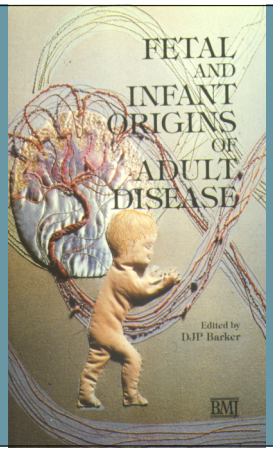
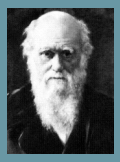




THE DUTCH HUNGER WINTER

In 1944 food supplies were cut off to western Holland by the Nazis, in retaliation for a railway strike

Over 10,000 people died from starvation and cold, the first such localized event in a literate, developed country

LIFE IN THE WOMB

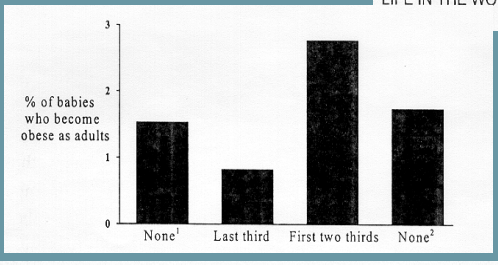


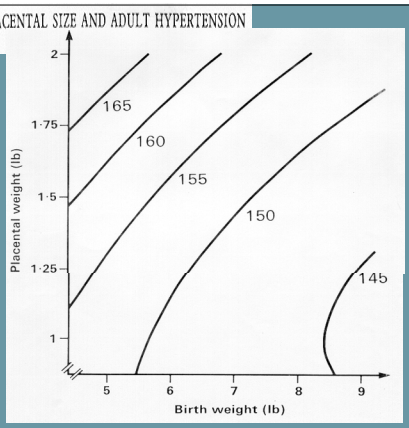
FIGURE 2.5

Portion of pregnancy during which the baby was exposed to low nutrition in the womb and the likelihood that the baby will be obese when s/he grows up. [1]Babies born before the Dutch Hunger Winter. [2]Babies born after the Dutch Hunger Winter.

The early 'Barker Studies' in the UK

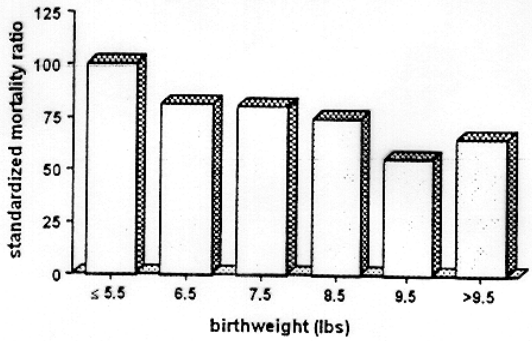
Dark areas high infant mortality rate (1901-1910) and high death rate from coronary artery disease (1959-78)

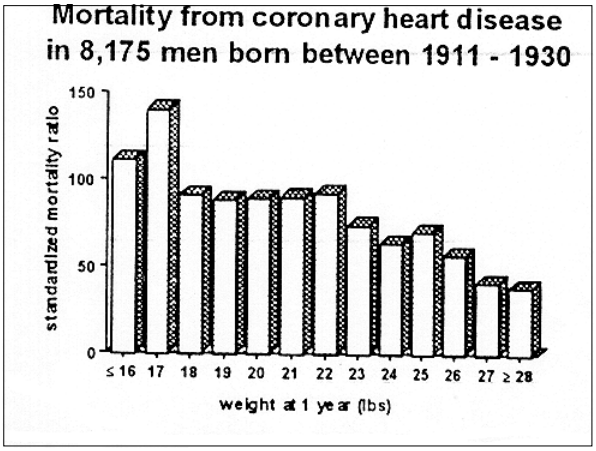
FETAL AND PLACENTAL SIZE AND ADULT HYPERTENSION

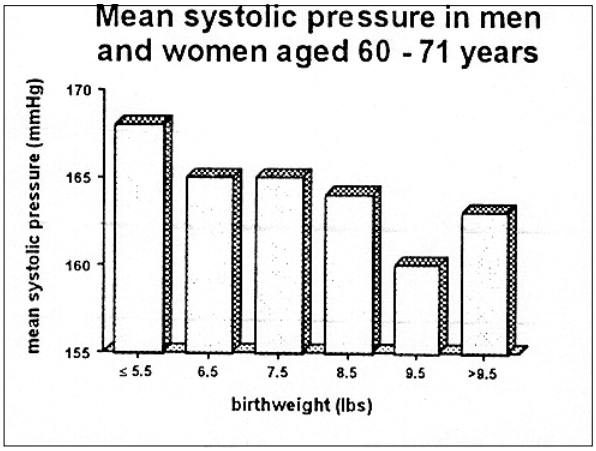


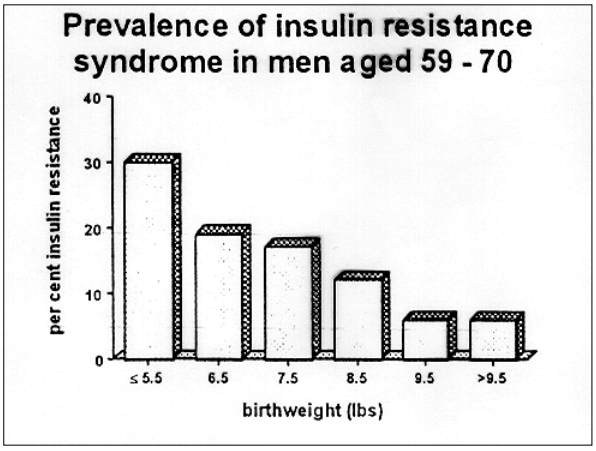
Systolic pressure (mmHg) according to placental weight and birth weight

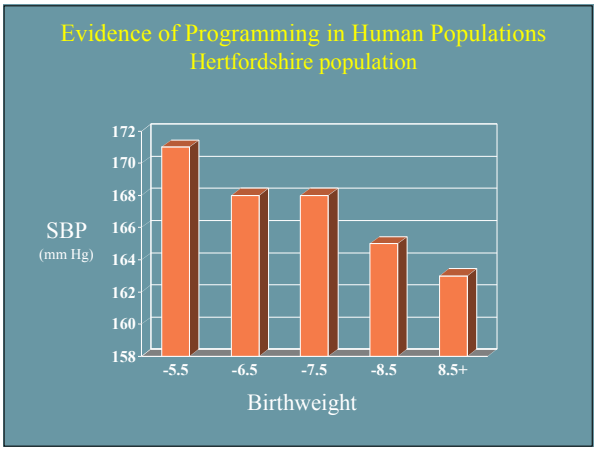
Death rates from coronary heart disease among 15,726 men and women











The Barker Hypothesis

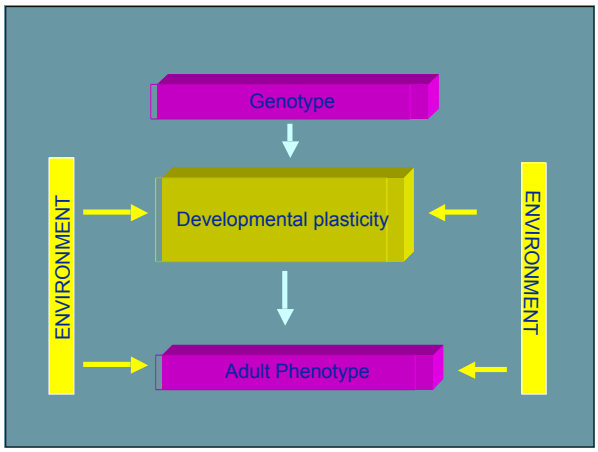
Fetal origins of adult disease hypothesis

Fetal programming:
Adverse environments in fetal life and early childhood lead to increased risk of disease in adult life

Programming

The process through which a *stimulus* or *insult* establishes a *permanent* response

Exposure during a *critical period* in development may influence later metabolic or physiological functions in adult life



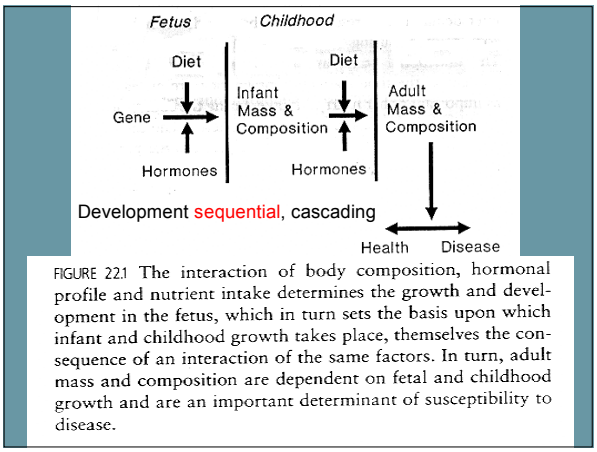


FIGURE 22.1 The interaction of body composition, hormonal profile and nutrient intake determines the growth and development in the fetus, which in turn sets the basis upon which infant and childhood growth takes place, themselves the consequence of an interaction of the same factors. In turn, adult mass and composition are dependent on fetal and childhood growth and are an important determinant of susceptibility to disease.

The Barker Hypothesis- basic version

Maternal Undernutrition

↓

Fetal Growth Retardation

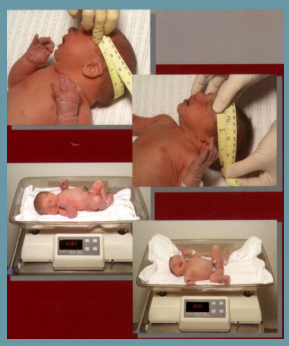
↓

Poor Childhood Growth ← Structural Change within Organs → Metabolic and Endocrine Dysfunction

↓

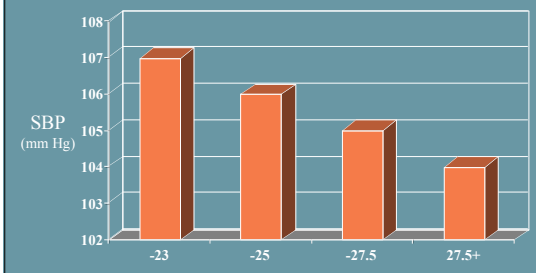
Disease In Later Life

Disproportionate Size at Birth (thin-ness) is also Implicated in Programming



Disproportion Predicts Cardiovascular Dysfunction

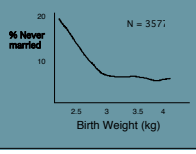
Blood pressure in 4yr olds in Salisbury, UK



Ponderal Index (length $^{1/3}$ x 100/height in cm)

Low Birthweight/Disproportionate size at birth are associated with:

- Coronary artery disease
- Hypertension
- Glucose intolerance
- Asthma in childhood
- Immune dysfunction
- Chronic renal failure
- Raised cholesterol
- Raised cortisol
- *and whether men get married or not*



Etiology of Intrauterine Growth Restriction (IUGR)

Maternal

- Impaired nutrient delivery- Maternal diet and body composition both before AND after conception are very important

Placental

- Impaired nutrient uptake

Fetal

- Impaired fetal uptake

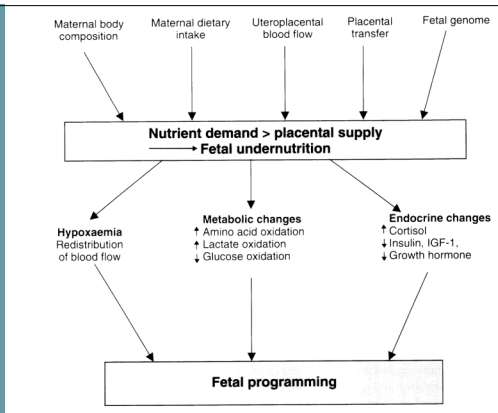


Fig. 8.2 Fetal adaptations to undernutrition: a framework.

Ten Principles of Programming

(1) During development, there are **critical periods of vulnerability** to suboptimal conditions. Vulnerable periods occur at different times for different tissues. Cells dividing rapidly are at greatest risk. Factors that increase risk include:

-too much of normal chemicals such as hormones, critical nutrients or vitamins
-deficiency of normal materials, chemicals such as nutrients, hormones, or vitamins
-abnormal chemicals such as alcohol or nicotine
-abnormal physical forces, such as high blood pressure

Ten Principles of Programming

2. Programming has **permanent effects** that alter responses in later life and can modify susceptibility to disease

3. Fetal development is sequential and **activity dependent**. Normal development is dependent on continuing normal activity of developing systems. Each phase of development provides the required conditions for subsequent development.

Ten Principles of Programming

(4) Programming involves several different **structural changes in important organs**.

- The absolute numbers of cells in the organ may increase or decrease.
- The relative proportions and distribution of different types of cells within the organ may be unbalanced.
- The normal blood supply to the organ may not form.
- Too many or too few hormone receptors may form with a resultant resetting of feedback and other control mechanisms.

Ten Principles of Programming

5. The **placenta** plays a key role in programming.

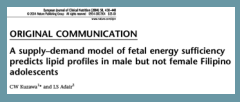
6. **Compensation carries a price**. In an unfavorable environment, the developing baby 'makes attempts' to compensate for deficiencies. Following compensation, birthweight may be normal or only slightly decreased. However, the compensatory effort carries a price.

7. **Attempts made after birth to reverse the consequences of programming may have their own unwanted consequences**.

Ten Principles of Programming

8. **Fetal cellular mechanisms often differ from adult processes.** Fetuses react differently to suboptimal conditions that do newborn babies or adults.

9. Programming can have **different effects in males and females**.


ORIGINAL COMMUNICATION

A supply-demand model of fetal energy sufficiency predicts lipid profiles in male but not female Filipino adolescents

10. The **effects of programming may pass across generations** by mechanisms that do not involve changes in the genes - involves physiological effects and epigenetic changes (eg heritable changes to gene expression patterns mediated by methylation and histone modifications) that are poorly understood

Transgenerational effects of programming:

Poor fetal development

↓

Poor development of organ systems, including reproductive systems

↓

Poor ability to nourish own fetus -> poor fetal development

↓

Mechanisms of Programming?

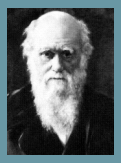
Nutritional Influence

Altered Cell Number or intracellular organization

Reorganisation of organ structure
Abnormal early cell-cell interactions?

Metabolic Differentiation
DNA Control?
(altered cell specific gene regulation)
DNA Environment?
(altered DNA binding proteins)
Altered DNA methylation?

Evolutionary basis of fetal programming



Relevant ideas:

-Mismatches between Ancestral & Modern Environments with regard to Food

-Adaptation, Tradeoffs and Maladaptation in Development and Life History

'Thrifty genotype' hypothesis (Neel 1962):

periodic famines in past selected for alleles that maximize metabolic efficiency, lipid storage,and food-searching behaviors. In modern environments, these alleles are maladaptive as they lead to diabetes and obesity.

Developed from comparative evidence on human groups, such as Pima Indians and South Seas islanders.

Population grouping	Region	Percentage prevalence
Europeans	Britain	2
	Germany	2
	Australia (1981)	2
	Australia (2002)	8
	United States	8
Native Americans	Chile Mapuche	1
	US Hispanic	17
	US Pima	50
Pacific Islanders	Nauru (1952)	0
	Nauru (2002)	41
New Guineans	Rural	0
	Urban	37
Aboriginal Australians	Traditional	0
	Westernized	23
Middle East	Yemen, traditional	4
	Yemenite Jews in Israel	13
	Lebanon, westernized	14
Black Africans	Rural Tanzania	1
	Urban South Africa	8
	United States	13
Chinese	Rural China	0
	Urban Singapore	9
	Urban Taiwan	12
	Urban Mauritius	13
Asian Indians	Rural India	0
	Urban Tanzania	11
	Urban India	12
	Urban Singapore	17
	Urban Mauritius	17
	Urban Fiji	22

Figure 1 Age-standardized prevalence of type 2 diabetes mellitus. Among the main features are the low prevalence among groups of European origin, especially those remaining in Europe; the high prevalence among Pima Indians and urban New Guineans, and among Nauruans today; and the higher prevalence in urban or westernized groups, compared with their rural or traditional counterparts.

One implication is genetically-based local adaptation to long-term nutritional conditions

Low prevalence in Europeans may result from history of *past* selection *against* highly thrifty genotypes

J. Diamond 2003, *Nature*

Box 1 The diversity of diabetes mellitus

The term 'diabetes mellitus' covers a wide variety of conditions that are linked only by shared symptoms arising from high levels of blood sugar. That diversity may be crudely partitioned[2,3,11,12] into type 2 (adult-onset) and the less-common type 1 (juvenile-onset). The respective prevalences among diabetics in the United States are 90–95% and 5–10%. Both diseases centre on the hormone insulin, which is responsible for mediating the uptake by cells of glucose from the blood.

Type 1 diabetes (insulin-dependent diabetes mellitus) is an autoimmune disease in which autoantibodies destroy the pancreatic-islet cells that synthesize insulin. Patients are thin, produce little or no insulin, and are prone to ketosis, a particular metabolic imbalance. They carry certain gene types — the HLA alleles *DR3*, *DR4* or both — that encode particular components of the immune system. Type 2 diabetes (non-insulin-dependent diabetes mellitus) involves altered insulin secretion and insulin resistance. Patients are often obese and are not subject to ketosis. They do produce insulin but become insulin-resistant — that is, unable to respond effectively to it.

Distinguishing the two forms can be complicated, however, because there is early-onset type 2 and late-onset type 1. Type 2 diabetes is itself very heterogeneous, both genetically and in the associated pathological and physiological symptoms. The disease arises from at least 60 identified genetic disorders, united only by the common feature of high blood-glucose levels due to insulin resistance. This heterogeneity reinforces the evolutionary puzzle: genes that predispose the bearer to type 2 diabetes must really convey some advantage, because they have evidently been preserved independently many times by natural selection. The 'thrifty gene' hypothesis, according to which such genes allow efficient food utilization in times of plenty, in preparation for famine, provides a possible explanation. **J.D.**

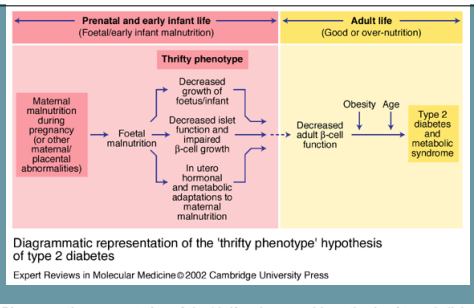
J. Diamond 2003, *Nature*

'Thrifty phenotype' hypothesis (Hale & Barker 1992):

Fetus in compromised prenatal nutritional environment adjusts organ growth to **spare brain** *in utero*, at cost of later disease, such as type 2 diabetes and high blood pressure

-Type 2 diabetes: costs >100 billion$ annually in USA, expanding exponentially in developing world (esp. Asia), considered an 'environmental epidemic'; increasingly-prevalent in younger Individuals

-Part of 'metabolic syndrome' (obesity, hypertension, type 2 diabetes)



Diagrammatic representation of the 'thrifty phenotype' hypothesis of type 2 diabetes

Figure 1. Diagrammatic representation of the 'thrifty phenotype' hypothesis of type 2 diabetes. It is proposed that type 2 diabetes is the outcome of maternal–foetal malnutrition, whether because of poor maternal diet (e.g. famine), low maternal fat stores or reduced transfer of nutrients as a consequence of placental abnormalities. The foetus adapts to this environment by being nutritionally 'thrifty', resulting in decreased foetal growth, islet function and β-cell mass (low glucose levels require low insulin levels), and other hormonal and metabolic adaptations. A transition to good or over-nutrition later in adult life exposes the impaired islet function and, exacerbated by obesity and age, type 2 diabetes results. Thus, the thrifty phenotype hypothesis can be envisaged as an altered programming of growth and metabolism that aids survival pre- and early postnatally

Evidence that 'thrifty phenotype' can be adaptive:

(1) Lab rats with higher type 2 diabetes risk survive starvation better

(2) Some wild species adapted to periodic food scarcity develop type 2 diabetes when maintained in lab on 'western diet'

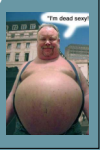
(3) Human populations with highest type 2 diabetes rates (eg Nauruan islanders, Pima Indians) were subject to periodic starvation in historical past - fattest tended to survive (parallel to fat deposition, survival in human babies)

Integrated suite of changes in fetus developing under nutrient stress

(1) Reduced body size, brain relatively spared

(2) Reduced muscle mass as adults - reduction in this insulin-sensitive tissue reduces overall nutrient requirements and contributes to later insulin resistance. Insulin resistance in muscle shunts glucose to brain and other key organs

(3) Fat deposition enhanced,and stored in highly-labile visceral deposits - can be rapidly mobilized by has severe disease risks



ALTERNATIVE HYPOTHESES FOR THE ADAPTIVE SIGNIFICANCE OF FETAL PROGRAMMING

(1) Predictive adaptive response

(2) *More or less adaptive trade-off:*
(a) Barker -> fetal tradeoffs, with negative later effects as consequences, not objectives
(b) Adaptive trade-off hypotheses-> see later effects as objectives that become maladaptive only in mismatched environment

(3) *Maladaptive and pathological* - traditional view, but now seen as unlikely, as response is complex and coordinated, and has some apparent adaptive components such as brain sparing

(1)Predictive adaptive response hypothesis

Idea that the fetal programming under nutrient stress optimally prepares the individual for poor conditions therefore predicted in later life. Thus:

Fetal Conditions	Adulthood conditions	Consequence
Poor	Poor	Adaptive
Good	Good	Adaptive
Poor	Good	Maladaptive
Good	Poor	Maladaptive

BUT degree of *long-term* predictability in *humans* is unclear, benefits from predictability may be shorter-term; evidence for adaptive outcomes is weak in humans

TABLE 1. Human life history stages and associated growth and development outcomes under adverse conditions

Life history stage—Adverse conditions[a]	Growth/development outcomes[b]
Prenatal-maternal nutritional deprivation; stress of hypothalamic–pituitary–adrenocortical (HPA) and HP-thyroid axes	Insulin resistance, more omental fat, reduced skeletal muscle mass, reduced bone mineralization, reduced capillary density in many tissues, impaired endothelial cells in heart and vasculature, reduced nephron number, reduced negative feedback of HPA axis (greater stress response), elevated adrenocortical and thyroid hormones
Birth/neonate (to 28 days postpartum)-outcomes related to adverse prenatal conditions above	Possible combination of low birth weight, prematurity, reduced brain growth/head circumference, reduced arm and leg length, impaired immune function
Infant[c]: 28 days to 2.9 years, and Child[d]: 3.0–6.9 years, undernutrition, lack of play/stimulation, infection, neglect/abuse; overfeeding and low physical activity	Growth faltering, short extremities especially the legs, infection-malnutrition synergism, motor and cognitive delays, HPA precocious sexual development, infant-child mortality; high BMI with excess fat, incipient diabetes and cardiovascular disease, reduced bone and muscle mass
Juvenile[e]: 7.0–10.0 years (pubarche), as above plus excessive physical labor	Continuation of above responses with possible exacerbation of responses due to additional physical labor and greater exposure to pathogens due to increased independence

Bogin et al. 2007

(2) Adaptive trade-off hypothesis

Idea that the fetal programming under nutrient stress involves an adaptive trade-offs between early survival and costs to health in later life

Nutritional stress is especially important around weaning, when brain growth and metabolism are high and food supply may be disrupted

-ability to store fat, mobilize fat fast, & spare glucose for brain via insulin-resistance, may be adaptive to protect brain, and survive, especially during this high-risk childhood period

A life-history perspective on the adaptive significance of fetal programming

(1) Growth, maintenance and reproduction are subject to trade-offs, which are more severe under nutrient stress.

(2) There are also tradeoffs *within* each of these three domains, such as between brain growth and somatic growth, or between current and future reproduction

(3) Trade-offs mean that health cannot be maximized simultaneously with respect to multiple criteria - need to choose between different risks, or better health (or survival) now vs better health later

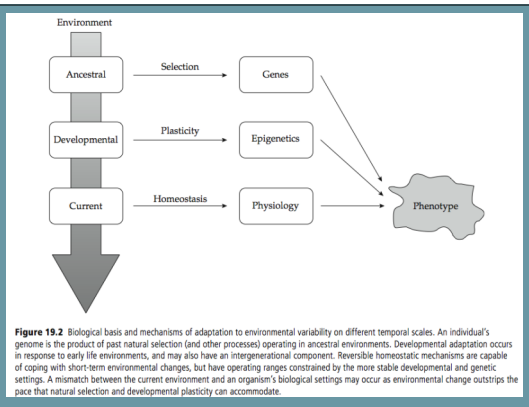
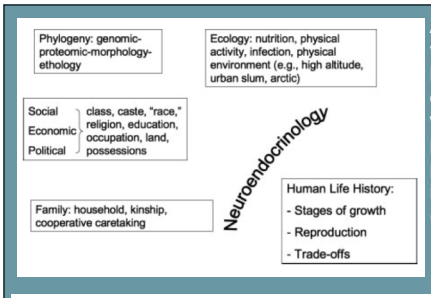


Figure 19.2 Biological basis and mechanisms of adaptation to environmental variability on different temporal scales. An individual's genome is the product of past natural selection (and other processes) operating in ancestral environments. Developmental adaptation occurs in response to early life environments, and may also have an intergenerational component. Reversible homeostatic mechanisms are capable of coping with short-term environmental changes, but have operating ranges constrained by the more stable developmental and genetic settings. A mismatch between the current environment and an organism's biological settings may occur as environmental change outstrips the pace that natural selection and developmental plasticity can accommodate.



A comprehensive view of effects on human development, in which fetal programming plays a key role in health (Bogin et al. 2007)

Fig. 1. Biocultural domains of influence on human life history. The "Phylogeny" domain has the most direct impact on genome, on the limits of the functional proteome, and on some aspects of human morphology and behaviors (such as the capacity for bipedalism). However, the "Phylogeny" domain has the most indirect influence on human life history, indicated by its distance from the "Human Life History" box, because it is mediated through the domains of "Ecology," "Social–Economic–Political," and "Family." All human beings share a highly similar "Phylogeny" domain, but live within highly variable ecologies, socioeconomic and political systems, and family groupings. The unevenness in these last three domains interacts with the phylogenetic factors to produce a range of variation in reaction norms of neuroendocrine production and activity. Neuroendocrine products have the most direct influence on the regulation of human life history, directing development through the stages of growth, adjusting the timing and frequency of reproduction, and modulating trade-offs in biology and behavior (original figure, based on Bogin, 2001).

Implications of fetal programming for public health

(1) To mitigate negative effects of fetal programming, best strategy is to *improve health of young* ***women***, via better nutrition, reduced stress, more exercise - size and health of baby depend in part on status of mother before & after conception

(2) *Populations at highest risk* (evolved in low-nutrition conditions, now in high-nutrition conditions) need to be recognized and informed (espec. China, India)

(3) Individuals at highest risk were born small and/or skinny but underwent fast compensatory growth; interventions for low birth weight should take account of these data

(4) Birth and childhood weight are affected by the outcomes of **conflicts** between mother and fetus; such conflicts require further study

(5) Transgenerational effects impose special urgency to act soon