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A critical appraisal of the predictive adaptive response hypothesis

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The explosion of information emerging from new genetic technologies has not produced the consequences that were widely anticipated—a close fit between DNA sequence and phenotype. Rather, 'epigenetic' parameters of gene expression are increasingly considered central to phenotypic variability. This issue has particular importance for understanding the aetiology of human chronic degenerative diseases.[1–3] In epigenetics, the 'developmental origins of health and disease' (DOHaD) field has found a key mechanism for the growing epidemiological literature on associations between early-life experience and later health status.

The epigenetic revolution is transforming not only medical research but also evolutionary biology and the concept of adaptation.[4–7] In this context, the new book *Plasticity, Robustness, Development and Evolution* by Bateson and Gluckman[8] focuses on two generic components of phenotype during development, which they term robustness and plasticity. The evolutionary significance of both plasticity and robustness has previously been addressed in detail by others,[9–12] and there is increasing recognition of their complex interactions, issues discussed in some detail towards the end of this book. What is different about the approach of Bateson and Gluckman, however, is their particular emphasis on anticipatory prediction, a focus that has attracted attention from epidemiologists working in the DOHaD field. This review will therefore concentrate on this issue.

Arguably, the first evolutionary approach to human developmental plasticity and health was the classic

paper of Nick Hales and David Barker, proposing the 'thrifty phenotype' hypothesis.[13] At the time of its publication, chronic diseases were widely assumed to derive from an interaction between genotype and adult lifestyle. The prevailing evolutionary perspective was that some populations were more prone to develop diabetes and obesity in Western environments due to possessing 'thrifty genes', hypothesized to have been favoured by ancestral famines.[14] Hales and Barker suggested instead that poor nutrition within the life-course increased susceptibility to diabetes and other chronic diseases. The proposed mechanism was that small babies, exposed to energy insufficiency *in utero,* prioritized growth of vital organs such as the brain and heart at the expense of other tissues, such as muscle and the endocrine pancreas. In evolutionary terms, such growth plasticity was suggested to be adaptive in enabling survival during early-life adversity. In modern environments, however, this plasticity would come at the cost of an enhanced predisposition to diabetes and other chronic diseases, due to decreased physiological capacity to tolerate increased adiposity and rich diet in later life.

Bateson and Gluckman have promoted a very different model of adaptive developmental plasticity, re-emphasized in their new book. In contrast to the thrifty phenotype hypothesis, to which they do not refer in their book, they argue that there are long-term advantages to the reorganization of growth deriving from fetal energy insufficiency. Their 'predictive adaptive response' (PAR) hypothesis was built around the metaphor of the 'weather forecast',[15] whereby developing organisms are assumed to receive information about the quality of the external environment, and in response, formulate predictions as to future ecological conditions. At the heart of the PAR hypothesis is the notion that organisms prepare themselves adaptively for their breeding or 'mature' environment.[16–18]

In relation to humans, the PAR hypothesis was specifically proposed to account for the developmental origins of the metabolic syndrome,[17,19,20] a cluster of phenotypic traits fundamental to chronic diseases. Among the supposed PARs characterizing low birthweight individuals are insulin resistance, a predisposition for central fat, reduced muscle mass and reduced nephron number, all proposed as adaptive for environments of long-term energy insufficiency.[16] According to the hypothesis, these traits should confer not only survival but also greater reproductive success,[16] otherwise they would not have been favoured by selection. The connection between PARs and human health is simple: if the 'prediction of the future' proves correct, the organism will be healthy; if the prediction proves incorrect or 'mismatched', then ill health is likely to develop.[17]

In the DOHaD community, the PAR hypothesis has been actively promoted by these authors in dozens of review papers on chronic disease risk, though not without criticism.[21–23] Even though evolutionary medicine remains in its infancy, the PAR hypothesis is already taught in some undergraduate medical courses. Given its prominence in medical research and teaching, the publication of this book presents a timely opportunity to consider the utility of the PAR hypothesis for understanding variability in chronic disease risk.

For PARs to be viable in humans, anticipatory predictions generated during a very brief period of development must hold successfully for several decades. Yet there is little evidence that environments occupied by present and past human populations were stable over such time periods.[24] Mathematical simulations based on stochastic data refute the notion that 'snapshot' or cumulative past indices can predict subsequent variability,[23] and this is supported by a study of data on rainfall (a proxy for ecological productivity and hence food supply) from India, where mean annual rainfall was found to have no systematic correlation with rainfall in the following year, or over the following 10 or 40 years.[25] Furthermore, mortality in human foraging populations, as in most apes, is greatest during the first few years of life.[26] Many of the traits that have proven strongly predictive of adult chronic disease risk (early growth rate and nutritional status) are strongly associated with survival in early life, making it difficult to see how such traits could be selected by adult stresses. Thus, on the grounds of both ecological instability and the importance of early survival, it is difficult to see how long-term accurate predictions of the future are viable in our species.

One generic criticism of the PAR hypothesis is that its proponents have been looking in the wrong direction:[23] rather than plasticity enabling cues deriving from the present to predict the future, a more robust model is of the past, as encapsulated in maternal phenotype, maintaining its influence during the window of offspring plasticity.[27,28] My own perspective on plasticity and adaptation is thus based on the fact that any signals conveyed to the fetus through the medium of nutrition do not derive directly from the external environment, but rather from maternal phenotype.[27] According to this approach, maternal phenotype is the primary component of the environment to which early adaptation is made.[28] Our two models, illustrated in Figure 1, may be compared in relation to their ability to explain human epidemiological data.

Building on the work of Kaplan *et al.*,[29] who proposed the term 'embodied capital' to summarize components of phenotype beneficial for reproduction, I suggested that offspring are exposed in early life to the 'magnitude of maternal capital'.[27,28] In any given environment and population, mothers may vary substantially in their capital. An example is social status that generates substantial phenotypic variability among female primates.[28] During development,

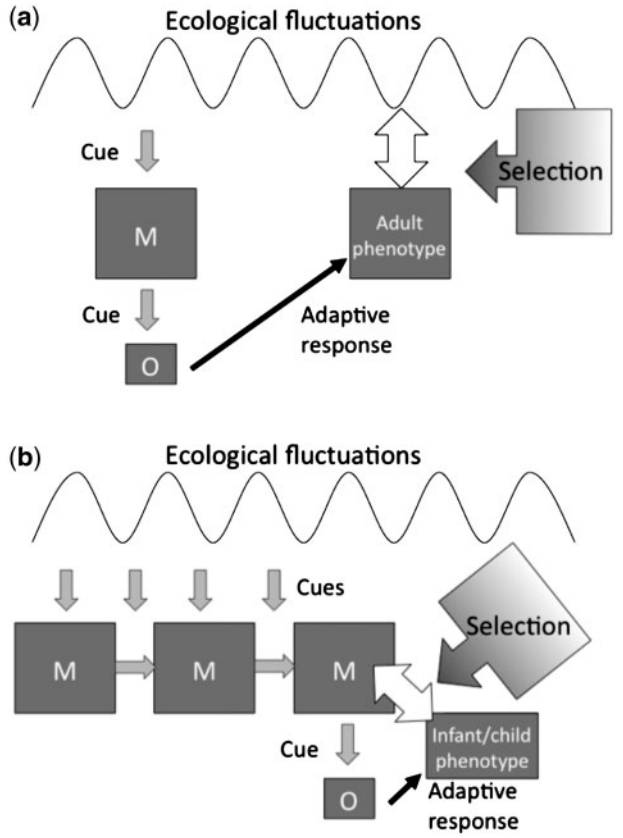

Figure 1 (a) In the PAR hypothesis, information on ecological conditions is assumed to pass from the environment through the mother (M) to the offspring (O), which responds adaptively by predicting the future environment in which breeding will occur. Selection acts in adulthood, on the fit of the organism with its breeding environment. (b) In the maternal capital hypothesis, the mother buffers the fetus substantially from current ecological conditions, and information passing to the fetus is therefore assumed to derive primarily from ecological exposures across maternal or grand-maternal development. The adaptive response of the offspring is to maternal phenotype, not future ecological conditions. Selection acts in early life, on the fit between offspring nutritional demand and maternal capacity to supply[71]

therefore, each offspring picks up the influence of such maternal capital variability, resulting in different developmental trajectories within and between mothers. I do not consider that offspring from a common population can predict different long-term futures; rather, I assume that they receive different amounts of maternal investment, and that this reflects long-term exposure to numerous and cumulative environmental factors acting on the mother and her recent ancestors.[28]

The maternal capital model was developed in particular to address associations between social inequality and health inequality.[28] However, the model also addresses other fundamental components of maternal phenotypic variability, such as nutritional status before and during pregnancy, infectious disease exposure, physical environmental conditions (heat stress and altitude) and reproductive schedule.[30] Any successful evolutionary model of developmental plasticity must be able to address all sources of fetal environmental variability.

For example, first-borns are typically smaller at birth than later-born offspring.[31,32] They may remain smaller throughout their life,[33] and hence have reduced height, tissue mass and blood pressure in adulthood, all traits with functional significance. If catch-up growth occurs, however, first-borns can achieve an overshoot in height and end up taller as adults, with increased adiposity, blood pressure and resting metabolic rate.[34–37] There is abundant evidence across many species that birth or hatching order may affect both sex ratio and phenotype.[36,38–40] Should first- and later-born offspring predict different future environments? This seems a very surprising suggestion. A more parsimonious approach is that mothers alter their investment strategy across their reproductive career for their own benefit, and that offspring must respond as best as they can to such differential investment.

My approach assumes that mother and offspring are engaged in a dynamic relationship, with each adapting to the other.[27] The existence of tension between the two parties is given theoretical support by the notion of 'parent-offspring conflict', first articulated in a classic paper by Trivers.[41] Trivers argued that because they only share 50% of their genetic material, parents and offspring are inherently subject to a conflict of interest regarding the optimal level of maternal investment in the offspring. Given finite resources, parents must inevitably restrict investment in any one offspring in order to allocate it more equally across several offspring.[41] Data on human birthweight and height provide support for this assumption.[42] For example, incorporating time-varying measures of changing family structure and socioeconomic environment, an analysis of the ALSPAC cohort showed that an increasing number of siblings was associated with decreasing stature. Compared with only children, those with four siblings were 0.9 cm shorter at birth, grew more slowly during early life and were 3.1 cm shorter by 10 years.[43]

Bateson and Gluckman suggest that the notion of conflict is overstated, and that both parties achieve a compromise (p. 74). Here, our models are seemingly in agreement, as I have written extensively about each party adjusting its strategy in response to the other's,[44,45] with neither party 'winning' but each gaining.[27] Yet, there is undoubtedly tension between mother and offspring, as reviewed for both prenatal and postnatal interactions,[44,45] and demonstrated in the growth study described above. It is specifically this tension that 'enables' adaptation,[46] and the key difference between my model and the PAR model is that we differ in defining what it is that the offspring

adapts to: for the PAR hypothesis, it is cues of the future environment, whereas I emphasize maternal phenotype, because the mother is the dominant influence on the offspring's nutritional supply during the primary window of plasticity.[28] In my approach, the mother signals what size of offspring she can support. The offspring adapts to this signal, because failing to do so would risk overloading the maternal capacity to supply energy and other nutrients during the window of maternal care.

One reason why the offspring cannot predict future conditions is because it is engaged in a dynamic process 'throughout' the period of plasticity. The offspring does not submit meekly to maternal strategy; if nutritional constraints are relaxed, it will catch-up in size. In the avon longitudinal study of parents and children (ALSPAC) cohort, for example, smaller babies including those of shorter mothers demonstrated catch-up growth in infancy,[47,48] taking advantage of reduced nutritional constraint after birth. During such changes in growth trajectory, the long-term 'future' has not changed, rather the offspring has increased its ability to obtain maternal investment. In chronically undernourished populations where breastfeeding is the norm, faster infant growth (representing more maternal investment) has been shown to confer multiple benefits to adult health and human capital.[49]

We may expect developmental plasticity to be particularly important in our species, because humans have a lengthy history of colonizing new environments, first in the exodus of *Homo erectus* from Africa around 2 million years ago, and more recently in the exodus of our own species within the last 100 thousand years.[26] Bateson and Gluckman suggest that predicting the future would be especially valuable for migrating organisms, yet such anticipation can only become harder when the habitat is changing across generations. My approach assumes that maternal effects act to 'dampen' the rate at which offspring phenotype is exposed to novel niches.[26,50] Whether ecological conditions improve or deteriorate, maternal buffering protects offspring from sharp perturbations during the most sensitive periods of development. Under the restraining influence of maternal phenotype, a shift in ecological conditions will only change phenotype of a lineage substantially if it acts across several generations in succession. This causes a slow but steady phenotypic change across generations, often termed a secular trend, whilst avoiding excessive change within a single generation (Figure 2). Such multi-generational change has been observed in primates exposed to changes in both energy availability[51] and climatic conditions.[52] This 'slow-response' damping is entirely in opposition to

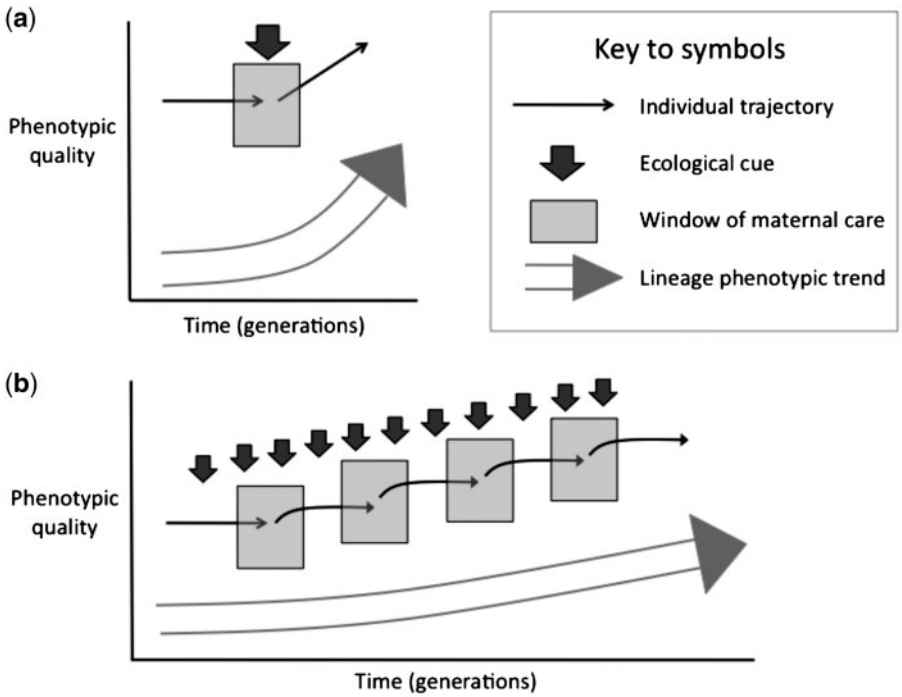

Figure 2 (a) In the PAR hypothesis, cues received by the offspring may provide a forecast of very different ecological conditions (e.g. famine) compared with those experienced by the mother in her own development, generating a major phenotypic shift between generations. (b) In the maternal capital hypothesis, phenotypic change is dampened by maternal buffering, and phenotype only changes substantially if ecological cues are maintained across multiple generations, gradually releasing matrilineal influence

the emphasis on anticipation of future conditions proposed by the PAR model.

An important point is that DOHaD experimental studies rarely detect such graded phenotypic trends, because protocols typically generate sudden and sharp shifts in nutrition between successive time periods, in order to show the effects clearly. In animal studies, this is often achieved by cross-fostering at birth,[53] whereas in humans an alternative is randomization to formula milks of differing nutritional content.[54] Under natural conditions, maternal phenotype functions to buffer exactly these kinds of nutritional perturbation across successive developmental periods, thereby damping the speed of response.[27]

Bateson and Gluckman argue that the 'acid test' of their PAR hypothesis is 'whether the small baby will be better suited to the poor environment predicted by the mother's low nutritional level than a big baby' (p. 74). However, the evidence that they cite to support their theory of long-term anticipation is that large babies develop rickets more often in famines than small babies;[56] and that small babies also develop a milder form of malnutrition (marasmus) than large babies, who are more likely to develop kwashiorkor.[57] These are not adult adaptations, they occur within the window of maternal care. My own interpretation of these data is that large babies more readily exceed their mothers' capacity to supply them with energy if exposed to nutritional scarcity in early childhood. Interestingly, the word kwashiorkor comes from the Ga language of coastal Ghana, and means 'the sickness the baby gets when the new baby comes'. Other studies have shown rickets to be more likely in infants with greater number of siblings,[58] indicating competition for maternal capital as predicted by Trivers' theory. Overall, offspring are predicted to have better health when they are allocated more resources, as demonstrated in many studies.[49,59]

A surprising omission from the bibliography of Bateson and Gluckman was a pair of animal studies, each of which could be described as addressing their 'acid test'. These cross-over studies, exposing individuals undernourished in early life to good quality adult environments, and *vice versa*, suggest that exposure to adversity in early life does not increase fitness in tough adult environments. Rather, those malnourished in early life do worst in all adult environments, but particularly so in tough conditions.[60,61] Contradictory evidence is also available in the reverse direction. In the 1930s, classic studies of rodents showed that caloric restriction increased longevity.[62,63] Recent studies confirmed that slower postnatal growth following adequate fetal growth likewise increased longevity.[64] Contrary to the PAR theory, this mismatch is 'beneficial' for health.

Let us look very carefully at one trait that is treated very differently by the PAR and maternal capital models—insulin resistance. This is a particularly valuable example, because insulin resistance is strongly implicated in many adult chronic diseases, not only metabolic (type 2 diabetes) and cardiovascular (stroke, hypertension and ischaemic heart disease) conditions,[65] but also some cancers.[66]

According to the PAR model, insulin resistance develops adaptively following fetal undernutrition, in anticipation of an adult environment of energy scarcity.[18–20] In fact, small babies are insulin-sensitive at birth, and only develop insulin resistance in early childhood,[67] in association with central adiposity and excess weight gain.[68] Bateson and Gluckman argue that through such insulin resistance, the individual captures the higher-energy fat-dense foods when available (p. 73), which helps them to prepare for a breeding environment of energy scarcity. They do not, however, offer any evidence that insulin resistant individuals have greater reproductive success in energy-scarce environments.

The maternal capital model assumes that the reduced muscle mass of low birthweight offspring makes them more 'affordable' for the mother, which in turn aids offspring survival. However, although this low muscle mass tracks onwards into adult life,[69] it is not assumed to be adaptive for reproduction, and the development of offspring insulin resistance is assumed to be protective against mitochondrial DNA damage under conditions of inflammation, stress and overnutrition.[30] Recent *in vitro* studies have shown that each of these stresses induces mitochondrial superoxide production, prior to the development of insulin resistance, and that pharmacological suppression of this superoxide restores insulin sensitivity.[70] These findings were supported by *in vivo* studies in transgenic mice.[70] According to the maternal capital hypothesis, therefore, early-onset insulin resistance is a penalty arising when maternal influence on the offspring's development is overridden. Studies of human populations inhabiting tough environments find no association between fetal growth and later insulin resistance,[71] presumably because those consuming a healthy diet and remaining physically active do not subject their muscle tissue to such nutrient excess.

In the final part of their book, Bateson and Gluckman discuss a variety of published studies on epigenetic variability. There is no doubt that forthcoming research will reveal much about the molecular basis of plasticity and adaptation, yet as an explanatory framework for human work in this area, the PAR hypothesis seems unsatisfactory. A major problem with the PAR hypothesis has been the lack of attempt at potential falsification. As discussed above, a variety of strands of evidence conflict with the fundamental PAR premise that human developmental plasticity is targeted at adult breeding conditions. Instead, much evidence, including some of the studies cited by Bateson and Gluckman,[56,57] supports the notion that human developmental plasticity is targeted at early development, which is the primary prediction of the

thrifty phenotype and maternal capital hypotheses. These contrasts are not trivial, rather the development of robust evolutionary models is critical for maximizing the potential benefits of the epigenetic revolution in efforts to improve public health.

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