Predictive adaptive responses and human evolution

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The importance of a single genotype being able to produce different phenotypes in different environments (phenotypic plasticity) is widely recognized in evolutionary theory and its adaptive significance is clear. In most cases, the developing organism responds to an environmental cue by producing a selectively and immediately appropriate phenotype. One subset of phenotypic responses to environmental stimuli, however, does not necessarily provide an immediate selective advantage. Rather, these kinds of responses, which we call ‘predictive adaptive responses’ (PARs), act primarily to improve fitness at a later stage of development. We argue that PARs have had an important role in human evolution, and that their recognition and interpretation has major significance for public health.

Introduction

Clinical and epidemiological research has identified numerous links between measures of early human development and the incidence of adult disease [1]. Most work has linked an impaired fetal environment, as reflected by small size at birth, to a greater risk of coronary heart disease and non-insulin dependent diabetes in middle-aged and elderly people [2–4]. This relationship has been termed the ‘fetal (or developmental) origins of adult disease’ [2] because it suggests that events in early development irrevocably alter components of homeostasis in such a way that, when amplified or challenged by postnatal environmental factors, disease becomes manifest. Hales and Barker [1,5] proposed this phenomenon to be the accidental effect of what they termed the ‘thrifty phenotype hypothesis’, an immediate fetal adaptation to altered nutrient supply that is mediated in part by insulin deficiency and/or resistance (insulin being a major fetal growth promoting hormone) for survival in a deficient intrauterine environment. These changes leave the growth-retarded fetus to cope with the consequences, which depend on whether the postnatal environment is nutritionally rich or poor. Experimental studies have readily replicated a relationship between early life experience and adult metabolic and cardiovascular function in a variety of mammal species [6]: the breadth of this demonstration suggests that some general biological process underpins it. Hales and Barker [1,5] recognized that there might be postnatal advantage for a ‘thrifty’ phenotype in a nutritionally deprived environment. We [6–8] and others [9] have proposed that these observations can be better interpreted as part of a broader set of developmental and evolutionary strategies that we have termed ‘predictive adaptive responses’ (PARs) [6,8]. Placing these strategies in this perspective has important implications for understanding changing patterns of human disease.

Predictive adaptive responses

We define PARs as a form of developmental plasticity that evolved as adaptive responses to environmental cues acting early in the life cycle, but where the advantage of the induced phenotype is primarily manifest in a later phase of the life cycle. The cue affects the processes of developmental plasticity and thus induces changes in the developmental trajectory of form and function such that the organism presets its physiology in expectation of that physiology matching its future environment. PARs, therefore, are a form of phenotypic plasticity [10,11] in which the resulting phenotype is not necessarily advantageous in the environment concurrent with or immediately following the inducing cue, but is likely to be advantageous in an anticipated future environment. The cue thus acts as a predictor of the nature of this environment. The adaptive value of a PAR depends on the fidelity of the prediction. Modelling suggests that the prediction need not be perfect for selective advantage [12,13].

Examples of PARs can be demonstrated in polyphenic organisms and in those with continuous phenotypes. In the migratory desert locust Locusta migratoria, for instance, the developmental switches affecting wing shape and metabolic phenotype that are triggered by high population density, as sensed by the egg-laying females, do not confer an immediate advantage on the larva [14–17]. Instead, adopting the migratory phenotype confers a survival advantage in adult life when food supplies are scarce, a probable and predictable scenario given the high population density experienced by the parent. Similarly, in the meadow vole Microtus...
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TRENDS in Ecology and Evolution  Vol.20 No.10 October 2005

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*peninsularicus*, coat thickness is determined before birth in anticipation of the predicted postnatal thermal environment. This prediction is informed by maternal sensing of day length, presumably affecting transplacental passage of melatonin, the pineal hormone that is secreted nocturnally [18]. There is no obvious immediate adaptive value to different coat thicknesses in the meadow vole because the intrauterine and nest temperatures are similar at the time the phenotypic difference is first manifest. Moreover, the difference in coat thickness is clearly not a simple by-product of a poor uterine environment.

In humans, the thermal environment during a crucial period soon after birth determines the number of sweat glands activated by cholinergic innervation (the connection of sweat glands to the sympathetic nervous system by nerves using acetylcholine as the neurotransmitter) [19], even though the ability to sweat is less important in infants because they have a higher surface area to volume ratio than adults and thus lose heat more readily. The individual is then committed to that pattern of thermoregulation for life, entailing, for example, a greater risk of heat stroke if a cold-reared individual is translocated to the tropics [19]. In rats, maternal nursing behaviour affects stress-induced hormone secretion of the adult offspring and their associated behaviour [20]. In this example, not only is the cue (dam’s nursing behaviour for the phenotypic change) temporally separated from the effect (adult stress response), but the sensor and effector systems are also distinct. Recent work has shown that this phenomenon is underpinned by highly specific epigenetic modification of the DNA coding for a stress hormone receptor in the brain [21]. Each of these examples represents a situation in which irreversible plastic responses establish a trajectory of development in expectation of a future environment.

Many well-known examples of phenotypic plasticity are excluded from our definition of PARs because there is no delay in the advantage conferred. For example, two classic cases of predator-induced dimorphism — the acorn barnacle *Chthamalus anisopoma* [22], and the water flea *Daphnia* spp. [23] — are driven by the immediate benefit from the plastic response. In both cases, the presence of predators induces the development of an adult morphology that affords a better defence against the predator than the form produced in the predator’s absence. Of course, some delayed aspects of a response to an environmental cue need not be PARs. For instance, studies in the grey treefrog *Hyla versicolor* show that higher levels of intraspecific competition induced plastic changes in tadpole morphology that are of adaptive value in that they have deep tail fins and short bodies, and can swim faster and compete better for food. However, there is a survival disadvantage for these same animals after metamorphosis into frogs in that they have persistent shorter limbs and bodies and a higher juvenile mortality [24]. Similarly, a reduction in fetal growth induced by poor prenatal nutrition could confer an immediate survival advantage, and, in the sense that a smaller individual at birth might require less food, this phenotype is ‘thrifty’. But smaller individuals could be more likely to fall prey to predators and might have compromised reproductive ability, such that their phenotype might not confer future advantage. The essential distinction is therefore that the evolutionary advantages of PARs arise from the increased fitness that they confer in a future environment, rather than as a benefit that arises as an immediate consequence of the response. We point out that, from this perspective, some plastic responses of *Daphnia* to predators are PARs because the selective advantages accrue to the offspring of those exposed to the threat [25].

The cue that initiates a PAR can encompass only a small part of the phase of developmental plasticity (e.g. a response to acute maternal stress hormone change) or be prolonged (e.g. an altered nutritional state throughout pregnancy). Thus, a compensatory effect on development after the initial cue can also be viewed in the context of PARs. For example, the catch-up growth exhibited by children who have experienced a period of nutritional restriction often entails significant health costs in later life (e.g. increased susceptibility to heart disease) [26]. Catch-up growth is thus an immediately adaptive response with potentially detrimental consequences, but it is catch-up growth against the background of already impaired growth, which itself is a reflection of an earlier phenotypic change. Thus, we would contend that the effects of improved postnatal nutrition must be evaluated in the context of earlier phases of development, including the prenatal period. Viewing such compensation in the light of the PARs concept enables us to see that the cost arises from the mismatch of pre- and postnatal environments, rather than from the altered (catch-up) growth trajectory *per se*. This distinction has clinical importance, for example, in interpreting recent observations of the longer-term consequences of bottle-versus breast-feeding in preterm infants [27]. We would argue that considering intervention in postnatal growth (e.g. to restrict rapid weight gain) is potentially dangerous in the absence of understanding the degree of mismatch between the pre- and postnatal environments.

**Developmental responses**

When considering effects of the environment on development, it is important to distinguish between responses that might be adaptive later in life from those that (i) merely disrupt development in a pathological manner (e.g. those causing fetal malformation) leaving the organism to ‘cope’ with the consequences [28]; and (ii) involve immediate adaptation for fetal survival (e.g. fetal growth retardation) having an incidental advantage later. Some responses to environmental stress could be non-adaptive by-products, and it might be difficult to decide if a response is adaptive in particular cases [28]. In this article, we focus on examples in which the response seems clearly adaptive.

Traditionally, the adaptive responses of individual organisms to environmental stimuli are considered to be short-term and immediate, in contrast to population-level changes which, being driven by selection, occur over a long time period. Short-term responses can be transient, buffering the individual from current stresses (i.e. homeostasis), or they can be permanent, changing the developmental pathway along which the organism
proceeds (i.e. the immediate advantage of phenotypic plasticity) [29]. In both cases, such responses are usually seen as reacting to, and being appropriate for, the current environment.

We have suggested that some responses are not for immediate survival advantage, but for anticipated future advantage. The advantage of such responses is obvious in the event that the prediction is accurate, but there can be a real disadvantage if the prediction is incorrect. This inaccuracy can arise in several ways [12,13]. PARs are triggered particularly at the earliest stages of development, even in some cases by the pre-implantation environment [30]. The developing organism must make predictive decisions based on its current information about the future environment. In mammals, this information is transduced through the mother and placenta. In the absence of placental or maternal disease, there is likely to be reasonable fidelity in this transfer of environmental information. The presence of such disease, however, can greatly limit nutrient availability to the fetus, thus signalling the probability of a deprived postnatal environment. Dieting or consumption of an unbalanced diet could have similar effects. In addition, the maternal environment and the future environment of the progeny might be mismatched by environmental change, either in situ or as a result of dispersal. In humans, such incorrect predictions are revealed as an increased disease risk [7].

Inappropriate plastic responses are easy to demonstrate experimentally. For example, in both rodents and sheep, manipulation of the maternal nutrient balance or administration of exogenous glucocorticoid to mimic the maternal response to stress permanently affects the functional development of the offspring, often without any effect on birth weight [31–34]. Importantly, these effects depend upon the developmental timing of the environmental stimulus. For instance, maternal glucocorticoid exposure leads to changes in the control of blood pressure in the adult offspring in later life, but only if the exposure occurs during a crucial window in early development [35]. In sheep, unbalanced maternal nutrition during the early part of gestation, a time at which the nutritional requirements of the conceptus are small, nonetheless induces changes in metabolic and cardiovascular function in the adult offspring [36,37].

PARs thus involve two fundamental components of development, namely plasticity and crucial time periods, to generate delayed but permanent effects in the offspring. Many of the mechanisms underlying PARs are likely to involve environmentally induced changes in gene expression (i.e. epigenetic change) [7] that regulate homeostatic responses to the environment in the adult [38,39]. Moreover, PARs operate across all developmental environments including the normal range of conditions. Thus, in considering nutritional effects on size and growth, we emphasize that PARs do not operate solely in the context of extreme developmental phenotypes, but also within the normal range of fetal development.

In the discussion of the linkage between the long-term consequences of developmental plasticity, the term ‘programming’ has been used extensively in the literature (e.g. [4]). This term, which is derived by analogy with computer software from the concept of ‘genetic programming’ [40], is unfortunate because it implies a predetermined trajectory of development insulated from any subsequent epigenetic or environmental input. Rather we would suggest that outcome of the interaction of the organism with its environment at each stage in life is partially determined by its developmental history and that PARs are important determinants of these later interactions. Although many of the issues that we discuss also pertain to non-mammalian species, we restrict our subsequent discussion to mammals and especially humans.

A general model of PARs
The presence of many similar PARs in diverse groups of organisms suggests that the capacity to induce PARs is adaptive [8]. This assumption implies that there has been an advantage in retaining and refining PARs because fetal predictive responses have generally been appropriate for the postnatal environment, and this choice has conferred a selective advantage on the bearers. In our view, it is the ability to mount a PAR itself that constitutes an adaptation, not only the phenotypes that it induces. The adaptive nature of a particular PAR might be to shift the position of the reaction norm for a particular environment-organism interaction and thus to mitigate what would otherwise be a debilitating disadvantage arising from an extreme environment. The advantage depends on the fidelity of the predictive component and there are multiple ways this prediction can be erroneous; in such cases, the PAR is disadvantageous. In Box 1, we list several properties of PARs that enable the development of a conceptual model (Figure 1). The Figure shows the predicted and the actual postnatal range of environments as varying in energy/nutrients, but this depiction is merely by way of example; many environmental variables,

<table>
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<th>Box 1. The properties of PARs</th>
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<td><strong>PARs are induced by environmental factors acting in early life; they need not induce an immediate physiological adaptation, but act via developmental plasticity to modify the phenotype so that it is matched to the environment predicted to be experienced at a later phase in the life history.</strong></td>
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<td><strong>PARs lead to permanent change in the physiology or structure of the organism.</strong></td>
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<td><strong>There are multiple pathways to the induction of PARs involving different environmental cues acting at different times in development.</strong></td>
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<td><strong>PARs occur across the full range of developmental environments rather than being a response only to extreme environmental challenge.</strong></td>
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<td><strong>PARs do not show a threshold effect; the responses form a continuum.</strong></td>
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<td><strong>The induction of PARs confers a survival advantage in the predicted reproductive environment.</strong></td>
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<td><strong>A PAR implies an environmental range in which the organism can thrive until and through the reproductive phase of its postnatal life.</strong></td>
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<td><strong>PARs can lead to disease or disadvantage when the predicted reproductive or post-reproductive environmental boundaries are exceeded (i.e. with inappropriate prediction).</strong></td>
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<td><strong>A population-level consequence of the short-term survival engendered by PARs is that genotypic variation is preserved, facilitating neodarwinian adaptation to subsequent larger or longer-term environmental challenges.</strong></td>
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<td><strong>In some cases, there can be transmission of PARs through maternal effects to more than just the immediately following generation.</strong></td>
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offspring at a time. The original demonstration particularly in species that usually produce a single Thus, it is not surprising that a mechanism has evolved to survive if it outgrows the pelvic canal of its mother. fetal growth because the mammalian fetus will not placenta. Maternal factors must dominate in determining created by its mother and, once developed, by the environment of the fetus is sensitive. This difference is revealed, for example, in the Variation in postnatal growth has a major genetic influence fetal growth, collectively termed ‘maternal constraint’. Others include maternal age, parity and example is one of several non-pathological factors that maternal constraint, and thus are affected by factors such as temperature, water availability or stress level can be considered in the same way. The model illustrates that there is a range of postnatal environments within which the genotype can live without an increased risk of disease, but that this range is determined by the fetal prediction of that postnatal environment.

Maternal constraint, normal variation in fetal growth and PARs

Variation in postnatal growth has a major genetic component, whereas fetal growth is more environmentally sensitive. This difference is revealed, for example, in the far greater correlation between siblings in adult height than in birth size. The environment of the fetus is created by its mother and, once developed, by the placenta. Maternal factors must dominate in determining fetal growth because the mammalian fetus will not survive if it outgrows the pelvic canal of its mother. Thus, it is not surprising that a mechanism has evolved to limit fetal growth in relation to maternal body size, particularly in species that usually produce a single offspring at a time. The original demonstration that the size of the foal at birth when horses of different size were crossed was determined solely by the size of the mare has recently been extended, using embryo transfer techniques, to eliminate any genetic effects. This example is one of several non-pathological factors that influence fetal growth, collectively termed ‘maternal constraint’. Others include maternal age, parity and multiple pregnancy. If maternal pelvic shape is limiting to delivery of the fetus (as it became when hominids adopted bipedalism), maternal constraint becomes crucial for fetal (and species) survival. The main point is that maternal constraint operates to limit nutrient signals even if the mother is well-nourished, and thus limits the growth of the fetus and influences its metabolic development. This limitation has had the effect of directing the human fetus towards adaptive responses that are more appropriate for an uncertain or deprived postnatal environment. In Figure 1, greater maternal constraint will thus shift the position of an organism towards the left with a corresponding decrease in the upper limit of the healthy postnatal environmental range.

Human evolution, longevity and PARs

This asymmetry in setting metabolic physiology could have had additional adaptive advantage because the large monotocous mammals are long-lived and slow reproducers. There would have been advantage in such species in having a metabolic physiology biased towards defending against the periods of nutritional limitation that would probably have appeared in the long pre-reproductive and reproductive phases; there would be little disadvantage in possessing such physiology in an enriched environment because energy stores would merely be accumulated. A disadvantage has only appeared in modern humans with their marked increase in longevity.

Thus, we suggest that the induction of PARs by the degree of maternal constraint led to a human phenotype that includes a propensity to accumulate labile fat stores, reduced muscle mass, lower vascular density in some tissues and a compact body shape. This phenotype produces a degree of insulin resistance and other hormonal changes that make possible the preservation of nutrients for reproduction, even in an uncertain energy environment. Thus, PARs might have assisted our ancestors in surviving transient environmental change within and between generations, as well as in fully utilizing periods of environmental wealth. Moreover, because of the short life expectancy prevalent in our hunter-gatherer evolutionary history, the default or survival phenotypes induced by most PARs (along with other adaptations) will have favoured early reproductive success at the expense of resistance to disease in later life.

In recent decades, modern medicine, the ability to control environmental conditions and social structure have enabled many humans to live well beyond their peak reproductive period. Further, because of the changed postnatal nutritional environment and the anchoring effect of maternal constraint, mismatch between the actual and predicted postnatal environments has become common. Thus, PARs that evolved for advantage and which would historically have had no (or few) adverse consequences even if mismatch occurred can now, in modern energy-rich environments and with increased longevity, become manifest as disease in middle age and later. This environmental change has sown the seeds of chronic disease, such as cardiovascular disease and type 2 diabetes mellitus, which are epidemic in the developed world and increasing rapidly in importance in the developing world.

The fetal environment can improve only relatively slowly between generations because the mechanisms determining it are dominated by processes such as maternal constraint, and thus are affected by factors...
acting on the mother when she was a fetus and child. Pelvic diameter is tightly linked to height in human females and thus we suggest that the intrauterine environment will only shift slowly between generations, paralleling any shifts in maternal height. There have been relatively small shifts in height since Neolithic times [47]. This intergenerational interaction acts as a brake on the response of the fetus to external environmental change. By contrast, the postnatal environment can shift rapidly. We argue that it is this differential rate of change between the limitations imposed by maternal constraint (which set the fetal prediction) and the reality of the enriched modern postnatal environment that has created the current high incidence of cardiovascular and metabolic disease in humans.

The major evolutionary consequences of PARs are the fitness advantages that they confer on individuals (Figure 2). Nevertheless, because it is difficult to demonstrate fitness differences among individuals convincingly [48,49], many of the examples that we cite cannot be unequivocally shown to have adaptive consequences. We argue, however, that several recent studies indicate that the environmental conditions experienced by several species of birds and mammals during development, as well as numerous maternal effects, alter reproductive performance and hence fitness (reviewed in [50–52]). We would also argue that the explanation afforded by the PARs model is the most parsimonious for the examples quoted above of coat thickness of the meadow vole and behavioural phase in the desert locust, among others.

**PARs and disease**

If the developing fetus predicts its future reproductive environment incorrectly, either because of failure of appropriate transduction of the state of the environment from mother to fetus or because the environment changes from that predicted, it will have an increased risk of disease (Figure 1). Because the default prediction is of a poor postnatal environment, the more common scenario is that of the offspring living in a richer environment than that predicted, especially with respect to nutrition and energy expenditure. Moreover, the pattern of a high level of postnatal nutrition with a low level requirement of energy expenditure operating against a background of constrained fetal growth is increasingly common, particularly in societies undergoing very rapid economic and nutritional transition.

Such considerations have an important role in our understanding of the current epidemic of obesity and its consequences as metabolic and cardiovascular disease in developed countries, but they are also of great relevance to developing societies and to those in economic transition. For example, children born in India, where there is severe maternal constraint owing to the short maternal stature, have increased fat mass in relation to skeletal muscle mass even at birth [46]. Similarly, women exposed to famine in the Netherlands at the end of World War II gave birth to children who developed truncal obesity and insulin resistance as adults [53]. Animal experiments confirm the wider biological operation of such processes. Rats exposed to undernutrition in utero have reduced muscle mass, altered appetite, obesity, altered handling of hepatic glucose and insulin resistance in adult life [54–56]. The offspring of mice undernourished in utero, but then given a rich diet postnatally have reduced longevity [57]. Moreover, reduced lifespan is also seen in undernourished pups fed standard laboratory chow [57], making it clear that it is the mismatch between the predicted and actual postnatal environment that matters (Figure 1). Such examples show that the responses we see are not simply the result of a poor fetal environment: they occur because of a mismatch between the prenatal prediction of the environment and the postnatal environment experienced.

There is less evidence of the effects of the reverse mismatch (i.e. a prenatal prediction of a richer environment followed by postnatal experience of a poorer one), but there is a recent report [58] that large babies whose growth falters after birth have an increased risk of diabetes in adulthood. Further possible examples include the anecdotal evidence of larger individuals dying earlier in Nazi concentration camps [59] as well as larger children having an increased risk of rickets when faced with a vitamin-D deficiency [60].

Modern diets, which evolved following the industrial revolution and which continue to change rapidly, provide high caloric intakes and nutrient balances that are well removed from those to which our ancestors were exposed during evolution. Our species’ physiology has been set to operate on a lower plane of postnatal nutrition than that to which current children and adolescents are exposed. Disease in later life in these young people is of great concern. But the PARs model also offers the prospect of successful intervention in early development. Such an approach will require greater attention to the health and nutrition of women before and during pregnancy as well as to ensuring appropriate growth of infants and children. In addition, it will necessitate further research to define...
the extent to which improving early developmental experience can ameliorate disease risk in a nutritionally rich environment.

Conclusion and future directions
PARs are a form of phenotypic plasticity with delayed selective benefits seen in many species. We argue that they have been retained in humans because they conferred survival advantage in the poorer nutritional and high-energy expenditure environment of our ancestral hominids. PARs are induced by environmental cues in development, utilizing the normal processes of maternal constraint as part of the mechanism of providing environmental cues to the fetus. In our evolutionary past, it was advantageous to anticipate a poor future environment, and indeed PARs induce by default a phenotype appropriate for such conditions. Many human PARs, however, now appear to be increasingly inappropriate. This inappropriateness has arisen because of a mismatch in which the fetal environment is set by the processes of maternal constraint, which can change only slowly over generations, whereas the postnatal environment has been enhanced relatively rapidly (especially in terms of the nature and calorie density of food and the energy required to obtain it). Coupled with the increasing longevity in developed societies, diseases resulting from such inappropriate PARs will also increase. The future elucidation of epigenetic and other processes underlying PARs will thus have important consequences for human health and disease.

Acknowledgements
We thank Patrick Bateson for many discussions. Comments from the referees also led to a significant improvement in the article. M.A.H. is supported by the British Heart Foundation.

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