Adult disease: echoes of the past

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Abstract

Disease occurs if an environmental challenge exceeds the ability of an individual to mount an effective adaptive response to it. Evolution has selected genomically determined traits, which are optimal for a species to survive the historical environment. However, this adaptive ability to withstand an environmental challenge varies among individuals and is itself a phenotypic characteristic: how is this determined? We argue that maternal and placental cues that constrain prenatal development, induce offspring to develop predictive adaptive responses more suited to a deprived postnatal environment, i.e. a more favorable phenotype for survival of the species than that which would be established by the genotype in the absence of environmental influence. This ‘survival phenotype’ can be exaggerated further by the postnatal environment. Since predictive adaptive responses maximize the chance of survival to reproduce, this phenomenon has itself been protected through evolution. Furthermore, such rapid adaptive responses may allow transgenerational transmission of phenotypic traits advantageous for survival of a species through transient environmental change. We argue that risk of disease is increased, when the actual postnatal environment does not match that predicted prenatally. In humans, this explains patterns of disease, especially those for which risk is determined in part during development, such as type 2 diabetes, cardiovascular disease and the rising risks of childhood obesity. The predictive adaptive response hypothesis extends foregoing concepts in this field and lends itself to experimental testing. It provides insights into ways to reduce the burden of certain common chronic diseases in both developed and developing countries.

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Most phenotypic changes in early life have immediate adaptive advantage, for example, altered regional blood flows are a fetal response to placental insufficiency and protect the fetal brain at the expense of fetal somatic growth. However, many phenotypic effects are the result of developmental plasticity and their appearance may follow the initiating cue after a substantial delay. Some such phenotypic changes induced in utero or in the neonate may confer their primary advantage well after birth by adapting the organism to have a greater chance of survival to reproductive success. Natural selection will favor conservation of such mechanisms even if they have a cost in later life, after peak reproductive competence has passed. Such costs will become increasingly apparent with greater longevity in a population.

There is much evidence that a sub-optimal fetal environment, as reflected in smaller size at birth, is linked to increased risk of coronary heart disease and type 2 diabetes in middle-aged and elderly people (1, 2). This relationship is continuous across the normal range of birth size: however, the fundamental processes underpinning it do not relate to the birth size per se, because such size is only one surrogate measure of the fetal environment, particularly in late gestation. Diverse effects on the fetus can have physiological consequences not reflected in birth size, for example, by altering nephron number (3), and early gestation, environmental cues can influence development without affecting birth weight. Developmental origins of disease have been termed ‘fetal programming’ (1), because they suggest that events in early life irreversibly alter development in such a way that the disease manifests when amplified or challenged by postnatal environmental factors.

Hales and Barker (4) proposed that programming of disease is the result of an adaptive mechanism, whereby the human fetus adopts a ‘thrifty phenotype’. In response to a maternally determined environment perceived as inadequate, the fetus makes irreversible changes to aspects of its development. Thus, relative insulin resistance develops in fetal life in response to maternal undernutrition, and leads to reduced somatic growth and energy conservation after birth to allow the offspring

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a better chance of survival in a postnatal environment where nutrition is poor. We suggest that the thrifty phenotype is one example of a broader strategy of predictive adaptive responses in development. We define these as a set of responses preserved through evolution, whereby the developing organism presets its physiology in expectation of its future environment, so as to maximize its chances of reproductive success. A mismatch between the preset physiology and the actual postnatal environment will lead to an elevated risk of disease, particularly in the post-reproductive period. In this case, the organism’s developmental prediction would have been maladaptive. The greater the degree of mismatch, the greater is the risk of disease.

Such effects are readily experimentally induced, against a constant genetic background, by manipulating maternal diet or endocrine status in a broad range of mammalian species, including sheep (5), guinea pig (6), rat (2) and mouse (7). In many of these experiments, birth weight was unaffected. The underlying mechanisms differ depending on when the adaptive response was cued by such environmental factors in development. Factors acting in the peri-conceptional period affect genomic imprinting (8) and other epigenetic processes, hormone receptor development and embryo/trophoblast cell allocation (9), whereas cues later in fetal development alter structural (2) and/or functional (10) differentiation of tissues. The range of environmental stimuli and the capacity to induce a similar postnatal phenotype from early or late gestation cues suggests multiple pathways to a common and evolutionarily protected phenotype. There is also evidence that the magnitude of the fetal adaptive response and its long-term outcome is influenced by specific genotypes (11).

Maternal factors are dominant in determining fetal growth, because species survival is not possible if the fetus can outgrow its mother’s reproductive tract. Thus, in monotocous species, a mechanism, termed maternal constraint (12), has evolved to limit fetal growth in relation to maternal body size. Its original demonstration (13), that when horses and ponies were crossed, fetal size was determined more by the size of the mare, has recently been confirmed using embryo transfer with donor oocytes (14), eliminating any confounding genetic element. ‘Normal’ birth size and functional phenotype are displaced from the one determined by genotype by maternal constraint, further exaggerated by any adverse environmental cue to a ‘survival phenotype’ best suited for survival in a poor environment. The extent of maternal constraint varies, being greater in primiparous, multiple or adolescent pregnancies and those, where the mother has smaller stature.

Poor maternal nutrition or placental disease signal erroneously to the embryo/fetus that the external environment is deprived. Maternal stress resulting in elevated glucocorticoids provides a related cue. Each of these processes drives the fetus to predict a more deprived postnatal environment and to extend its adaptive responses beyond the survival phenotype already set by maternal constraint. This increases the likelihood of mismatch between the prenatally predicted environment and the one that actually exists, consequently increasing the risk of disease (Fig. 1).

The major features of the survival phenotype are insulin resistance, altered exercise and feeding behavior (including appetite and food preference), reduced skeletal muscle mass (also giving insulin resistance), central fat deposition (15), reduced vascularity in some tissues and alterations in the hypothalamic–pituitary–adrenal axis. After birth, this phenotype is advantageous in a deprived environment, because it conserves resources via reduced growth, and diverts substrate from metabolism to fat deposition to provide energy stores. The phenotype is highly appropriate to any mammal with restricted food supply and to the hunter–gatherer lifestyle, in which the individual will favor fat ingestion and, in the human, store when available as central fat. This is analogous to the camel’s hump, and indeed this hump and human omental fat have remarkable similarities as both represent the major labile fat storage depot for episodic feeders. Recently, it has been shown that there is a greater propensity for

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**Figure 1** Effect of the developmental (prenatal, infancy and early childhood) environment on the range of adult nutrition/energy expenditure in relation to increased risk of disease in later life. The circles show the range of postnatal environments associated with a low risk of adult disease for various developmental environmental (e.g. nutritional) levels. These adult ranges are those predicted by developmental adaptive responses. If the level of adult nutrition/energy balance is above the level shown by the broken line, then the risk of disease is enhanced. Western lifestyle, especially with rapid socio-economic transition, moves many individuals above this range (vertical arrows). Maternal constraint (during prenatal life) and poor infant environment shift the phenotypic traits of the developing offspring to those better matched to a relatively poorer adult environment (horizontal arrows). Again disease risk is greater. Low levels of environmental agents such as endocrine disruptors can act to lower artificially the level of adult environment associated with health. The diagram emphasizes that risk is determined by the relative match between the developmental and adult environment, and not by the absolute level of the adult environment itself.
relative obesity to develop in the offspring of primiparous women, in whom we predict the operation of greater maternal constraint (16), and follow-up of the Hertfordshire cohort, in which low birth weight was associated with features of the metabolic syndrome in middle age shows that those born small have greater trunk–limb fat mass ratio and lower skeletal muscle mass and resting energy expenditure (17, 18).

Williams’ theory of antagonistic pleiotropy (19) made the generally accepted point that natural selection favors characteristics that confer benefit in the reproductive phase of life, even if they are subsequently deleterious. Thus, a genomic mutation that enhances reproductive fitness, will be selected even if it reduces longevity. This implication can be extended to epigenetic transformations of the genome passing across several generations (8): such a mechanism may explain the multigenerational nature and evolutionary role of predictive adaptive responses. Trade-off theory (20) has also been used to explain species differences in lifespan. The development of predictive responses is a further example of a biological trade-off within a single species.

Natural selection acts over many generations, because species survival, or the evolution of a new species, is related to long-term (effectively permanent) changes in the environment; but species must also survive through environmental stresses that act within one or a few generations, often with the environment returning to its pre-existing state. Moreover, they must make rapid adaptive changes to the phenotype of many individuals within a generation or two, rather than waiting for the long-term and random process of a beneficial mutation of the genome arising in a single individual. We argue that predictive adaptive responses have evolved as a mechanism to allow a species to survive short-term environmental change in a highly cost-effective way.

Modern diets favor high caloric intakes and nutrient balances well removed from those to which Homo sapiens was exposed during evolution. Exercise levels have also fallen dramatically, and recently a greater proportion of children are from primiparous or adolescent pregnancy. We hypothesize that evolved predictive responses have set human physiology to operate on a lower plane of postnatal nutrition than the one to which current children and adolescents are exposed. One implication of this hypothesis is that the factors favoring the development of childhood obesity are themselves determined pre-natally. It is important to note that although being born small does not cause obesity, it sensitizes the individual to be at greater risk of visceral obesity in a high-nutrient, low-expenditure environment. This has been well demonstrated experimentally (21, 22). The other developmental pathways to obesity of gestational diabetes and maternal obesity or neonatal overfeeding can intersect with this pathway as they are not mutually exclusive (23). Thus, antenatal factors not only create the physiological settings for long-term disease risk, such as insulin resistance, but also influence the likelihood of their amplification in the modern environment after birth.

It is likely that predictive adaptive responses constitute true adaptations, in that they have been selected during evolution to improve reproductive fitness in our ancestors. However, formal proof is required before we can state that predictive responses are an evolutionary adaptation. The hypothesis can be tested in experimental animals and a recent experiment in which leptin was administered to neonatal rats born to undernourished mothers is certainly compatible with the model. The leptin-treated animals behaved throughout their life-course as if they had not been undernourished in utero (24). This might suggest that the high levels of leptin ‘tricked’ the pups into thinking they were fatter and better nourished than they were and adjusted their prediction accordingly. As noted earlier, the early induction of permanent phenotypic traits has focused attention towards epigenetic mechanisms, that may underlie the process. There is strong support for such effects in animals, related to altered DNA methylation patterns of the promoter regions of genes linked to hepatic function (25), kidney development (26) and stress responses (27), some being reversed by maternal dietary folate supplementation (25). These new insights will change the focus of our research towards identification of new prognostic markers of adult disease in childhood, and ways of controlling the operation of cues that influence development in utero or in infancy. Such knowledge may permit novel insights in the management of the postnatal environment in ways appropriate for both the genotype and developmental phenotype of children.

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References


