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Why evolution needs development, and medicine needs evolution

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For much of the past century, adaptive evolution has been defined as the differential replication of genes that influence the survival or reproduction of their host. Although Darwin is perhaps best remembered today for having co-discovered this principle of natural selection, its evolutionary importance was not widely accepted until several decades after his death. This is in part because Darwin lacked an understanding of the material basis of heredity. His speculations about the mechanism of inheritance, reflected in his Lamarckian model of *pangenesis*, had fatal flaws. Notably, Darwin envisioned maternal and paternal hereditary contributions to offspring as blending together at conception; his critics noted that this would inevitably lead to the dilution of any novelties, and thus could not explain the gradual rise of complex adaptations via the accumulation of small changes as Darwin's model required. This left a major problem unsolved.

Working with his famous peas, Mendel showed that crossing a pea plant possessing yellow seeds with another having green seeds did not produce offspring with yellowish-green seeds; rather, the offspring were either yellow or green. Nor was it the case that two pea plants, one having smooth and one having wrinkled peas, would yield offspring with slightly wrinkled peas, as would be expected if the characteristics of parents were blended at conception. Instead, inheritance, at least for these traits, appeared to be all or nothing, implying that the mode of inheritance was particulate in nature (Figure 1). Mendel's work thus showed a means by which novel traits could be passed on to offspring with high fidelity, and helped pave the way for widespread acceptance of the Darwinian idea of natural selection.

Without knowledge of the molecular basis for genetic transmission, it was inevitable that the first examples of inheritance to be worked out would be simple traits like pea colour. Although this simplicity helped early geneticists infer that inheritance had particulate rather than blending qualities, and thus advanced the field of evolutionary biology

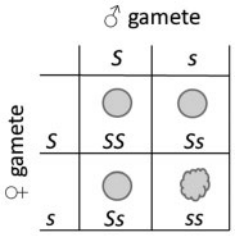

Figure 1 Traits that follow a Mendelian pattern of inheritance, in this case smooth and wrinkled peas, are determined predictably by genotype; environmental input and developmental plasticity are not important. Although such traits are rare, they were among the first clear examples of heredity to be worked out using the simple technologies available to 19th- and early 20th-century researchers. This is one among many reasons that developmental biology was largely ignored within the foundations of modern genetics and evolutionary biology

tremendously, it also fostered the illusion that evolutionary biology could focus solely on the transmission of hereditary material without considering the role of developmental biology in the construction of phenotypes.[1]

The limitations of this assumption are now clear, and the importance of developmental biology in shaping individuals and as an influence on evolution are hot topics in evolutionary biology.[1–4] With rare exceptions, most phenotypic traits develop not as a simple expression of genotype but contingent upon interactions with other biological systems within the organism, and also with its surrounding environment. Consider, for example, how weight bearing and functional loading influence bone development, or how many aspects of physiology and metabolism develop in response to hormones and nutrients *in utero*. It is now increasingly clear that evolutionary biology desperately needs developmental biology if it hopes to explain the expression of most phenotypes that natural selection acts upon and shapes across generations.

In 'Plasticity, Robustness, Development and Evolution', Patrick Bateson and Peter Gluckman, two highly distinguished biologists, provide a compact and nicely written introduction to some of the issues that lie at the heart of the emerging synthesis of developmental and evolutionary biology. For students of this literature, this is a handy review and synthesis of this field and many of the current debates, with some new gems to mull. Bateson and Gluckman work particularly hard to break down traditional but artificial dichotomies such as nature vs nurture, or plasticity vs robustness, showing that they are often best viewed as flip sides of the same coin. For those new to this field, the book is an excellent entry point into this literature. The chapter that defines terms and concepts is among the best and most elegantly written of the book, and was a joy to read. Copious well-written and up-to-date details of epigenetic mechanisms of inheritance are described, and their importance for individual development and evolution are explored.

In addition to providing this informative review, the book culminates by making an especially timely point, and one that is at the centre of many current debates within the field of evolutionary biology: that developmental adaptation, including the contribution of epigenetic mechanisms, is an important influence on genetic adaptation. For the first part of my review I will focus on this prominent theme as developed by the authors. In the second section, I will explore several ways in which the principles discussed by Bateson and Gluckman help bring new insights to pressing issues in molecular biology, medicine and public health. Finally, I conclude by arguing that biomedicine will benefit further by incorporating into its conceptual and methodological arsenal the comparative approach that is a starting point for many evolutionary analyses.

Why evolutionary biology needs development

One important focal point for current debates within evolutionary biology, and an important theme of this book, has to do with the mechanisms of phenotypic and developmental plasticity and their evolutionary implications. Plasticity refers to the abilities of an organism to modify its structure and function in response to environmental inputs, which can take many forms. One example is accommodation, in which traits modify their structure and regulatory set points under functional loading, such as the stresses and strains that influence the robustness and trabecular configuration of developing bones, or the role of pathogen exposure as an influence on the repertoire of antibodies acquired during infancy. Developmental changes may also be triggered by cues such as hormones or nutrients experienced early in life, beginning *in utero*. Many of these responses are increasingly being traced to underlying epigenetic changes that lead to modified patterns of gene expression in cells and tissues. Recent work has emphasized the ability of plasticity to lead to at times radical changes in the structure and function of an organism within a single lifetime when activity patterns or stressors change abruptly.[4] In this sense, work on plasticity illustrates that many genes do not code for single outcomes, but rather for flexible ranges of phenotypic possibility that depend upon the organism's experiences during development.

What are the implications for genetic evolution of this plasticity in how traits develop, and the organism's ability to generate novel adaptive phenotypes spontaneously within its own lifetime? Traditionally, it was often assumed that plasticity decoupled the specifics of phenotypes from underlying genetic variants, and thereby relaxed selection and slowed the pace of adaptive genetic evolution. A separate intellectual thread is currently re-gaining the spotlight, and is reviewed at some length by Bateson and Gluckman. Here the idea is that plasticity and behaviour might serve as an 'adaptability driver', to use the authors' term, leading the way for organismal adaptation to novel conditions, and thereby allowing the gradual consolidation of genetic changes that allow the new phenotype to be generated with greater efficiency or lower cost. The key idea here is that developmental adaptation precedes genetic adaptation, which only follows more gradually after the fact.[4] Bateson and Gluckman review several possible scenarios by which this might occur.

One idea reviewed and lent empirical support in the book is that the tendency of plasticity to decouple genotypes from phenotypes allows novel mutations

to arise that are not expressed phenotypically; because these 'silent' genes are selectively neutral, they can accumulate in the gene pool. When individuals later experience different environments, perhaps as a result of a novel source of stress or movement into a different niche, developmental pathways could be perturbed sufficiently to allow this cryptic genetic variation to be expressed phenotypically. According to this model of genetic 'capacitance', plasticity could allow the gene pool to amass a larger set of variants for natural selection to sift through when individuals are faced with environmental change. Although this could facilitate genetic adaptation as Bateson and Gluckman review, it is also important to note that the functional change in the phenotype induced by the shock is assumed to be random with respect to any changes in functional demands that the shock represents. Thus, only by chance could this reservoir of genetic variants improve the adaptive fit of a population faced with a challenging or novel environment.

There are other, less random ways by which plasticity might facilitate and speed up genetic adaptation. One relates to how populations move across fitness landscapes. The fitness landscape is a graphical representation of the adaptive fit between a population and its environment. There are peaks representing local adaptive optima, which are separated by less adaptive valleys. Because organisms that bear genes that improve survival or reproduction tend to leave more offspring, the frequency of these more-fit genes increases, and the gene pool is nudged up the slope of the local adaptive peak. Plasticity might speed up this process of genetic adaptation. If the phenotypic change generated by plasticity is an improvement in fitness, but fails to attain the fitness optimum of the peak itself, subsequent genetic adaptations could be selected to improve upon the efficiency with which that phenotype is generated.[5] In this way, plasticity might lead the way up the slope, and accelerate the pace of genetic adaptation.

Others have speculated that this phenomenon might help explain the observation of rapid genetic evolution documented in some species.[5] As one example, when the Laurentide Ice Sheet retreated from its maximum extent across northern North America at the end of the last ice age about 10 000 years ago, new lakes were formed across northern Canada. Today, there are related but distinct fish species inhabiting different lakes and regions, pointing to relatively rapid evolution and speciation.[6] There is evidence that the traits that evolved the fastest among these species were in fact those that were most plastic. Similarly, when the Mosquitofish was introduced into regions of Hawaii in the early 20th century, the traits that evolved most rapidly were those exhibiting the greatest degree of plasticity, suggesting that plasticity might under some circumstances accelerate genetic adaptation.[7]

Bateson and Gluckman provide a thorough review of evidence for more direct bridges between epigenetic malleability and the rate of mutation, and thus the potential for genetic evolution, at a particular genetic locus. There is evidence that genes that are highly methylated may be more prone to copy errors, thus enhancing the pace of mutation at these loci. This implies that the occurrence of mutations may not in fact be fully random.[3] In this way, the capacity for environment-driven epigenetic adaptation and for genetic adaptation might be linked, contrary to traditional assumptions in evolutionary biology. If novel mutations are most likely to appear in those chromosomal regions with the greatest environmentally driven epigenetic sensitivity, this has potentially important implications for genetic adaptation. As the authors note in their culminating model, environmentally induced epigenetic adaptations could be gradually replaced by more durable genetic adaptations. This suggests one intriguing way in which epigenetic and developmental adaptability could 'lead the way' in adaptive evolution, with genetic adaptation bringing up the rear.[4]

Why medicine and public health need developmental biology

Evolutionary biology is by no means the only biological subfield currently grappling with the complexities of phenotypic development. One strength of this volume is that the authors represent two different disciplines—evolutionary biology and medicine—and thus bring the insights from their respective fields to bear upon the themes discussed in this book. In fact, Bateson and Gluckman are both prominent scholars and contributors to the literature focusing on the developmental origins of health and disease (DOHaD), which is demonstrating the importance of epigenetic change and developmental plasticity as influences on adult chronic disease development. Because medicine and evolutionary biology are both tackling the problem of phenotypic development, the synthesis of developmental and evolutionary principles discussed by Bateson and Gluckman have immense implications for medicine and public health.

For one, developmental plasticity, which allows individuals to modify and fine-tune their biological structure in response to local environmental conditions, helps clarify the limited success of attempts to decipher the genetic architecture of many common chronic diseases, as exemplified by genome-wide association studies (GWASs). GWASs assume that many genes with small individual effects contribute additively to trait variance, and use bioinformatics techniques to identify relationships between disease outcomes and hundreds of thousands or even millions of single nucleotide polymorphisms (SNPs) typically measured in tens of thousands of individuals. During

GWAS analyses of most complex phenotypes, few common variants have been identified that have large effects, and typically only a small fraction of trait variance is explained by all of the identified loci combined. Given the complexity of phenotypic development, it seems unremarkable that most genes have relationships that are more complex than implied by the assumption of additive inheritance.

Our emerging understanding of environment-driven developmental plasticity shows why even concepts such as gene-by-environment ($G \times E$) interaction, if we had the sample sizes necessary to test for them more routinely, still fall well short of capturing the true complexity underlying relationships between genotypes and many phenotypes. After all, which environment experienced by an individual is implied by the 'E' in $G \times E$? The same environmental stimulus can have very different phenotypic effects depending upon the age at which it is experienced. Most obviously, early life critical periods can permanently modify the regulatory or functional properties of a trait or system. Importantly, this can then alter the ways in which that system responds to the same stimulus at later ages. Environments do not simply interact with genes, but with phenotypes, which are themselves the products of genetic and phenotypic interactions with prior environments. Thus, we might imagine the genetic contribution to the adult phenotype as having a nested and recursive quality that evades simple mathematical specification. At time T_1, the phenotype is a product of $G \times \mathbf{E_1}$. At T_2, it is a product of the existing phenotype $(G \times E_1) \times \mathbf{E_2}$. At T_3, it is a product of the existing phenotype $((G \times E_1) \times E_2) \times \mathbf{E_3}$ and so on.

Furthermore, the growing list of phenotypes that are passed on transgenerationally via phenotypic and epigenetic inheritance add yet another layer of complexity to this puzzle by revealing that environments preceding conception, experienced by mothers, fathers and even grandparents throughout their own lives, are often important determinants of offspring development. This can involve direct germline inheritance, in which environmentally induced epigenetic markings (e.g. microRNA or DNA methylation) are passed to offspring via sperm or egg, or when phenotypic qualities in parents may directly influence how the same or related phenotypes develop in offspring.

As one well-documented example of the latter, a fetus born to an obese mother who is diabetic during pregnancy is exposed to high levels of glucose and insulin, and is born large and prone to developing diabetes and obesity later in life. Among female offspring, this increases the chances that the grand offspring will experience a similarly over-nourished gestational environment, perpetuating the phenotype into the future. Siblings born to mothers after they have lost weight by gastric bypass surgery have much lower risks of disease development than their siblings born before their mother's weight loss, showing that these effects are not primarily due to shared genes, but are phenotypic and epigenetic in origin.[8] One lesson is that not only genotypes—but also phenotypes—are products of historical lineages. Another lesson is that there is not one but many environments that are relevant for understanding any given phenotype. Past environments interact with genotype to influence current function and health, both through the fact that an individual's early life experiences modify their biology in a durable fashion, and also via the epigenetic and phenotypic pathways that link paternal and especially maternal experience with offspring phenotypes.

Of course, there are examples of common chronic disease risk factors that have relatively straightforward underlying genetic architecture. For instance, the relative simplicity of the metabolic pathways regulating cholesterol production allow for the clinical success of statin drugs in lowering low-density lipoprotein (LDL) cholesterol levels. These drugs block the gene product of a single gene (*HMGCR)* that encodes for the enzyme *HMG-coA reductase*, which is rate limiting for endogenous cholesterol synthesis. They can lead to large reductions in total and LDL cholesterol. It should come as no surprise that the *HMGCR* gene was among the strongest genetic signals identified in a recent GWAS meta-analysis that explained between 15 and 25% of the heritability in lipid profiles in a large multi-national sample.[9] In contrast, there is no drug for obesity, nor is there likely to be one for the foreseeable future, because there are no comparably simple pathways governing the gain and maintenance of excess body fat in most people. Research investigating the developmental and epigenetic contributions to obesity reveals the importance of past environments in determining disease risk, starting with the experiences of ancestors and maintained and even amplified via phenotypic and epigenetic mechanisms throughout lifecycles and across generations.

Techniques such as GWASs will continue to nudge us closer to understanding the biological pathways that are involved even in complex traits of this sort. However, the lesson of this work is that the genes and pathways involved are many and that each has an often miniscule effect on the phenotype. It seems clear that GWASs will not be a rapid path to new interventions aimed at alleviating most complex diseases. For it is not the nucleotide sequences, but the phenotype, governed by its environmentally contingent process of development, that relates predictably to environments, and thus is potentially amenable to our interventions. As the authors point out here, and at length elsewhere,[10,11] the rapid pace of DOHaD research, with its emphasis on early life critical periods and environmental contingency, is illustrating why simple gene–disease risk association studies are destined to yield modest insights into many common chronic health conditions.

Why medicine needs the evolutionary and comparative approach

Although DOHaD research shows the power of embracing developmental biology as a causal influence on health, this field has yet to fully incorporate some core principles that are common in evolutionary biology. To be sure, there is enthusiasm for the potential of an evolutionary approach to bring order to this field, as illustrated by publications hypothesizing the possible function of fetal plasticity.[10–12] Many of these ideas are reviewed by Bateson and Gluckman in this volume. Despite this interest, empirical DOHaD work has thus far remained firmly rooted in the medical tradition. Although the authors require no introduction to the distinction between medical and evolutionary research, it is worth reviewing some of the key differences here for the benefit of those who may be less familiar with these fields and their differences. Evolutionary biology and medicine approach biological problems with distinct goals, and with the aid of different method and theory. Medical research typically begins with a disease state and then works backwards to identify the molecular and cellular changes that contribute to pathology. The use of animal model experiments is a primary tool for probing pathways and establishing their causal importance. For animal model research, species that are easy to breed and maintain in captivity, and that have conveniently short generation times (e.g. mice and rats), are used to infer mechanisms present in mammals generally, and by extension, in humans. This approach is justified by the fact that all mammals share the same basic physiological and developmental architecture.

In contrast, within evolutionary biology, the variation in traits across species is of primary interest, and is used to gain insights into the function and evolutionary origins of a trait. For many traits, the phenotypes of interest in the published literature might be available for hundreds of species measured in the wild, spanning small to large species, allowing the identification of important patterns that speak to underlying laws or causal forces. Whereas a biomedical focus on mammalian similarities allows us to infer that maternal–fetal programming of human biology is plausible based upon findings in rodents, an evolutionary comparative approach leads us to predict that such effects will vary across species as distinct as human, mouse or rat. As we have recently argued elsewhere,[13] distinct features of the human life history likely help explain why prenatal exposure to the Dutch Famine Winter during the Second World War resulted in relatively minor changes in birthweight and adult cardiovascular disease risk factors. Figure 2 plots the percentage change in birthweight and several adult cardiovascular disease (CVD) risk factors measured in individuals exposed to the Dutch Famine *in utero;* here the human population is compared with mice, rats, guinea pigs and sheep born to mothers exposed to a similar magnitude of nutritional restriction during pregnancy. The figure shows clearly that the larger and longer-lived species tend to exhibit attenuated responses compared with smaller and shorter-lived species, with the human cohort showing the smallest phenotypic responses of all.

Although these data are clearly sparse, this simple analysis begs important questions. Might the greater impact on offspring in smaller species point to the importance of simple allometric scaling laws in generating these outcomes, as a competing hypothesis to maternal–fetal signalling and adaptation? As one possibility, differences in effect size across species might be epiphenomena of how metabolic and reproductive expenditures scale to body size.[13] In a species, such as a mouse, that devotes a large fraction of its metabolism to reproduction, restricting maternal intake might have proportionately large negative impacts on offspring. In contrast, the human mother, with her smaller fractional metabolic allocation to reproduction, is likely better able to buffer the metabolic demands of the fetus from nutritional perturbation.

Alternatively, these findings might speak to differences in the strategies of anticipatory adaptation across species varying in lifespan. Although conditions during the season of birth are informative about conditions across much of a rodent's short life, perhaps we should expect human biology to adjust developmental trajectory in response to more stable and reliable longer-term cues that integrate information over the lifecycle or perhaps several generations. In other words, an adaptively relevant cue for a mouse, which will live for months, may be little more than short term, transient 'noise' to be buffered and ignored by the long-lived human, who will live for decades.[12].

Regardless of what accounts for these species differences, they have important practical implications. If human fetuses are more buffered against transient maternal stress during pregnancy than is true for commonly studied animal model species, it likely follows that the negative effects of maternal stressors on offspring will be reduced in humans compared with these species. By the same token, short-term *improvements*, as reflected in the typical design of many interventions, may similarly reap comparably modest long-term benefits. Might this help explain why human pregnancy supplementation trials, which aim to improve birth outcomes, are notoriously so limited in efficacy?[14] And what does this imply for effective strategies to improve the conditions of the gestational environment sufficient to modify fetal biology and reduce long-term chronic disease risk?

Clearly, there are limits to what can be learned by focusing on the similarities between all mammals. There are important differences across species, and these are arguably essential to recognize as we seek to translate the findings from experimental animal

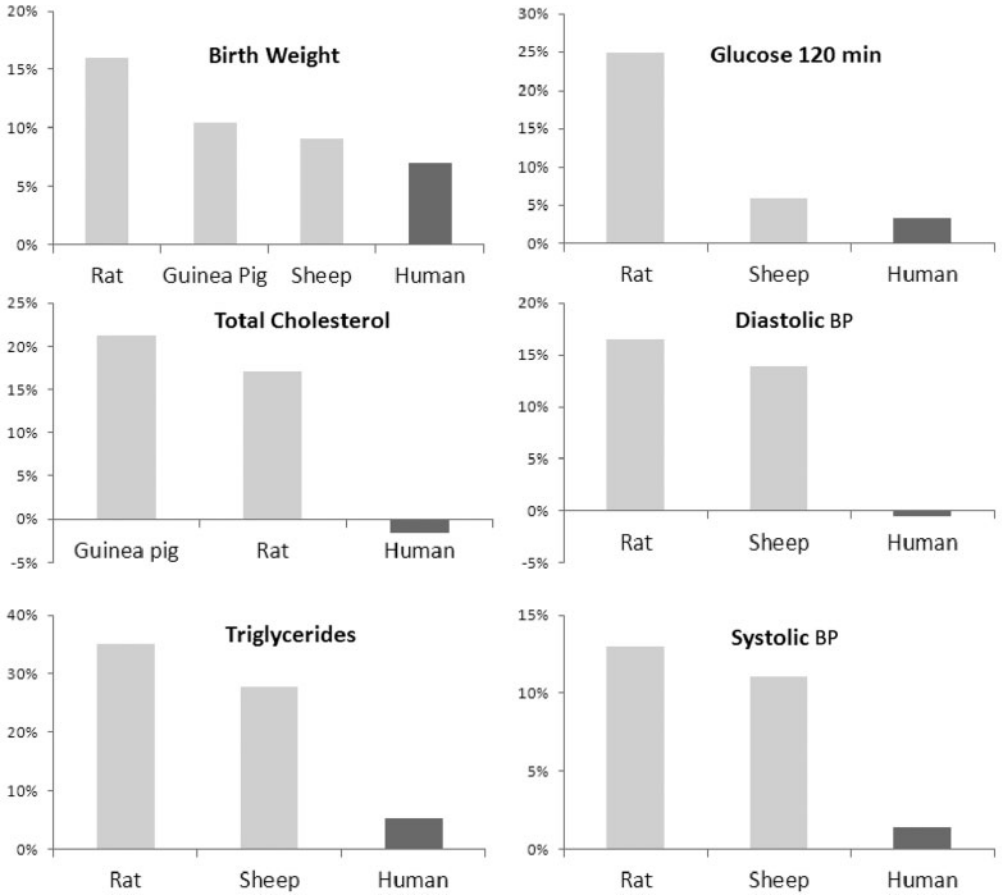

Figure 2 The magnitude of change in offspring outcomes induced by maternal diet restriction during pregnancy by species (modified after Kuzawa and Thayer;[13] see original for references). All animals born to mothers who experienced caloric restriction during early gestation (30–50% global caloric restriction). All values are calculated as the percentage difference between the control group and the case group, and represent averaged male and female values. All human data are from the Dutch Famine Winter adult cohort with those who experienced famine in middle or late gestation compared with the control group of those conceived after the famine.[15] BP, blood pressure

model research into concrete policies aimed at improving human health and well-being. It should be clear that the biomedical and evolutionary/comparative perspectives—which respectively describe structure, and explore the function and evolutionary origins of *variation* in that structure—are not competing but fundamentally complementary. Medicine is increasingly integrating epigenetics and developmental biology into its causal models. Additional benefits for medicine will be reaped once it embraces more fully the principles of comparative biology that lie at the heart of evolutionary analyses.

As Bateson and Gluckman elegantly argue, developmental biology has been missing from modern biology for far too long. One of the biggest challenges currently faced by the biomedical fields is how to integrate the complexity of epigenetics and developmental biology into models of the transmission and development of common chronic diseases. In parallel, evolutionary biology is grappling with the implications of these issues as they pertain to the origins of form, and the pace and direction of genetic evolution. It will be important for medicine and evolutionary biology to combine their respective strengths—as discoverers of structure and explainers of variation, respectively—to address these shared goals. Bateson and Gluckman's elegantly written volume serves as a handy guide to these issues and an excellent entry point into this complex and promising scientific arena. I highly recommend it to anyone interested in the future of medicine or evolutionary biology, and especially those who see the pressing need for their synthesis.

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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