

# Intrauterine Programming of Physiological Systems: Causes and Consequences

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The intrauterine conditions in which the mammalian fetus develops have an important role in regulating the function of its physiological systems later in life. Changes in the intrauterine availability of nutrients, oxygen, and hormones program tissue development and lead to abnormalities in adult cardiovascular and metabolic function in several species. The timing, duration, severity, and type of insult during development determines the specific physiological outcome. Intrauterine programming of physiological systems occurs at the gene, cell, tissue, organ, and system levels and causes permanent structural and functional changes, which can lead to overt disease, particularly with increasing age.

Epidemiological studies in humans have shown that impaired intrauterine growth is associated with an increased incidence of cardiovascular, metabolic, and other diseases in later life (4). Low birth weight, in particular, has been linked to hypertension, ischemic heart disease, glucose intolerance, insulin resistance, type 2 diabetes, hyperlipidemia, hypercortisolemia, obesity, obstructive pulmonary disease, and reproductive disorders in the adult (Table 1). These associations have been described in populations of different age, sex, and ethnic origin and occur independently of the current level of obesity or exercise (4, 21). Detailed morphometric analyses of the human epidemiological data have shown that certain patterns of intrauterine growth can be related to specific adult diseases. For instance, it is the thin infant with the low ponderal index, rather than the symmetrically small baby, that is more prone to type 2 diabetes as an adult (42). These observations have led to the concept that adult disease originates in utero as a result of changes in development during suboptimal intrauterine conditions often associated with impaired fetal growth (4). The process by which early insults at critical stages of development lead to permanent changes in tissue structure and function is known as intrauterine programming (33).

Intrauterine programming of postnatal physiological function has been demonstrated experimentally in a number of species using a range of techniques to compromise the intrauterine environment and alter fetal development (see Ref. 35). Induction of intrauterine growth retardation (IUGR) by maternal stress, hypoxia, glucocorticoid administration, dietary manipulation, or placental insufficiency leads to postnatal abnormalities in cardiovascular, metabolic, and endocrine function in rats, guinea pigs, sheep, pigs, horses, and primates (16, 35). Similarly, in naturally

occurring IUGR in polytocous species, low birth weight is associated with postnatal hypertension, glucose intolerance, and alterations in the functioning of a number of endocrine axes, including the pancreatic islets, renin-angiotensin system, and hypothalamic-pituitary-adrenal (HPA) axis (16). Animal studies have also demonstrated that the timing, duration, and exact nature of the insult during pregnancy are important

**Table 1. Adult diseases associated with suboptimal intrauterine conditions in humans**

Physiological System	Disease
Cardiovascular system	Hypertension Coronary Heart disease Stroke Atherosclerosis Coagulation disorders Pre-eclampsia
Metabolic system	Impaired glucose tolerance Insulin resistance Dyslipidemia Obesity Type 2 diabetes
Reproductive system	Polycystic ovary syndrome Early adrenarche/ menarche Early menopause
Respiratory system	Chronic obstructive pulmonary disease Asthma
Endocrine system	Hypercortisolism Hypothyroidism
Nervous system	Neurological disorders Schizophrenia Dementia
Skeletal system	Osteoporosis

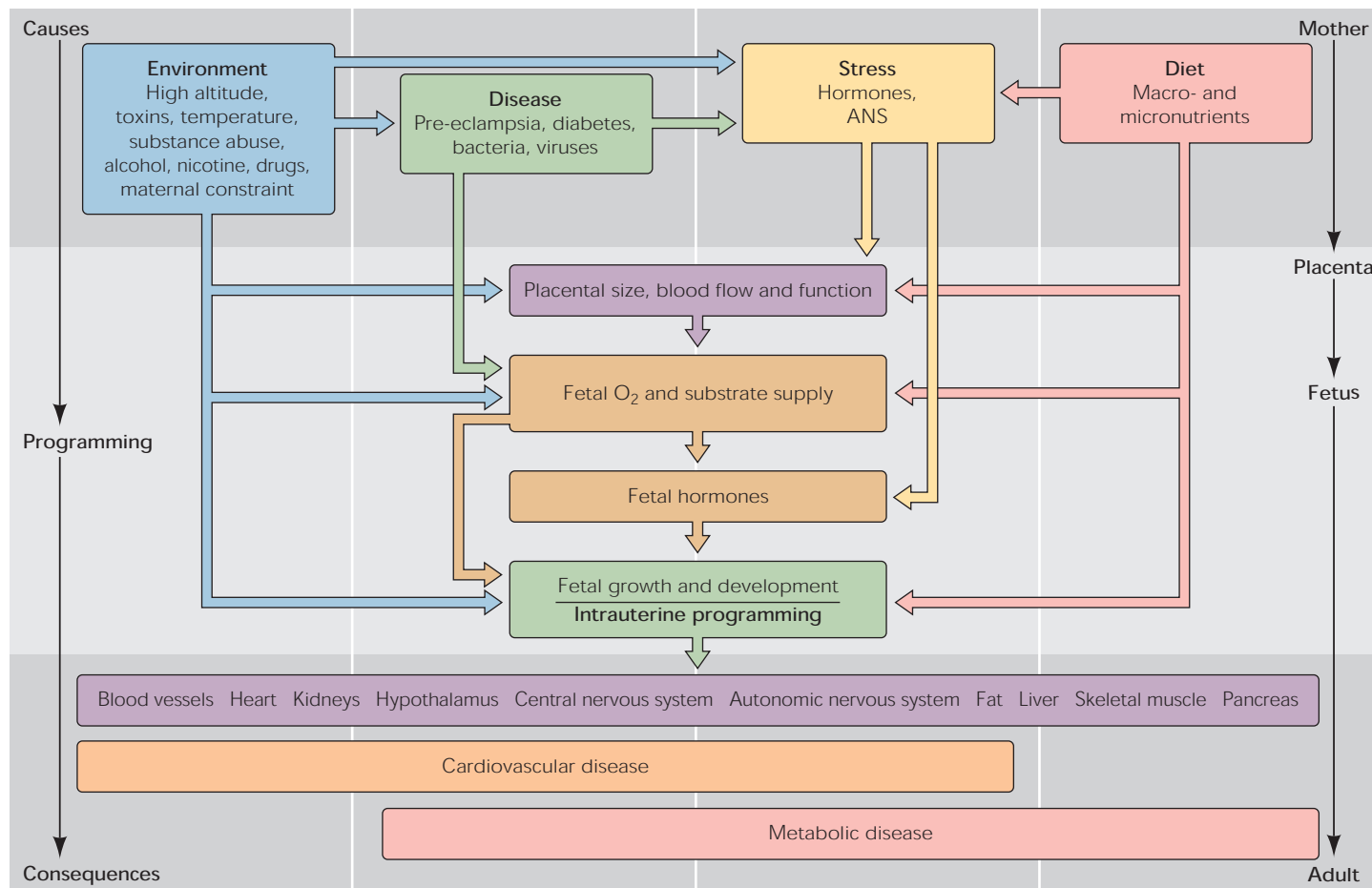


FIGURE 1. Causes and consequences of intrauterine programming

determinants of the pattern of intrauterine growth and the specific physiological outcomes (7). Furthermore, these studies have shown that maternal insults with little, if any, effect on birth weight can alter subsequent cardiovascular and metabolic function (5). Together, animal experiments and human epidemiological data show that a wide range of individual tissues and whole organ systems can be programmed in utero with adverse consequences for their physiological function later in life (FIGURE 1). This programming occurs across the normal range of birth weights with the worst prognoses at the extremes (4, 35).

### Causes of Intrauterine Programming

In mammals, programming by internal and external cues during early postnatal life is well established. It is the concept that the adult phenotype also depends on environmental signals operating during intrauterine development that has recently received the most attention. Since fetal growth and development depend primarily on nutrient and oxygen supply (25), the associations between low birth weight and adult phenotype have been linked to poor nutrition and oxygenation during early life (FIGURE 1). However, since

nutrient and O<sub>2</sub> availability invariably affect the endocrine environment, the role of hormones as programming signals has also been examined in humans and experimental animals (15).

### Nutritional programming

Prenatal nutritional programming of postnatal physiological functions has been demonstrated experimentally in a wide variety of laboratory and farm animals by manipulating the availability of macronutrients and micronutrients during development. A range of techniques has been used to reduce the fetal availability of macronutrients used for tissue accretion (7). These include calorie restriction, isocaloric protein deprivation, placental restriction, and reductions in umbilical and/or uterine blood flows. All of these procedures impair fetal growth and lead to abnormalities in cardiovascular, metabolic, and endocrine function both before and after birth (see Ref. 35). Altered postnatal physiological function has also been observed after maternal fat feeding and dietary manipulation of specific micronutrients, such as minerals (calcium, iron), cofactors (folic acid, taurine), and vitamins (A and D) (2). In some instances, the programming effects of macronutrient restriction can be ameliorat-

ed by supplementation of the altered diet with single cofactors and amino acids (2). Indeed, it may be the balance of micro- and macronutrients that is more important in programming than the absolute amount of nutrient per se.

### ***Programming by alterations in oxygenation***

Several of the techniques used to induce fetal undernutrition also reduce fetal O<sub>2</sub> delivery. In rats, chronic hypoxia during pregnancy causes disproportionate IUGR and leads to abnormalities in cardiovascular function in the adult offspring (9, 11). Similarly, in human populations, the hypobaric hypoxia of high altitude is associated with reduced birth weight and asymmetric growth retardation (19, 37). However, the developmental changes induced by hypoxia may also have a nutritional component, because high-altitude populations are often impoverished and chronic hypoxia during pregnancy in experimental animals reduces maternal food intake (11, 19). The relative contributions of fetal hypoxemia and undernutrition to programming in these circumstances have been investigated experimentally by pair-feeding pregnant rats at normal PO<sub>2</sub> and by using chick embryos. In avian species, the specific developmental effects of O<sub>2</sub> deprivation can be studied in ovo without the confounding effects of a hypoxic placenta and/or reduced maternal dietary intake (47). Both of these approaches show that hypoxia alone during early development can program the cardiovascular system and, more specifically, the blood vessels. In the chick embryo, hypoxia during the mid to late incubation period exaggerates responses to periarterial sympathetic nerve stimulation and downregulates nitric oxide-dependent dilator function in the vessels of the adult birds. In rats, prenatal hypoxia but not nutrient restriction impairs endothelium-dependent relaxation in the mesenteric circulation of the adult offspring (56).

### ***Endocrine programming***

Hormones have an important role in regulating normal growth and development in utero, and their concentrations and bioactivity change in response to many of the environmental challenges known to cause intrauterine programming (15). Undernutrition, hypoxemia, and stress can alter both maternal and fetal concentrations of many hormones including growth hormone (GH), insulin-like growth factors (IGFs), insulin, glucocorticoids, catecholamines, leptin, thyroid hormones, and placental hormones such as the eicosanoids, sex steroids, and placental lactogen. Because some of these hormones cross the placenta, the fetal endocrine response to adverse conditions reflects the activity of both maternal and fetal endocrine glands and depends on the type, duration, severity, and gestational age at onset of the insult. In general, suboptimal intrauterine conditions lower anabolic hormone levels and increase catabolic hor-

mon concentrations in the fetus (13). These endocrine changes then affect fetal growth and development either directly or indirectly by altering the delivery, uptake, and metabolic fate of nutrients in the fetoplacental tissues (13). Certainly, direct manipulation of glucocorticoid, androgen, and thyroid hormone levels in utero alters fetal development and has long term consequences for cardiovascular, reproductive, and metabolic function (17, 45).

Of the hormones known to regulate fetal development, it is the glucocorticoids that are most likely to have widespread programming effects in utero (see Refs. 8 and 48). They are growth inhibitory and affect development of all the tissues and organ systems that are at increased risk of adult pathophysiology when fetal growth is impaired (17). In rats, guinea pigs, and sheep, fetal overexposure to either endogenous or exogenous glucocorticoids leads to hypertension, glucose intolerance, and abnormalities in HPA function after birth (8, 36, 48). The specific postnatal effects of these treatments depend not only on the gestational age at onset and the duration of exposure but also on the sex of the offspring (8, 36). In addition, the programming effects of undernutrition can be prevented by abolishing maternal glucocorticoid synthesis by adrenalectomy or metyrapone treatment (30). Glucocorticoids can, therefore, program tissues in utero and may also mediate the programming effects of nutritional and other environmental challenges during pregnancy (15).

### **Critical Periods of Intrauterine Programming**

Environmental insults can cause programming at many stages during development (FIGURE 2). During the periconceptual and preimplantation periods, nutrient, O<sub>2</sub>, and hormone levels affect development of the oocyte and blastocyst, with consequences for the distribution of cells between the trophoblast and inner cell mass. Exposure to excess progesterone and metabolites, such as urea, specifically during these periods leads to enhanced birth weight in sheep and pigs (34). In addition, dietary restriction during the periconceptual period has also been shown to shorten gestation and cause hypertension and abnormal HPA function in adult sheep (29). Developmental changes arising before implantation are likely to affect many cell lineages, although adaptations later in gestation, such as upregulation of placental nutrient and O<sub>2</sub> transport, may compensate for the early defects and normalize birth weight. Once placentation has begun, the programming effects of environmental signals may be mediated via changes in placental development (22). However, the extent to which early insults program the placenta per se remains unknown.

During organogenesis, environmental insults may cause discrete structural defects that permanently

reduce the functional capacity of the organ. If the insult occurs during gametogenesis, reproductive potential of the next generation may be impaired (45). During the phase of rapid fetal growth, insults, which alter the supply, uptake, and utilization of nutrients, will influence tissue growth and may switch the cell cycle from proliferation to differentiation with adverse consequences for total cell number (17, 25). Because different fetal organs grow at different rates, the timing of the insult is important in determining the tissue specificity of the programmed effects. In late gestation, there is a period of fetal maturation during which many tissues undergo structural and functional changes in preparation for extrauterine life (17). These processes are often glucocorticoid dependent and can be activated prematurely by early glucocorticoid exposure. In addition, birth itself activates physiological systems that have little or no function in utero but are essential for neonatal viability, such as ventilation, thermoregulation, gluconeogenesis, enteral nutrition, and appetite control (17). Changes in parturition maturation in relation to the timing of delivery may, therefore, have consequences for the set point and sensitivity of key physiological systems during the perinatal period, which can then persist, revert, or amplify in later life.

Although the sequence of developmental changes is broadly similar in all mammalian species, there are differences in their precise timing between animals. In altricial species that are immature at birth (e.g., rodents and rabbits), several of the physiological systems known to be programmed in utero continue to develop after birth (FIGURE 2). The period of developmental plasticity, therefore, extends after birth in these species in contrast to precocial species (e.g., human, sheep, pig) that are more physiologically mature at birth (17). Certainly, changes in nutrient availability, hormone concentrations, and maternal behavior during the immediate neonatal period in rats alter their subsequent cognitive, neuroendocrine, and

reproductive function (40, 46, 55). Consequently, postnatal environmental changes, particularly before weaning, may ameliorate or exaggerate the morphological and functional changes programmed in utero (46).

### Mechanisms of Intrauterine Programming

Intrauterine programming can occur at any level within the affected physiological system and may involve structural and functional changes in genes, cells, tissues, and even whole organs (Table 2). These changes may be isolated or widespread events with either discrete or cumulative effects on development depending on the nature and timing of the programming stimulus (see Refs. 21 and 35).

#### Genes

The associations between birth weight and later risk of degenerative disease may be due to a direct genetic link between intrauterine growth and disease susceptibility inherited at conception (57). In part, this reflects the survival value of genes selected for reduced fetal growth yet rapid postnatal growth and fuel storage during evolution in populations subjected to periodic undernutrition (6, 46). The observation that mutations in the pancreatic glucokinase gene result in reduced fetal insulin secretion, lower birth weight, and adult glucose intolerance indicates that fetal growth and disease susceptibility can be linked through a single gene (26). However, these monogenic disorders are rare and cannot explain the variation in disease risk across the normal birth weight range. In populations like the Pima Indians who have a high incidence of type 2 diabetes, there is evidence for both a genetic and an intrauterine origin of the relationship between birth weight and adult insulin resistance (18). The discordant disease risks in monozygotic twins of discrepant birth weights compared with the concor-

**FIGURE 2. Critical periods of development at which intrauterine programming may occur**  
Composite data are from rodents and humans.

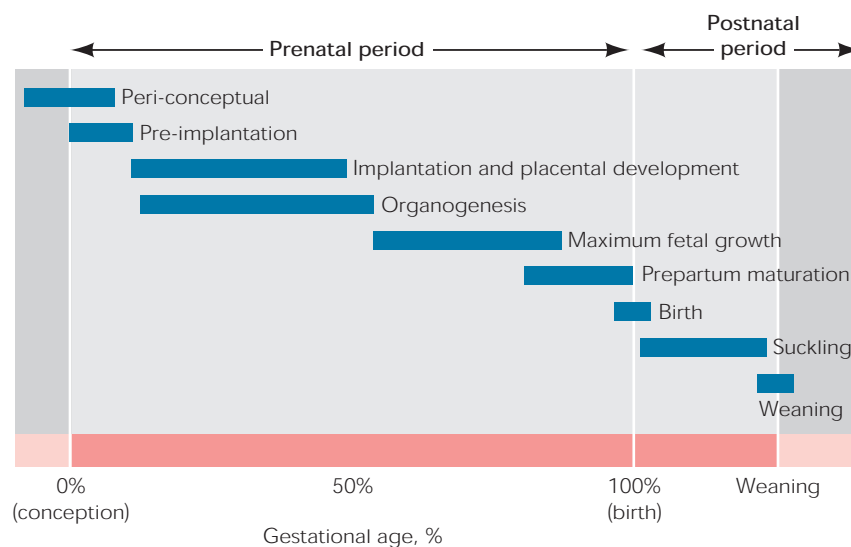


Table 2. Consequences of suboptimal intrauterine conditions<sup>†</sup> on different organs at different levels in rats before and after birth

	Endocrine Pancreas	Liver	Skeletal Muscle	Kidney	Heart	Blood * Vessels
Genes	↓ <i>Ins2</i> ↑ <i>Glucagon</i> ↓Genes for RNA/DNA metabolism ↓ <i>Igf2</i> mRNA ↑Ribosomal S4 mRNA	↑ <i>GLUT1</i> mRNA ↑ <i>PGC-1</i> mRNA ↑Redox pathways ↑↓Fatty acid-metabolising enzymes	Δ <i>PGC-1</i> in different muscles	↓ <i>c-ret</i> ↑↓AT1 and 2 mRNA ↑ <i>GR</i> mRNA ↓11βHSD2 ↓p53	↑β1-adrenoceptor mRNA ↑HIF-1α mRNA ↑Caspase 3 mRNA ↑Fas mRNA ↑Antiapoptotic protein 14-3-3 ↑Genes related to oxidative stress ↓Genes related to cell signalling, communication, defence, proliferation, and survival	↑O <sub>2</sub> <sup>-</sup> generation ↓Antioxidant enzymes ↓eNOS ↓sGC expression
Cells	↓Glucokinase	↓Glucokinase ↑Insulin receptor ↑PEPCK activity ↓Proliferation rate ↑Glutathione reductase abundance ↓Glucagon receptor	↑ <i>GLUT4</i> protein ↓PKC-ζ protein ↑↓Insulin receptor	↑GR ↑BSC1 and TSC Na transporters ↑Apoptosis ↑Teleomere shortening	↑β1-adrenoceptor ↑β2-adrenoceptor ↑G <sub>s</sub> :G <sub>i</sub> α ↓Ventricular eNOS ↑Cytochrome c ↑Fas protein levels ↓Bcl-2 proteins ↑HIF-1 protein ↓HSP 70 protein ↑Apoptosis	↓Ca-sensitive K channel ↓Angiogenesis ↓NOS activity ↓Tetrahydrobiopterin pathways ↓cGMP levels
Tissues	↓β-Cell number ↓β-Cell mass ↓Islet proliferation	↓Perivenous cell number ↑Periportal cell number ↑IGFBP production ↑↓Glycogen content	↓Glycogen content ↓Primary/secondary myofiber numbers	↓Branching of ureteric bud Glomerular hypertrophy and sclerosis ↓Renin and All content	↑Ventricular hypertrophy ↑Myocyte hypertrophy ↑Binucleated myocytes	↓Capillary density in muscle
Organ	↓Insulin content ↓Vascularity ↓Insulin release	↓ATP production ↑Glucose output Fewer, larger lobules Abnormal glucogenic response to hormones	↓Skeletal muscle mass ↓Insulin sensitivity ↓ATP production	↓Nephron number ↓GFR, RBF ↑Urinary PGE <sub>2</sub> and albumin excretion	↓Ejection fraction ↓Cardiac output ↓Coronary flow ↓Contractility ↑Cardiac afterload ↑Arrhythmia ↑Susceptibility to I/R injury	↓α1 and ET1 sensitivity ↓NO-dependent dilatation ↑↓α1 sensitivity ↑Sensitivity to thromboxane A2 mimetic and potassium ↑Responsesiveness to β-adrenergic stimulation and sensitivity to adenylyl cyclase activation
System	Glucose intolerance, Dyslipidemia, Insulin resistance			Hypertension		

\*Renal, cerebral, carotid, mesenteric, and other peripheral blood vessels. †Reduced maternal dietary intake, manipulation of maternal dietary composition, uteroplacental insufficiency, hypoxemia, and maternal anemia. AT, angiotensin II receptor; GR, glucocorticoid receptor; 11βHSD2, hydroxysteroid dehydrogenase; All, angiotensin II; GFR, glomerular filtration rate; RBF, renal blood flow; BSC1, bumetanide-sensitive Na<sup>+</sup>-K<sup>+</sup>-Cl<sup>-</sup> cotransporter; TSC, thiazide-sensitive Na<sup>+</sup>-Cl<sup>-</sup> cotransporter; HIF, hypoxia-inducible factor; FADD, Fas-associated death domain protein; HSP, heat shock protein; I/R, ischaemia/reperfusion; sGC, soluble guanylate cyclase, NOS, nitric oxide synthase; PEPCK, phosphoenolpyruvate carboxykinase; GLUT glucose transporter; PGC-1, peroxisome proliferator-activated receptor-γ coactivator-1; IGFBP, IGF binding protein; *Igf2*, insulin-like growth factor-2; *Ins2*, rat insulin gene. Data are from Refs. 1, 2, 8, 12, 14, 15, 16, 20, 27, 30, 35, and 38.

dant risks when birth weight is similar also shows that different adult phenotypes can develop from the same genotype when intrauterine growth is compromised (42). However, different specific polymorphisms of genes involved in growth and metabolism, such *Igf1*, *PPAR $\gamma$* , and the *VNTR* region of the insulin gene, may alter susceptibility to environmental signals and account for some of the genetic variation inherent in intrauterine programming (see Ref. 38).

During development, DNA can be modified epigenetically to alter gene expression without a change in DNA sequence (see Ref. 52). In mammals, these modifications occur primarily by DNA methylation and/or posttranslational alterations to the histones packaging the chromatin. In turn, these conformational changes alter the interaction between DNA and its regulatory proteins at the promoters, with effects on gene activation and repression (53). DNA methylation is particularly important in genomic imprinting, the process by which one allele of a gene is silenced in a parent-of-origin manner (10). Imprinting has a major role in early mammalian development, and many of the 80 known imprinted genes are involved in controlling placental and/or fetal growth (10, 44). Epigenetics, therefore, provides a molecular mechanism for programming that links genes, the prenatal environment, intrauterine growth, and subsequent susceptibility to disease.

There are two main periods of epigenetic modification: gametogenesis and early embryogenesis (52). These are the times of widespread demethylation and resetting of the epigenetic marks by de novo methylation. They are, therefore, particularly vulnerable to changes in the availability of methyl donors and cofactors essential for one-carbon metabolism, such as folate and glutathione (see Ref. 53). Once established, the epigenetic marks are stable mitotically and create unique, lineage-specific patterns of gene expression and/or silencing. Epigenetic modifications can also occur later in development, as changes in DNA methylation and imprint status have been observed during the perinatal period in several species (10, 53). For example, in ovine and human liver *Igf2* imprinting switches from monoallelic expression in the fetus to biallelic expression in the adult, whereas in rodents *Igf2* is completely silenced in all somatic tissues at weaning (see Ref. 14).

Both nutritional and endocrine factors have been shown to influence the epigenotype (54). Glucocorticoid administration causes DNA demethylation associated with increased gene expression of a hepatic aminotransferase in rats during the perinatal period (51). In cultured preimplantation sheep and mouse embryos, the amino acid composition of the culture medium alters the methylation state of key imprinted genes and changes intrauterine growth after embryo transfer (57). Similarly, in neonatal rat kidney, uteroplacental insufficiency induced by uter-

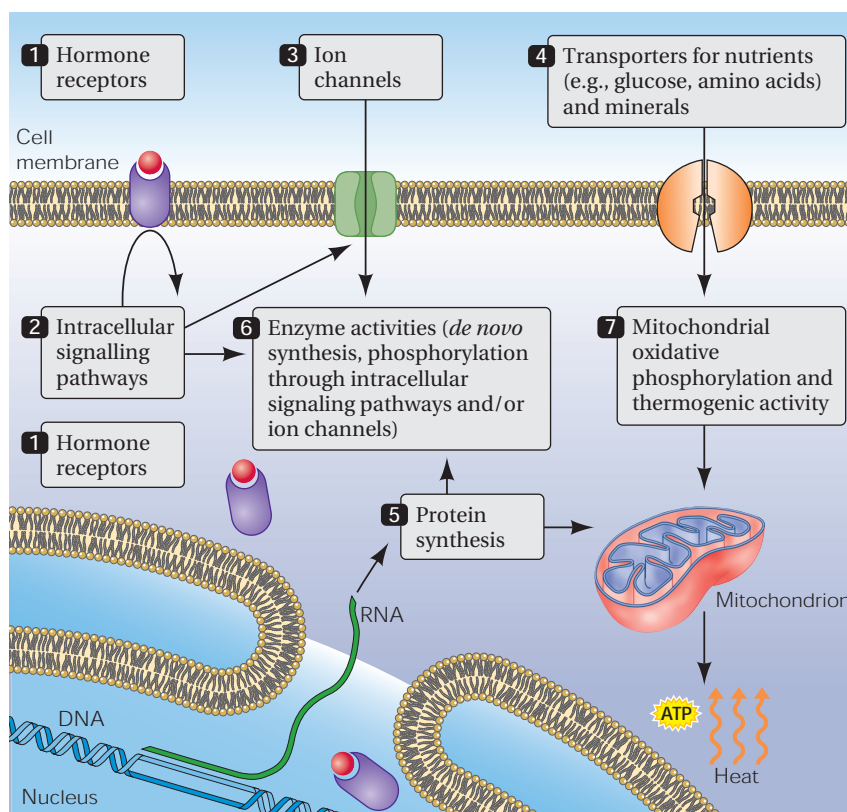
ine artery ligation during late gestation causes hypomethylation of *p53*, a gene involved in apoptosis (41). When methyl donor availability is altered by a low-protein diet during pregnancy, the pattern of hepatic DNA methylation is changed in both the fetus and adult offspring (32, 43). Addition of folate or methyl donors, such as glycine and taurine, to the low-protein diet restores normal patterns of DNA methylation and prevents the abnormalities in adult cardiovascular function that are programmed by the un-supplemented diet (2).

Environmental challenges may, therefore, cause programming by altering gene expression via several mechanisms (Table 2). These include loss of imprinting, differential promoter usage, and up- or downregulation of expression from the active allele(s) mediated epigenetically or via transcription factors (53). Certainly, in several genes with multiple mRNA transcripts, the relative abundance of the different splice variants is altered by undernutrition and glucocorticoid exposure in a tissue-specific manner, with potential consequences for protein translation in fetal tissues (14).

### Cells

Changes in transcription induced by environmental challenges lead to altered protein synthesis and permanent changes in cellular protein abundance (Table 2). These proteins include receptors, ion channels, transporters, enzymes, growth factors, cytoarchitectural proteins, binding proteins, and components of several intracellular signaling pathways (FIGURE 3). In particular, there are changes in the adenylyl cyclase and insulin-signaling pathways in cells, such as adipocytes, hepatocytes, and myocytes, in response to nutrient and O<sub>2</sub> deprivation, which persist after birth and influence adult metabolic activity (see Refs. 35 and 40). Similarly, prenatal undernutrition and hypoxemia induce permanent changes in the abundance of membrane and nuclear receptors for several hormones including glucocorticoids, catecholamines, insulin, IGFs, GH, leptin, and prolactin (8, 15, 16, 35). Overall, these changes in protein synthesis alter cell metabolism and growth and modify sensitivity to subsequent challenges.

Environmentally induced changes in cell physiology can occur at any point in development but are more likely to have long-term consequences during the formation of cell lineages and when cells are differentiating during late gestation in preparation for extrauterine life (FIGURE 2). In addition, when cells are growing at their maximum rate, undernutrition and hypoxemia may reduce cell proliferation directly by limiting substrate availability for tissue accretion and energy generation. Indeed, restriction of uterine blood flow near term is known to reduce DNA synthesis in fetal cells with a high proliferation rate in utero (3). Suboptimal intrauterine conditions may, therefore,



**FIGURE 3. Cellular processes that may be programmed by intrauterine manipulation of the nutritional or hormonal environment**

1) Hormone receptors. 2) Intracellular signalling pathways. 3) Ion channels. 4) Transporters for nutrients (e.g., glucose or amino acids) or minerals. 5) Protein synthesis. 6) Enzyme activities by *de novo* synthesis or phosphorylation through intracellular signalling pathways and/or ion channels. 7) Mitochondrial oxidative phosphorylation and thermogenic activity.

induce changes in the function, number, and size of cells by altering proliferation, clonal selection, and apoptotic remodeling of cell populations.

### Tissues and organs

The changes in cell structure and function, in turn, alter the morphology and physiology of tissues and organs as a whole (Table 2). If the insult occurs at the time of organogenesis, the changes may be severe and lead to a permanent developmental deficit. For instance, glucocorticoid administration to pregnant ewes for 2 days when the mesonephric kidney is developing at the end of the first month of gestation causes a permanent reduction in nephron number and leads to hypertension in the adult offspring (38). More subtle changes in cell composition of tissues, induced by suboptimal conditions in utero, can also influence postnatal physiological function. For example, there are changes in the relative proportions of different cell types in the pancreatic islets, liver, and skeletal muscles after IUGR that are associated with adult insulin resistance, glucose intolerance, and hypertension (see Refs. 27, 35, and 40). In organs like the placenta, early changes in development at the gene (imprinting), cell (transporter abundance), and tissue (vascularity) levels may impair fetal nutrient and O<sub>2</sub> delivery through-

out gestation with implications for tissue programming long after the original insult (see Refs. 22 and 44).

### Systems

The postnatal physiological abnormalities observed after suboptimal intrauterine conditions are multifactorial and involve several organs and endocrine systems (FIGURE 1 and Table 2). The severity of outcome is, therefore, determined by the number of organs and systems adversely affected by the intrauterine insult, which, in turn, depends on the nature and duration of the insult in relation to the stage of development (4, 21). In sheep, for instance, maternal glucocorticoid treatment early in gestation leads to hypertension but not glucose intolerance, whereas treatment late in gestation has the opposite effects in the adult offspring (see Refs. 15 and 38). In some systems, a specific trigger, or a second challenge, is required postnatally to unmask the intrauterine programming. In pancreatic islets, the abnormalities in insulin secretion induced by mild prenatal undernutrition only become evident in the adult when the demand for insulin rises during pregnancy (27). Similarly, in the heart, an ischemic challenge in adulthood is required to expose the underlying abnormalities in development induced by prenatal hypoxia or cocaine exposure (31). In several

physiological systems, sex-linked differences in intrauterine programming do not appear until puberty when the onset of gonadal steroidogenesis uncovers physiological abnormalities in peripheral tissues or in the hypothalamic-pituitary-gonadal axis itself (36, 45). However, in the majority of physiological systems studied, the adverse consequences of intrauterine compromise become more evident with increasing age as compensatory adaptations in other tissues and organ systems fail (35).

### Consequences of Intrauterine Programming

The consequences of intrauterine programming depend on whether the developmental deficit is the inadvertent outcome of an insult acting as mutagen or a specific adaptation to an environmental challenge designed to maximize survival to reproductive age (20). With mutagenesis, the structural and functional deficits are permanent and invariably detrimental to long-term survival. In contrast, the physiological adaptations made in response to suboptimal intrauterine conditions may improve viability in the short to medium term but at the risk of later morbidity (24). The adaptations in functional capacity programmed in utero may, therefore, be a trade-off to maintain development of essential tissues, such as the brain and placenta, and/or a mechanism for setting an appropriate phenotype for the environmental conditions ex utero (6, 35). When the functional capacity set in utero does not match that required postnatally, homeostasis may be compromised and lead to abnormal physiological parameters, which, eventually, result in overt disease. For example, the enhanced sensitivity of the HPA axis programmed by suboptimal conditions in utero is essential for survival in poor conditions but is inappropriate when nutrients and O<sub>2</sub> are plentiful and may cause hypertension and metabolic disorders in the adult (see Ref. 16). Similarly, intrauterine programming of a thrifty phenotype by prenatal undernutrition will lead to increased growth and fat deposition if postnatal nutrient availability is better than predicted in utero (23, 40, 50). In turn, the increased adiposity will lead to adult insulin resistance, glucose intolerance, and finally type 2 diabetes, particularly as the counterregulatory mechanisms deteriorate with age (23). Certainly in humans, the risk of developing adult type 2 diabetes is greatest when poor prenatal growth is coupled with catch-up growth and adiposity rebound during childhood (21). Indeed, the accelerated growth often observed after IUGR may be more important than the intrauterine changes per se in programming adult-onset degenerative diseases (49).

Intrauterine programming also has consequences for the next generation. The physiological perturbations programmed by environmental challenges in

utero can be transmitted from one generation to the next by either the mother or father (12, 46). This transgenerational inheritance of programming may be due to changes in the primordial germ cells from which the next generation develops or to recapitulation of the metabolic and endocrine conditions that the mother experienced as a fetus in utero due to the programmed adaptations in her physiology (1, 28). Alternatively, it may reflect meiotic inheritance of the epigenetic marks as a result of aberrant demethylation (52, 57). Incomplete erasure of the epigenetic marks may lead to an inheritable “memory” of epigenetic state at specific alleles.

Because nutrition has improved progressively in most developed and developing countries over the past 50 years, many people will have developed a phenotype in utero that is programmed for a significantly lower level of nutrition than currently available. This may explain, in part, the epidemic of hypertension, obesity, and type 2 diabetes in populations worldwide. As food intake, lifestyle, and dietary advice during pregnancy change in response to these trends, the physiological adaptations now being programmed in utero by Western high-fat/high-calorie diets may lead to adult phenotypes no better suited to the prevailing environmental conditions in the next generation than those programmed by poor nutrition a generation ago. However, improved knowledge of the pathophysiology induced by transgenerational oscillations in dietary intake and other environmental factors may enable the development of nutritional and other interventions to ensure that intrauterine programming is beneficial and not detrimental to adult health. ■

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