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BOOK SYMPOSIUM

A niche for the genome

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Abstract In their considered reviews both Thomas Pradeu and Lindell Bromham introduce important topics not sufficiently covered in our book. Pradeu asks us to enlarge on the epigenetic and ecological context of genes, particularly in the form of symbioses. We use the relationship between eukaryotes and their symbiotic organisms as a welcome opportunity to clarify our concept of the developmental niche, and its relationship to the developmental system. Bromham's comments reveal that she is primarily interested in identifying macroevolutionary patterns. From her vantage point eco-evo-devo, the study of phenotypic plasticity, epigenetic and exogenetic inheritance, have not yet demonstrated the need for any revolutionary change in evolutionary thought. For us they highlight the extent to which proximate developmental mechanisms can inform ultimate biology.

Keywords Molecular epigenesis · Developmental niche · Developmental system · Exogenetic inheritance · Epigenetics

Introduction

We are privileged to have two such well-qualified reviewers. As well as offering considered responses to our work, the particular interests of philosopher of biology Thomas Pradeu and macroevolutionary biologist Lindell Bromham allow them to introduce important topics not covered in our book. Pradeu suggests that we could

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have strengthened our central argument by more attention to metagenomics and developmental symbiosis. Bromham introduces a whole new identity of the gene—the gene as history—that certainly deserved a chapter in our book. Indeed, as we discuss below, it very nearly got one!

The closing chapter of our book is entitled 'Four Conclusion'. First, the gene today has several identities that have accumulated as genetics and molecular biology have developed and diversified. Both reviewers agree that the question 'what is a gene' can only be asked in a specific biological context, and that different answers are required in different contexts. Our second conclusion is that genes are only one factor in the production of biomolecules through a process of 'molecular epigenesis'. Pradeu agrees, and even thinks we do not go far enough. Bromham has reservations, and thinks we are too uncritical in our embrace of some aspects of contemporary genomics. Thirdly, we conclude that while molecular biology has amply demonstrated the power of reductionism as a scientific research strategy, reduction is not enough and the contemporary molecular biosciences are both reductionistic and integrative. Pradeu agrees; Bromham does not address this aspect of the book. Finally, we concluded that contemporary molecular bioscience renders the distinction between nature and nurture incoherent and unhelpful. Pradeu agrees, but Bromham thinks that a distinction between what is inherited and what is not remains important when thinking about the process of evolution.

Response to Pradeu

Pradeu's rich and illuminating discussion ends with four questions regarding the concept of the 'developmental niche' and its relationship to our earlier work on 'developmental systems theory'. We answer these four questions before addressing his other major points.

Is the "developmental niche" equivalent to the "Developmental System"?

Around a century ago, inheritance was reduced to germ line inheritance, which soon became understood as genetic inheritance. Recently, in what Pradeu justly labels the 'epigenetization of genetics', inheritance has extended to include epigenetic inheritance, but only narrowly conceived as chromatin marks and other modifications of DNA inherited through the germline. All of heredity continues to pass through a single-celled bottleneck.

In contrast, we embrace a much broader extension of inheritance, although for clarity we are happy to restrict 'epigenetic inheritance' to the inheritance of patterns of gene expression across generations in the absence of a continuing stimulus. We use the term 'exogenetic inheritance' (West and King 1987) to refer more broadly to the inheritance of phenotypic features via causal mechanisms other than the inheritance of nuclear DNA. As we wrote, "Organisms construct their life cycles through the interaction of the contents of the fertilized egg, the genome and its narrowly epigenetic surroundings, with a 'developmental niche' which is the result of epigenetic inheritance in a wider sense … 'exogenetic inheritance'…" (Griffiths and Stotz 2013, 5).

As we discuss below in our response to Bromham, even narrow epigenetic inheritance is sometimes distinguished from true heredity on the grounds that epigenetic marks are not stable for many generations, and therefore, it is argued, cannot have evolutionary significance. Pradeu agrees "with Griffiths and Stotz that this is not a sound argument, as an influence over a single generation can perfectly be evolutionarily significant". This is because evolutionary dynamics depend on the pattern of transmission of characteristics from one generation to the next. Even the introduction of one-generation 'parental effects' (correlations between parent and offspring character independent of correlations between genotypes or between environment), which is the pattern produced by unstable germ-line epigenetic inheritance, will change the outcome of evolutionary processes (Wade 1998). But another kind of exogenetic inheritance may, in fact, be more stable than germ-line epigenetic inheritance. Parental effects often occur not via the germ line, but by the induction of epigenetic modification in offspring as a result of parental behavior. This can have long-term, often lifelong effects on offspring phenotype. In some known cases these offspring phenotypes include the very parental behavior that induced them, so that the offspring reproduce the effect in the next generation, and so forth. These behaviorally transmitted but epigenetically mediated effects contribute to the long-term stabilization of aspects of the developmental niche, and hence may evolutionarily be more significant than epigenetic inheritance narrowly conceived.

To answer Pradeu's first question, in our updated reading of Developmental Systems Theory (DST) the developmental niche is a better way to conceive of the environmental part of the organism-environment system that comprises the developmental system. It is worth emphasizing that the fundamental unit of analysis for DST remains the *life cycle*—a series of events. The life cycle extends what is traditionally thought of as the process of development to include the whole of life. We can think of this process as occurring within (and feeding forward into the construction of) a developmental system. Or we can think of the life-cycle as consisting of the regulated expression of an epigenetically modified genome through its interaction with a developmental niche.

It is unfortunate that the developmental niche continues to be conflated with the 'niche' which features in niche-construction theory (Odling-Smee et al. 2003). Niche construction theory concerns the influence of past generations on the selective pressures that act on future generations. This activity partially constructs the *selective niche*, the set of parameters that determine the relative fitness of competing types in the population. The *developmental* niche, however, is the set of parameters that must be within certain bounds for an evolved life-cycle to occur (in more traditional terms, for the organism to develop normally). The two niches will often share many parameters. They are, however, conceptually quite distinct. Signals from parent to offspring that induce transgenerational adaptive phenotypic plasticity, for example, when *Daphnia* signal their offspring to grow additional defenses against predators, are a central example of developmental niche construction. But to regard that as *selective* niche construction would be as absurd as calling the inheritance of an advantageous mutation 'niche construction'! The

organism is altering itself to fit the selective environment, not altering the selective environment.

Does the developmental niche expose itself to the same possible objection as the developmental system, namely that it is too inclusive and therefore imprecise?

If anything, the idea of the developmental niche is a way to respond to this accusation against the original idea of a developmental system, since it has been introduced to clarify the very loose term 'environment'. Several animal behavior labs have applied the concept of the developmental niche successfully to study phenomena of non-genetic inheritance. It has been used to great effect in such different fields as the development of social behavior and communication in birds, the normal species-typical development in general or the development of fear reactivity and learning abilities in particular in rat (Alberts 2008; Champagne et al. 2006; Meaney 2001; Meaney and Szyf 2005; West and King 1987, 2008).

Beyond this, the criticism that DST is too inclusive and too imprecise was always quite unfair. It reflects the need of many philosophers for a holistic position to act as a foil for their own arguments. If no real holists are available, then it is necessary to invent some. Pradeu describes how Philip Kitcher criticized DST for its impractical holism and notes that, "the idea of 'causal democracy' (all causes are of equal weight) is a straw man". However, 'causal democracy' was actually the position that Kitcher advocated in opposition to what he took to be the excessive holism of DST:

> Interactionists ought to support a principle of causal democracy: if the effect E is the product of factors in set S, then, for any $C \varepsilon S$, it is legitimate to investigate the dependence of E on C when the other factors in S are allowed to vary. (Kitcher 2003, 290)[1]

Kitcher's principle has been more or less universally misrepresented, so Pradeu is in good company. Causal democracy requires equality of opportunity, not equality of outcomes. Nevertheless, like conservative political commentators, conservative philosophical commentators have represented causal democracy as the demand that all causes be dragged down to the same level, and the refusal to acknowledge that some causes are more significant than others. It is thus ironic that the 'parity principle' advocated by DST and widely regarded as the epitome of holism was always only the same, sensible principle that Kitcher advocated under the name of 'causal democracy'. The name itself is derived from 'parity of reasoning'—if some feature of DNA makes DNA important in development, then other developmental factors which share this feature should be granted the same importance (Griffiths, In Press).

Hence we believe that the concept of the developmental niche is neither too inclusive nor too imprecise to be of use in developmental studies. It comprises those parts of the developmental environment that are transmitted to the next generation

[1] This paper appeared in (Singh et al. 2001) before being reprinted in Kitcher's collected papers.

and used to reconstruct and modify the life-cycle of the next generation. What these resources are and what are the channels of their transmission are empirical questions, and they will be answered in a piecemeal fashion, studying some factors while holding others artificially constant.

Is development (rather than evolution) the main focus of a "developmental systems perspective"?

As Griffiths and James Tabery describe in their recent history of DST (Griffiths and Tabery 2013) the majority of the theorists in the developmental systems tradition have been developmental psychobiologists, notably Daniel Lehrman, Gilbert Gottlieb, Donald Ford and Richard Lerner, and Susan Oyama. Many of these theorists were explicitly concerned to keep evolutionary and developmental questions separate. But that need not imply that answers to one sort of question are irrelevant to answering the other. Investigating the lifecycle is a transgenerational exercise, with a focus on mechanisms to achieve both transgenerational stability and plasticity. These are the proximate mechanisms of inheritance, the production and transmission of developmental resources to the next generation and their use to reconstruct a new life cycle. The focus is developmental because DST accepts that the study of inheritance, the hereditary relations between parents and offspring, depends on developmental processes that link the phenotypic states of parent and offspring via the transmission of developmental resources and their use in the production of a new life cycle.

The results of these investigations, however, are highly relevant to understanding evolution, as we discussed in Chapter 8 of our book, and as we elaborate in our response to Bromham below.

Is the organism an adequate level of analysis for this perspective?

The traditional organism, bounded by its skin, is not an adequate unit of analysis for DST, nor is the 'extended phenotype' bounded by the range of phenotypes that co-vary with changes in the sequence of some set of nucleic acid molecules. DST needs to pay attention to all the developmental resources that sustain the life cycle, not only as far as reproductive maturity, but all the way to the grave. The research of developmental psychobiologists Meredith West and Andrew King is a paradigm of DST in action. Their subject is the brood parasitic brown-headed cowbird, *Molothrus ater*. Since cowbirds are raised by foster parents, they do not acquire species-typical behaviors, such as the typical cowbird song, from either foster or biological parents; so these traits were assumed to be genetically determined (Mayr 1961). Early experiments apparently confirmed this: freshly weaned male cowbirds confined in cages without access to other adult cowbirds developed quite potent songs, which may not resemble the typical song closely but to which young females reacted strongly. Only painstaking research of three decades revealed that young cowbirds join other cowbirds after weaning to form flocks. Male birds learn to sing the right song through the feedback of mature females. Only those parts of the songs that received a positive feedback are retained. Singing non-cowbird-like song is

strongly policed by the flock. In addition, males have to learn how to *use* the song by copying mature male cowbirds: mating success requires not a great solo performance but successful counter-singing with another male. Young females, in a complementary phenomenon, learn their judgment of songs from mature females. According to West and King, the social group forms the most important developmental niche of the cowbird, since it is the flock as a whole that 'gates' the information that is available to be learned.

> For this parasitic species, it is clear that evolution has trusted an exogenetic system to transmit information vital to reproduction from one generation to the next. The 'safety net' is the social structure of the flock. The ontogenetic niche can be considered at several levels, but at the most basic level, an individual's niche is defined by his or her status or position within the flock. This position defines what is available to be culturally transmitted or learned throughout the lifespan. (West and King 2008, 393)

Every organism is made up in part of its developmental niche. This is easy to see in the cases to which Pradeu urges us to pay more attention, cases of symbiosis in which one partner is an inherited developmental resource for the other(s). The development of literally all life forms is influenced by microbes, with which every organism is more or less tightly associated. James Griesemer's molecular conceptualization of the life cycle of malaria parasites or the HIV virus shows its dependence on many features of their respective hosts that 'scaffold' their development (Griesemer 2014). The developmental niche framework can be used to understand the role that our symbionts play in the development of both of our intestines and our immune system, as Scott Gilbert and David Epel (Gilbert and Epel 2009) describe in their book *Ecological Developmental Biology*.[2] The developmental niche concept provides an equally useful way to accommodate the complex multi-genomic and multi-generational features of the 'simple' life cycles of microbes and viruses. Just as the rat pup passes through a series of consecutive developmental niches (the uterine niche, the dam, the huddle and the coterie (Alberts 2008)) which provide sustenance, warmth, protection, and necessary experiences for learning, so does the HIV virus or the plasmodium pass through a series of different 'niches' that support different stages of development.

Pradeu on eco-devo and symbioses

Pradeu's main criticism of our book is its relative neglect of ecological developmental biology, and particularly the all-pervasive phenomenon of symbiosis. We accept this criticism and agree that we should have given these topics more room. Pradeu points out that such a discussion would have strengthened some of our arguments in favour of molecular epigenesis. Given our DST perspective, particularly with its more rigorous treatment of the inherited environment

[2] The authors explicitly utilize a niche concept here, but do not sufficiently distinguish the developmental niche from the better-known *selective* niche.

conceptualized as the developmental niche, we are naturally quite close to an ecological developmental biology with it's increased emphasis on phenomena of developmental plasticity. In our defense we can say that conceptually the whole of chapter five fits under the umbrella of an ecological developmental biology, at least insofar as nongenetic inheritance is concerned.

We are less sanguine than Pradeu that dwelling more on the developmental importance of symbiotic microorganisms would have strengthened our argument for molecular epigenesis. Pradeu suggests that microbial symbionts support our claim that sequence specificity cannot ultimately be reduced to the influence of the genome, since, "even epigenetic regulations can always be described as ultimately coming from the host genome, but this view is invalid in the case of microbe-regulated development." However, while one could—and should—interpret the microorganisms within us as part of the wider developmental environment, metagenomics often sees them as merely an extended genome. This shouldn't be too surprising, considering that even parental effects are often reduced to the effect of the parental genome on offspring phenotype via parental behavior. So in conclusion, we don't think that the above argument would sway the genetic determinist any more than they would be swayed by arguments regarding parental effects. As soon as the environment is seen to be produced by another organism, the primacy of genes is invoked.

The identities of the gene

Both reviewers identify the book's main target as the changing concept of the gene. This is understandable given chapter titles such as 'Mendel's gene', 'The material gene', 'The gene as information', 'The behavioural gene'. Chapter 4 is entitled 'The Reactive Genome', but it contains a long discussion of the gene in the postgenomic era, and describes the three gene concepts that we believe exist today alongside one another. So indeed one of our aims had been to address a major traditional question in the philosophy of biology: "Has the Mendelian gene been reduced to the molecular gene?" We conclude that it has not. Instead, the development of genetics has left us with more than one scientifically productive way of thinking about DNA.

We appreciate Pradeu's effort to capture the evolution and diversification of the gene concept diagramatically (Fig. 1). We wish we had included such a figure ourselves as a reference point for the reader. Pradeu pictures the Mendelian gene splitting into the instrumental and hypothetical material gene, and juxtaposed with a 'functional gene' becoming the molecular gene which in turn gives rise to both the nominal and the postgenomic gene. We recognize most of the 'speciation events' here, but have some concerns about how the tree is rooted. We doubt that the lower portion of the tree is best regarded as containing a distinctively *functional* gene concepts. While the postgenomic gene concept comes close to a purely functional conception of the gene, the molecular gene grew out of a structural conception, even though it was quickly aligned with an updated functional understanding. The instrumental gene could be understood as a purely functional conception—but the search for its material basis—the 'hypothetical material unit of

heredity'—shows that there was a desire to align the functional concept to a structural one. So we prefer to think of the evolution of the gene concept as driven by continuing attempts to keep structure and function aligned. Progress in understanding structure tended to undermine existing ideas about function, and vice versa. As Pradeu himself says: "it seems difficult to maintain the traditional idea that the molecular gene must be at once a structural (a well-delineated and reasonably continuous sequence of nucleotides) and a functional unit (that which makes a gene product, typically a protein)."

Pradeu describes one of the main lessons of the book as "that *genes are best conceived as tools*". He means this in two senses, first "tool in the sense that it is an instrument used by geneticists to account for and predict [their] results", and second, in the sense that certain gene concepts, such as the postgenomic concept, see genes as "tools used by cells and organisms according to the spatial and temporal context". We agree that, if genes are "things you can do with your genome" (Griffiths and Stotz 2013, 223), then the coding and regulatory resources in the genome might be seen as the tools with which these things are done.

In a paper analysing the relationship between philosophy of science, the sciences and society we elaborated the idea that scientific concepts are 'tools' for research and that a philosopher of science might function as a 'conceptual ecologist' (Stotz and Griffiths 2008, 39). Gene concepts are,

> …ways of classifying the experience shaped by experimentalists to meet their specific needs. Necessarily, these tools get reshaped as the demands of scientific work change. In the study of conceptual evolution, the history of genetics provides a "conceptual phylogeny" of the gene. … "conceptual ecology"… [is] an attempt to determine some of the pressures that caused the gene concept to diversify into a number of different epistemic niches. (Stotz and Griffiths 2008, 41)

Response to Bromham

Bromham summarizes our book as follows: "The scope of this book is not so much genetics as a whole but the gene itself, and in particular, the thorny problem of how we are to define the word 'gene'. This book is primarily concerned with the gene as an actor in the construction of phenotype (morphology and behaviour), so discussions in the book revolve around the details of gene expression, development and environmental influence, with relatively little coverage of inheritance per se, and even less on genomic evolution."

We accept that our book does not cover all the main fields of genetics. We explained in the introduction our decision to exclude population genetics. We felt that it would be better addressed as part of the philosophy of evolutionary biology. We also pointed out that population genetics is based on a few principles of high generality and on the mathematical exploration of the consequences of those principles. As such it represents a very different kind of science from the molecular biosciences, and raises distinct philosophical issues. But we do not think that the

book can be said to neglect *inheritance*. It begins with a chapter on Mendelian transmission genetics, has a chapter on behavioral genetics, in which heritability necessarily occupies a major role, and epigenetic and exogenetic inheritance are a major focus of other chapters. Bromham is right, however, to draw attention to the absence of genome evolution and molecular phylogenetics. We planned a chapter on 'The gene in history', but abandoned it when we realized that our preliminary work was drawing too much on popular presentations rather than on original research. Philosophy of biology "…must be 'bioliterate,' engaging with the science at the same level as practitioners rather than via popular representations" (Stotz and Griffiths 2008, 38–39), and these genetic disciplines are ones we have not published on previously and where we felt we could not readily meet this standard. In these disciplines, we suspect, the gene takes on yet another identity as a trace of history, carrying information about pattern and process, whose interpretation both depends upon and helps to shape theories of evolution and development.

Molecular epigenesis

The idea of molecular epigenesis is that development is epigenetic all the way down to the molecular level. No phenotype, not even the primary sequence of a gene product, exists preformed or predetermined in the resources that the organism inherits. Instead, they are produced anew in each generation by developmental processes. In particular, the coding sequences in the genome are not the sole source of the specificity for the primary sequence of a biomolecule. Instead, this 'Crick information' as we have termed it is distributed across a range of developmental resources.

Bromham seems to accept molecular epigenesis as long as it is confined to the genome. "If the gene consists of all the sequences needed to make a gene product, then it can also be said to depend not only on the coding sequence but also the regulatory sequences that modulate gene expression" and, "a postgenomic gene has distributed specificity, in that critical sequences are spread over the genome". But molecular epigenesis is not merely about extending the gene to include regulatory sequences. To the extent to which any developmental factor is involved in decisions about the activation, selection and creation of sequence information, that factor is a source of specificity (Crick information) for the sequence seen in a gene product. The specificity for a product can be distributed among coding sequences, sequences with regulatory functions both proximate and quite distal from the coding sequences, regulatory gene products, and environmental signals, many of which are provided reliably in each generation by the inherited developmental niche.

Bromham also suggests that our claim that DNA sequences are not the only source of biological specificity is related to the "complexity of the interaction between the genotype and environment, and the complex web of regulatory factors that are required to regulate gene expression, as evidence in favour of the reactive genome". But although the mechanisms that we describe are complex, their complexity is not relevant to why they support the thesis of distributed specificity.

Crick's 'sequence hypothesis' proposed that the order of elements in a gene product was determined solely by the order of bases in the DNA. While a brilliant and progressive suggestion at the time, it is now clear that this is not true. Many gene products can be made from the same coding sequence, and several coding sequences can contribute to one gene product. It follows that the information in the coding sequence alone is insufficient to specify which gene product will be produced. Bromham recognizes that this information must be sought in non-coding sequences of the genome. We think that it is necessary to look further afield as well, for one reason because we need to explain why specific combinations of regulatory and coding sequences are used on one occasion rather than another. There is no complexity-worship going on here, only the demand that the explanation be adequate to the observed phenomena.

Bromham notes that some biological commentators think that some of the aspects of postgenomic biology we discuss have seen "more hype and inference than dispassionate observation". She wonders whether we have been sufficiently critical in our assessment of these developments (one eminent biologist put this charge to us more directly—"I hear you've drunk the ENCODE Kool-aid"). Bromham points out that "we need to consider that some of the error in the system is biological. Alternative splicing can produce multiple functionally relevant transcripts from the same DNA sequence… But this does not mean that all alternative transcripts are functionally relevant to phenotype." This is certainly correct—some of the apparently ubiquitous transcription of the genome must be transcriptional noise. We also take the point that the more complex the regulatory architecture gets the more error prone it may become. But we would still maintain that the only reason for the existence of errors in alternative splicing lies in the prior existence of the functionality of alternative splicing as a mechanism to create protein diversity. It may be, as Michael Lynch has argued, that some of the complexity of genome architecture does not have adaptive origins (Lynch 2007). However, in extant organisms these aspects of the genome have been adapted as mechanisms of gene regulation. Only if adaptation has played no significant role in shaping the rich array of *trans*-acting RNA-binding proteins (splicing factors that we have come to call splicing activators and repressors) and their corresponding *cis*-acting binding sites within both the exons and introns of the gene (usually called exonic or intronic splicing enhancers and silencers) would our case for distributed specificity be discredited. Bromham is also right to warn that higher complexity does not necessarily increase reactivity. But so far our insight into the regulatory mechanisms of alternative splicing and editing in eukaryotes suggests that they are highly context-sensitive and open to environmental inputs (Fu and Ares 2014).

Information and inheritance

Like most biologists, Bromham has a limited appetite for semantics. She wonders why the fact that 'information' means many things is any more problematic than the fact that 'gene' means many things. This is a good question. Like 'gene' the term 'information' occurs in many technical contexts and here it is plausible that the

context makes clear exactly what is meant. In theoretical biology, and in the kind of critical examination of biology that we are engaged in our book, however, slippage of meaning can cause problems.

We are not the first, for example, to object to the idea that genes 'code for' phenotypic characteristics. We follow Peter Godfrey Smith (Godfrey-Smith 2000) in insisting that it is unhelpful to use the phrase 'codes for' to mean nothing more than 'makes a difference to'. This is why, as Bromham notes, we "are adamant that genes cannot be said to 'code for' any aspect of phenotype because the code written in DNA is a code for a series of amino acids only, not for phenotype as a whole, which may (sometimes) be affected by external factors." The issue is not that the relationship between genes and phenes is affected by the environment. The issue is that Crick's sequence hypothesis was a substantial scientific hypothesis, and that this hypothesis did not apply to (and is not true of) the relationship between nucleic acids and more distal phenotypes. We can use the word 'code' however we like, but we need some way to mark what was distinctive in Crick's proposal.

In Chapter six we distinguished between information *in* genes and information *about* genes. The genetic information your doctor is not allowed to share without your consent is information *about* your genes. Our focus in the book is on the information that genes contain irrespective of what anyone knows about them, and which leads to genes having one effect rather than another. For example, the information *in* genes produces the primary structure of proteins. But the kind of genetic information that Bromham is interested in as a biologist who studies macroevolutionary pattern and process falls somewhere between these two. It is information about what happened in the evolutionary past:

> But all DNA sequences, functional or not, carry historical information incidentally, as a by-product of descent with modification. … But they are very interesting to someone like me, who uses DNA primarily as a source of information on evolutionary past and processes. … The gene as a carrier of information about history may sometimes overlap with the gene as a unit of function, but sometimes it will not.

Bromham suggests that "the most critical area where sorting out what we mean by 'information' may have real impact on the way we talk about genes is in evaluating the role of non-genetic forms of inheritance." She compares the information in the form of antibodies received in the mother's milk to the information in a genetic sequence enabling you to produce an antibody. It seems that she rejects antibodies in the mother's milk as inherited information because of its transient form—you inherit the antibody, but not the information about how to make antibodies. Also, you may inherit epigenetic modifications but not the instruction of how to make them, that would be genetic information. Epigenetic modifications in this sense are part of the phenotype (in contrast to inherited resources, one must presume?). Phenotype, Bromham goes on, belongs to the realm of matter, while the genotype is information, message or content.

We have no objection to stipulating that a developmental factor only contains information if it leaves a trace that can be used to reconstruct evolutionary history. It would be mere semantics to object to this because we ourselves choose to say that

any factor which has a specific effect on development contains information for development (for a formal, information-theoretic treatment of our approach, see Griffiths et al. 2015). It is easy enough to separate these, if necessary, as 'historical information' and 'developmental information'. But we do object to the idea that only information that persists over evolutionary time can affect the process of evolution. To use a rough analogy, the fact that a football carries traces of who kicked it, but not of the cross-wind does not mean that the cross wind was irrelevant to the trajectory of the ball. Evolutionary dynamics depend on the pattern of transmission of characteristics from one generation to the next and epigenetic inheritance is part of this pattern.

Bromham has better reason than most to insist that information which persists over evolutionary time is special, since her primary concern is with reconstructing the course of past evolution from current evidence. She writes that,

> Nongenetic inheritance is clearly important in determining phenotype, but may be less so in stably transmitting variation across evolutionary timescales because it can be easily overridden or changed.

But for the reasons just indicated, this point does not really speak to the issue of whether incorporating epigenetic inheritance is a substantial amendment to evolutionary theory, an issue we take up in the final section of this response.

We suspect that Bromham and others who think that the significance of epigenetic inheritance is overstated are relying on the idea that epigenetic inheritance is an inevitable downstream consequence of genetic inheritance. For example, Bromham stresses that "genes specifying epigenetic marking are a critical part of the adaptation of the genome". That may be true, but there is more to epigenetic inheritance than this. We start Chapter five, which deals with non-genetic inheritance, with a discussion of the different kinds of epigenetics and epigenetic inheritance. In our terms, Bromham is talking about 'narrow epigenetic inheritance' defined as stable modifications in gene expression that persist through meiosis in the absence of a continuing stimulus. Moreover, when she emphasises genetic instructions for epigenetic markings then what she is talking about is gene-imprinting, parent-of-origin expression effects, which need to be tightly genetically regulated. But narrow epigenetic inheritance also includes environmentally induced epigenetic marks, which cannot be specified by the parental genome (although, obviously, the capacity to respond to the environmental stimulus requires that the genome has the correct structures in place). We also distinguish 'transgenerational epigenetic effects', a form of exogenetic inheritance in which environmental conditions (often parental behavior) re-establish epigenetic marks that were erased in the germ cells.

Information and development

Bromham emphasises what she sees as a fundamental asymmetry between the ways in which genes and environment effect development. The precise effect of a genetic difference is independent of the environment, but the precise effect of an

environmental difference is not independent of genes. In terms of the framework we develop in our book, genes are specific difference makers, but environments are not. For example, you can tell someone's eye-colour from a blood sample without any information about their environment, but,

> The same can rarely be said, to anything like the same degree, for the environment: you can't often predict phenotype from information about the environment without also having the genetic information. You can't tell me someone's eye colour just by knowing where they grew up, unless I also give you information about their genetic inheritance (e.g. their parents eye colour or ethnicity).

The contrast that Bromham draws here is the received view of how genetic causes differ from environmental causes in development. But we do not think it is correct—indeed, much of our book is making the case against it. It's apparent plausibility has various sources, one of which is simply the usual choice of examples.

Brohman mentions eye colour and Huntingdon's disease as phenotypes reliably predicted by genetics. But it is a truism in medical genetics—both physiological and psychiatric—that when a genetic variant associated with a disease is first discovered a screen of the general population will reveal many asymptomatic individuals with the genetic variant. Conversely, a screen of the patient population will reveal many sufferers without this particular genetic variant. So eye colour and Huntingdon's disease are not representative examples of the predictability of phenotype from genotype. Conversely, it is actually quite easy to find examples of deterministic environmental factors to match the genetic examples. We can predict that someone will have beriberi or rickets merely by knowing that their environment contains no vitamin B1 or no vitamin D, without needing to know anything about their genotype.

One way to find a deterministic relationship between a phenotype and a cause, whether genetic or environmental, is to choose an essential component of a mechanism as a cause and the effect of the whole mechanism as a phenotype. The difference between possessing and lacking the essential component will be a powerful predictor of the phenotype. Another is to choose an *immediate* cause of a phenotype. Genetic differences predict blood type very well because the molecular structure of the antigens that constitute blood type is an almost immediate causal consequence of the coding sequences from which they are constructed. In the same way, geographic origins predict isotope signatures in tissues very well because isotope signatures are an almost immediate causal consequence of the composition of the foodstuffs that went into constructing the tissues.

A more important point to make in this context is that when a genetic difference reliably predicts a phenotypic difference this is often because the person making the prediction can safely assume a normal developmental niche. The values of environmental parameters required for normal genome expression are within ranges that are usually far from what they would be if genomes were randomly assigned to environments. Few environments contain antibody-rich human milk, but most

human infants find themselves in environments that do. This is the result of developmental niche construction.

Bromham acknowledges this, of course,

> the environmental niche is heritable and important to phenotype: we should never allow ourselves to ignore that most offspring inherit more from their parents than their genes, even those that never actually meet their mum and dad. But the continuity of environment can be altered much more easily and substantially than the genetic inheritance.

The substitution of 'environmental niche' for 'developmental niche' is telling, since it directs attention away from the causal processes by which parents regulate development and replaces this with a passive environment that exists independently of the organisms that inhabit it. Bromham says she can remove a newborn squirrel from its environment niche and raise a normal squirrel, but that squirrel has already spent 44 days in its mother's womb.

Do we need an extended synthesis?

"It is not clear to me the extent to which the complexity of gene action revealed by modern techniques, and the role of environment in shaping phenotype, contributes to an extended synthesis", writes Bromham. To some extent the debate about whether the synthesis needs 'extension' is a debate about how many stones make a heap. In our Chapter 8 we tried to remain fairly non-committal, but it seems clear that we are more struck by the recent impacts of the study of developmental on evolutionary thinking than Bromham. We don't think that evolutionary developmental biology, and the study of phenotypic plasticity and epigenetic inheritance, should be seen as merely bringing a wider range of phenomena within an unchanged theoretical framework.

In Chapter 8, which discusses a range of developments that have been said to constitute, singly or together, an extension of the evolutionary synthesis, we suggest various ways in which epigenetic and exogenetic inheritance systems may be of evolutionary significance. Non-genetic forms of heredity may not be as unstable as normally supposed (Jablonka and Avital 2001; Jablonka and Raz 2009). Moreover, the evolutionary significance of inheritance systems need not turn on their stability across generations. As discussed above, the role of a theory of heredity is to specify how offspring and parent phenotypes are related. Since the phenotype of parents has an effect on offspring phenotype beyond their genetic relatedness, any model neglecting this part of the equation will produce inaccurate predictions about the population's evolutionary trajectory. Finally, and perhaps most interesting, the study of heredity is no longer solely about understanding phenotypic stability, but also about understanding plasticity. The purpose of some inheritance systems—against a background of fluctuating environments—may be to allow the inducibility of heritable phenotypes. In summary, the main reasons for extending the original modern synthesis involve the realization that proximate developmental mechanisms can inform ultimate biology.

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