_{12} and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. *Diabetologia* 51: 29–38, 2008.

669. Yates Z, Tarling EJ, Langley-Evans SC, Salter AM. Maternal undernutrition programmes atherosclerosis in the ApoE*3-Leiden mouse. *Br J Nutr* 101: 1185–1194, 2009.

670. Yazbek SN, Spiezio SH, Nadeau JH, Buchner DA. Ancestral paternal genotype controls body weight and food intake for multiple generations. *Hum Mol Genet* 19: 4134–4144, 2010.

671. Young TK, Martens PJ, Taback SP, Sellers EA, Dean HJ, Cheang M, Flett B. Type 2 diabetes mellitus in children: prenatal and early infancy risk factors among native canadians. *Arch Pediatr Adolescent Med* 156: 651–655, 2002.

672. Youngson NA, Whitelaw E. Transgenerational epigenetic effects. *Annu Rev Genomics Hum Genet* 9: 233–257, 2008.

673. Yzydorczyk C, Gobeil F Jr, Cambonie G, Lahaie I, Le NL, Samarani S, Ahmad A, Lavoie JC, Oligny LL, Pladys P, Hardy P, Nuyt AM. Exaggerated vasomotor response to ANG II in rats with fetal programming of hypertension associated with exposure to a low-protein diet during gestation. *Am J Physiol Regul Integr Comp Physiol* 291: R1060–R1068, 2006.

674. Zambrano E, Martinez-Samayoa PM, Bautista CJ, Deas M, Guillen L, Rodriguez-Gonzalez GL, Guzman C, Larrea F, Nathanielsz PW. Sex differences in transgenerational alterations of growth and metabolism in progeny (F2) of female offspring (F1) of rats fed a low protein diet during pregnancy and lactation. *J Physiol* 566: 225–236, 2005.

675. Zemojtel T, Kielbasa SM, Arndt PF, Behrens S, Bourque G, Vingron M. CpG deamination creates transcription factor-binding sites with high efficiency. *Genome Biol Evol* 3: 1304–1311, 2011.

676. Zhang J, Zhang F, Didelot X, Bruce KD, Cagampang FR, Vatish M, Hanson M, Lehnert H, Ceriello A, Byrne CD. Maternal high fat diet during pregnancy and lactation alters hepatic expression of insulin like growth factor-2 and key microRNAs in the adult offspring. *BMC Genomics* 10: 478, 2009.

677. Zhang TY, Hellstrom IC, Bagot RC, Wen X, Diorio J, Meaney MJ. Maternal care and DNA methylation of a glutamic acid decarboxylase 1 promoter in rat hippocampus. *J Neurosci* 30: 13130–13137, 2010.

678. Zhang Y, Croft KD, Mori TA, Schyvens CG, McKenzie KU, Whitworth JA. The antioxidant tempol prevents and partially reverses dexamethasone-induced hypertension in the rat. *Am J Hypertens* 17: 260–265, 2004.