Embryology, Epigenesis, and Evolution

Taking Development Seriously

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The Problem of Development

> It is not good enough to answer [questions regarding development] by saying it is simply a matter of turning some genes on and others off at the right times. It is true that molecular biology provides numerous detailed precedents for mechanisms by which this can, in principle, be done, but we demand something more than these absolutely true, absolutely vacuous statements.
>
> – *Sydney Brenner* (1974)

The central problem of developmental biology is to understand how a relatively simple and homogeneous cellular mass can differentiate into a relatively complex and heterogeneous organism closely resembling its progenitor(s) in relevant respects. This is not a new problem. It has been with us since Aristotle, at least. However, it is only recently that we have established a handle on how possibly to solve it. I am not convinced that we have yet grasped the right handle, though.

A decade ago, an advertisement for *The Encylopedia of the Mouse Genome* appeared in a biotechnology serial. The tagline read: 'The Complete Mouse (some assembly required)' (cited in Gilbert and Faber 1996: 136). The parenthetical clause refers, of course, to development. As those of us who have purchased ready-to-assemble furniture know all too well, this is indeed an onerous requirement, for the assembly process may very well have the greatest impact on final outcome! What is true of ready-to-assemble furniture is also true, I contend, of organisms believed to be 'ready-to-assemble' from DNA and assorted other material.

No one honestly believes that development can be achieved unilaterally by genes acting alone or in concert. Rather, everyone agrees that genes are important to, but not sufficient for, development. This is so, ontogenetically at

least (and perhaps also ontologically, for those concerned with ontology), and serves as the basis for the recent 'interactionist consensus' on development: the view that neither genes nor environments, neither nature nor nurture, suffices for the production of phenotypes.

I want to take this further: genes are important to, but not sufficient for, not only development but also the *explanation* of development. This epistemic and methodological claim is more controversial than the ontogenetic truism at the core of the interactionist consensus. My burden is to diminish the controversy surrounding this claim, in part by unpacking the interactive assembly of organisms.

In this chapter, my strategy is to explore a number of methodological principles used in biology; the first two of them are general, and the next three are used specifically in the context of understanding development. I provide arguments, abstracted from the biological and philosophical literature, for both the use of heuristics as such (the first principle) and for the use of particular heuristics (the second principle). For rhetorical purposes, I interpret the five principles as premises in an argument aimed at explaining development. I then illustrate how variance in the interpretation and application of the second principle yields inconsistent results and biases our biological knowledge in various ways. I argue in favour of an unorthodox reading of one of the heuristics, but a reading required by the imperative to take development seriously. In the chapters that follow, I further explore this imperative.

HEURISTICS

It is fair to say that biological phenomena are a messy lot. Though this may often be true in other domains as well, in biology, at least, a staggering number of simplifying assumptions must be made just to get a research programme off the ground. Historically, the most significant simplifying assumptions (or heuristics) employed in genetics and developmental biology have resulted in the elision of the organism as both nexus and nadir of developmental interactions. For the most part, these heuristics are well justified; they are, at least, widely accepted. Nevertheless, differences in how they are interpreted and applied generate differences in what we can claim to know about development.

Let us define 'heuristics' as *simplifying strategies to be used in situations of cumbersome investigational complexity* (Wimsatt 1980, 1986c; Gigerenzer et al. 1999). One crucial caveat about heuristics is that they are purpose

relative. As Wimsatt notes, 'all instruments in the natural, biological and social sciences are designed for use in certain contexts and can produce biased or worthless results if they are used in contexts that may fail to meet the conditions for which they were designed' (Wimsatt 1986c: 297). Examples might include the use of analysis of variance as a surrogate for the analysis of causes (Lewontin 1974; Sober 2000); the application of the methods of quantitative genetics where the assumptions of quantitative genetics (linearity, additivity, constancy, and so on) do not hold (Pigliucci and Schlichting 1997); or the use of linkage analysis in psychiatric genetics where the conditions of successful linkage (single gene of major effect, clear diagnostic criteria, known pattern of inheritance, and clinical homogeneity amongst affected family members) are not met (Robert 2000a). In using heuristics, then, we must be careful to select the right one(s).

That notwithstanding, without the use of heuristics, we would be much further from solutions to pressing biological problems than we currently are. Here, then, is a universally acknowledged premise of biological research:

1. Simplifying strategies and assumptions, as such, are absolutely necessary in biological science.

This is an heuristic dealing with the use of reductionistic heuristics. There are at least twenty reductionistic heuristics in widespread use today, including those used in conceptualisation, model building, theory construction, experimental design, observation, and interpretation; Wimsatt has documented these heuristics, and also their characteristic biases (Wimsatt 1980, 1986c).

Unlike Laplacian demons, human investigators of all stripes have limited intellectual, computational, temporal, and financial capacities. Any biological system to be studied must be simplified in various ways to make it tractable for agents like us. The very reason that we build simplified models is that we are limited beings, and most of the systems we want to understand are too complex in their natural state; thus we abstract from them what seem to be the most important or the most easily manipulated variables in order to generate a manageable representation of their workings.

One of the most common heuristic strategies is to simplify the *context* of a system under study. If we want to learn about *intrasystemic* causal factors – that is, if we want to learn about what's going on inside a particular system – we build a model or design an experiment wherein the context of the system is simplified rather than the system itself. Of course, we sometimes have to do both, especially if the system of interest is particularly complex; in such

a case, we might use another kind of reductionistic strategy. But a golden rule of experimental design is this: simplify the context first. Hence, a second general principle of biological methodology:

2. Simplifying the context of a system is advantageous if we want to learn about intrasystemic causal factors.

Amongst those who hold to the interactionist consensus, the strategy of context simplification is extensively employed in investigations of the role of genes in development, usually in the form of 'environmental control'. Here, one holds environmental variables constant across experiments or, worse, actually believes that the environment simply is invariant. One standard approach is to vary genetic factors against a common, invariant background of environmental factors – a standard environment. Context simplification, instantiated as environmental control, is the basic methodological framework of many researchers creating and employing genome sequence data, for instance. Sequence data are produced by isolating strands of DNA, cloning them, and employing a variety of techniques to ascertain the order of nucleotides and their physical relationship to each other. Genomes, or even individual strands of DNA – the systems under study – do not exist in isolation from natural environments except in the pristine artificiality of the lab; moreover, as we shall see in later chapters, there are good reasons to believe that even the structure (let alone the functions) of strands of DNA cannot be understood in isolation from their organismal context. Nevertheless, the environments, broadly construed, of DNA were abstracted away and held constant in the effort to generate the sequence of the human genome. (The same is true, of course, of the genome sequences of model organisms, such as the mouse and the nematode worm.) The context was simplified, the experimental work proceeded, and draft versions of the genome sequence are now at hand.

For the most part, and despite occasional slips to the contrary, biologists are careful in employing the strategy of context simplification. For instance, with rare but notable exceptions – such as Hamer and Copeland (1998), but see Hamer (2002) – very few scientists or commentators would today suggest that either nature (genes) or nurture (environments) is singularly decisive in organismal development. Despite the standard use of experimental or interpretive techniques to partition causation into internal (natural, genetic) and external (nurturing, environmental) components, techniques which may be unable by their very design to detect interactions between genes and environments (Wahlsten 1990; Sarkar 1998), most scholars grant that phenotypic

traits arise from complex, possibly nonadditive, interactions between multiple factors at many hierarchical levels.

However, not all varieties of interactionism are equivalent, and a vigorous debate has arisen over which varieties in fact take interaction seriously, and which simply pay 'lip service' to interaction in a reflexive refrain masking secret adherence to the old nature–nurture debate (Robert 2003). This debate will figure prominently in the paragraphs that follow, as well as in later chapters in the discussion of how best to interpret the second premise.

EXPLORING DEVELOPMENT

Let me now briefly spell out three additional premises, again universally granted, which are employed as additional steps, beginning with the first two premises, in (roughly) a chain of argument putatively leading to a conclusion about development.

The third premise, already alluded to, states the following:

3. Genes by themselves are not causally efficacious, as genes and environments (at many scales) interact (differentially, over time) in the generation of any phenotypic trait.

Whereas, once upon a time, biologists and commentators may have been happy to claim that genes determine organisms, body and mind alike, just as other scientists (mainly social scientists) and commentators were happy to claim that the organism is a kind of tabula rasa to be inscribed, shaped, and structured entirely by experience, no one seriously (or, at least, no one justifiably) entertains either of those perspectives today. It is for this reason that scientists are happy to declare the nature–nurture debate dead, settled in favour of both (Goldsmith et al. 1997). There are no (overt) genetic determinists these days, even though some environmental determinists persist (usually in an effort to ward off the spectre of genetic determinism). As Russell Gray has put it, 'nowadays it seems that everybody is an "interactionist"' (Gray 1992: 172). So much so, in fact, that those perceived to be stirring the ashes of the nature–nurture debate are called nasty names and relegated to the periphery of accepted scientific practice. This is the legacy of the interactionist consensus.

The fourth premise is designed to permit investigation of interacting variables in development (in line with premises 1 and 2):

4. We decide to focus on the causal agency of genes against a constant background of other factors, for pragmatic or heuristic reasons.

Experimental tractability is a core scientific *desideratum*. It is nice to imagine the world as full of interconnected parts not meaningfully separable from each other; but just try to analyse the world so imagined and science grinds to a halt. It turns out that genes are much more experimentally tractable than a wide range of other interacting factors and agents. This may be, of course, simply because we have spent so many decades perfecting techniques for genetic manipulation, and that huge amounts of money are available for such activities compared with others (Griffiths and Knight 1998: 255; Robert 2001b). Given the enormous amount of money available to study gene sequences, it is little wonder that genetic manipulation is quite easy compared with the experimental manipulation of other factors in development.

Nevertheless, it is worth briefly describing two scientifically well-regarded philosophical analyses justifying premise 4, such that premise 4 is universally acknowledged. First, Schaffner has published a careful study of the role of genes in the behavioural development of the nematode worm, *Caenorhabditis elegans*. Though he (and the scientists he studies) is well aware that genes must be coupled with other molecules within an organism in order to be causally efficacious (premise 3), Schaffner contends (in line with premises 1 and 2, and in support of premise 4) that '*epistemically* and *heuristically*, genes do seem to have a *primus intra pares* status'. This is in part because 'methods have been developed to screen for mutants, map "genes for" traits (as a first approximation), localise those genes, clone them, and test their role as "necessary" elements for a trait using sophisticated molecular deletion and rescue techniques' (Schaffner 1998: 234). With such methods in place, not starting with genes seems methodologically foolhardy. The embryologist Ross Harrison aptly noted early in the twentieth century that 'the investigator enters where he can gain a foothold by whatever means may be available' (Harrison 1918; cited by Gilbert and Sarkar 2000: 4).

A second, and related, justification for premise 4 is laid out by Gannett. She has analysed how genes come to be identified as causes primarily for pragmatic reasons (Gannett 1999). Having ruled out as unsuccessful the efforts of those who attempt to apply objective criteria (namely, causal priority, nonstandardness, and causal efficacy) to single out genes as causes, she argues that practical, and not theoretical, considerations are at play. Drawing on the work of Collingwood and van Fraassen on the context dependence of causal explanations, Gannett shows that what we identify as 'the' cause, amongst competing, equally necessary causes, depends jointly on the capacity to manipulate it (scientists' 'handle' – or, in Harrison's term, their 'foothold') and also the specific purposes of investigators (what sorts of questions are found meaningful and worthy of attention).

Pragmatic factors structure both of these contingencies: the capacity for manipulation is a function of past choices in, for instance, the development of particular technologies, and the questions found meaningful are decided by investigative aims, the practical end sought – for instance, the treatment or prevention of disease. Both contingencies are also deeply influenced by the availability of research funds; with the Human Genome Project, countless lab scientists suddenly saw a need for expensive gene-sequencing machines. Gannett concludes that, given the (necessary) incompleteness of causal explanations, whatever causal explanation offered will be both partial and pragmatically determined.

What we identify as a cause has its causal effects only in combination with additional necessary conditions (which, for other pragmatic reasons, might have themselves been identified as causes). This idea is epitomised in a fifth and final premise, one that may seem more controversial than the first four but is nonetheless widely acknowledged:

5. A trait x is caused by a gene y only against a constant background of supporting factors (conditions), without which x would not be present (even if y is present).

Prima facie, given premise 2, this fifth premise is a close relative of premise 3. Variations on this fifth premise have been employed as definitions of a 'genetic trait'. Consider Sterelny and Kitcher's sophisticated treatment:

> An allele A at a locus L in a species S is for trait P^* (assumed to be a determinate form of the determinable characteristic P) relative to a local allele B and an environment E just in case (a) L affects the form of P in S, (b) E is a standard environment, and (c) in E organisms that are AB have phenotype P^*. (Sterelny and Kitcher 1988: 350)

In other words, as long as that particular allele, in genetic and standard environmental context, is associated with the relevant phenotypic outcome, then that particular allele may be deemed an 'allele for' that phenotype. Given the necessity of simplifying assumptions (premises 1 and 2), as long as we recognise the critical contextual qualifications (premise 3) and also that we focus on allele A for heuristic and pragmatic reasons (premise 4), then we may deem premise 5 to be a plausible singling out of a gene as a cause in organismal development. So far, so good.

To reiterate, the five premises we have before us are as follows:

1. Simplifying strategies and assumptions, as such, are absolutely necessary in biological science.

2. Simplifying the context of a system is advantageous if we want to learn about intrasystemic causal factors.
3. Genes by themselves are not causally efficacious, as genes and environments (at many scales) interact (differentially, over time) in the generation of any phenotypic trait.
4. We decide to focus on the causal agency of genes against a constant background of other factors, for pragmatic or heuristic reasons.
5. A trait *x* is caused by a gene *y* only against a constant background of supporting factors (conditions), without which *x* would not be present (even if *y* is present).

These five premises taken together are usually thought to justify the following conclusion:

6. Therefore, organismal development is a matter of gene action and activation, as particular alleles have their specific phenotypic effects against standard environmental background conditions.

This conclusion coheres nicely with the standard explanation for why organisms develop as they do: there is a programme or set of instructions for development inscribed in the genes. Of course, genes alone do not an organism make. The genetic program must be activated or 'triggered', as there is no unmoved mover in the world as we know it; and the DNA must be suitably housed in appropriate cellular and extracellular contexts, which may themselves be very complex, in order for development to proceed. However, given these caveats, the specificity of development – the reliable, transgenerational reconstruction of form – is widely held to be best explained as a matter of gene action and activation.

But is that in fact true? Is development in fact *explained* in terms of gene action and activation? My argument is that it is not, though we all happily agree, at least in the abstract, with the five premises thought to generate it. Are we then illogical or, worse, illogical because we are ideologically motivated? Or is it rather the case that the five universally acknowledged premises do not actually generate the inference to the usual conclusion? I interpret the inference to the orthodox conclusion as invalid: the conclusion does not follow from the premises we have before us, because there are two mutually exclusive possible readings of the second premise just detailed, only one of which could be taken to support the conclusion. (Even were the second premise perfectly straightforward, as it does, indeed, seem to be, and even were we therefore justified in asserting the conclusion on the basis of the five

premises, we would be mistaken to interpret the conclusion as specifying an *explanation of development* – a point to which I return in later paragraphs.)

A FLAWED HEURISTIC?

Recall that premise 2 stipulates that simplifying the context of a system is advantageous if we want to learn about intrasystemic causal factors. Context simplification is usually achieved by holding certain factors constant while solving for others, and decisions about what to hold constant and what to investigate are pragmatically motivated, as already explained. However, the pragmatic dimension of these decisions renders the second premise crucially ambiguous: what counts as a system is not a matter of objective determination but is itself influenced by pragmatic factors, such that what counts as intrasystemic or extrasystemic is decided by a range of considerations and not, as it were, thrust at us by nature. Accordingly, our results are constrained by the experimental design and not the facts of nature.

Several systematic problems (what Wimsatt calls 'biases') are associated with environmental control as a context simplifier. First, context simplification is biased toward lower explanatory levels, so simplifying the environmental context stems from, and leads to, focusing on simple components of a system. Higher-level components of systems, and higher-level systems, are legislated out of epistemological and methodological existence in favour of lower-level systems and their components. Consequently, an investigator who simplifies the context in line with premise 2 may well be guilty of simplificatory asymmetry (Wimsatt 1986c: 300, 301). Second, we may be prone, should we forget or fail to appreciate the gravity of the simplifying assumption, to draw unjustified causal inferences; it is remarkably easy to fall into the trap of generating causal stories about genes against a constant environmental background (which itself exists only in the laboratory) – hence our fifth premise. We must be eternally vigilant, in simplifying the context, not to exaggerate the conclusions we draw.

I suggested earlier that premise 5 strikes us as entirely justified by appeal to premises 1 through 4. However, there is no necessity in my particular formulation of premise 5, nor in Sterelny and Kitcher's instantiation of this premise. Consider that, by parity of reasoning, we might just as well have (again for some pragmatic reason) postulated not an 'allele for' P^* but rather an 'extracellular environment for' P^* given standard allelic, cytoplasmic, and other environmental contexts (Gray 1992; Smith 1992; Mahner and Bunge

1997; Robert 2000c). That we do not postulate such 'extracellular environments for' does not imply that they do not exist; it implies, rather, that we have decided, for whatever reasons, that 'alleles for' are more important to establish. We are thereby guilty of explanatory asymmetry inasmuch as we a priori construe the relevant system in strictly reductionistic terms, thereby inviting inference to the conclusion that development is a genetic affair.

This result is fostered by only one of the 2 possible interpretations of premise 2. Both interpretations are heuristics in their own right. I shall refer to the suspect one as the 'hedgeless hedge' heuristic (HHH); the other, to be explored and defended in later paragraphs, is the 'constant factor principle' heuristic.

The phrase 'hedgeless hedge' is attributed to Roger McCain, who diagnosed hedgeless hedging as a major limitation of early sociobiological thinking (McCain 1980; see also Neumann-Held 1999). The notion, though, is more broadly applicable than that. A typical definition of 'hedging' is protecting oneself from loss or failure by undertaking a counterbalancing action, as in hedging one's bets by not placing all one's eggs in a single basket (an awkward mixture of metaphors, to be sure!). Hedgeless hedging is a win–win strategy, denoting a fail-safe type of hedging: one puts virtually all one's faith in *A* and relatively little in *B* and then attempts to establish *A* but not *B*; but betting on *B* at all (say, by publicly announcing that *B* is true, likely, or possible) provides a measure of safety just in case *B* and not *A*. Less formally, in proceeding according to the HHH, 'one admits the existence of an anomaly or problem of theory and then proceeds as though one had not. If one is then accused of neglecting the anomaly, one then produces the admission of its existence as conclusive evidence of one's innocence of the charge' (McCain 1980: 126). The hedgeless hedge is well characterised as a simplifying assumption, in particular a simplification of context: one admits the implausibility of the simplifying assumption but proceeds with the simple model nonetheless, generating results inadequate to the reality of the situation; when challenged, one refers back to the original admission of implausibility for exoneration.

McCain's example of this strategy is sociobiologists' treatment of inheritance. Although complexes of many genes (polygenes) are involved in the generation of any trait, for purposes of tractability the early models of sociobiological inheritance – such as that advanced in E.O. Wilson's *Sociobiology: The New Synthesis* (Wilson 1975) – reverted to one-locus theory, according to which we assume that one and only one gene is associated with a given inherited trait. As Wilson's mathematical models depend so heavily on one-locus theory, and the assumption of single loci is so inadequate to the reality

of both inheritance and development, the model is rendered immediately suspect. McCain observes that Wilson is well aware of his simplifying assumption, and Wilson notes that future models will have to take polygenism into consideration; but to take polygenism into consideration is so completely to undermine the model on which Wilson's treatment of sociobiology rests that the one-locus model itself is virtually worthless. Nevertheless, admitting the limitations of the model functions as a hedge against the probability that the model is in fact not at all a good one.

The HHH shares with all heuristics the property of fallibility, which is a function of the cost effectiveness of heuristic use. However, the failures of heuristics tend to be systematic rather than random, such that we might identify these failures and correct for them (often by applying a new heuristic). That is, thanks to the systematic biases of simple heuristics, we are able to learn from our false models in generating truer, more complex theories (Wimsatt 1987). What is unique about the hedgeless hedge is that the limitations of the heuristic are so obvious that, even though a hedgelessly hedged model may initiate the production of more adequate models, such models will themselves be so drastically different from the original model that its catalytic role may be overestimated. Moreover, the HHH wears its bias on its sleeve, implying that its putative openness is sufficient to make the heuristic appear honest and true. Unlike other context simplification heuristics, the HHH contains within itself the additional mechanism of theoretical exoneration, thereby providing an excuse for denying, say, complexity while nonetheless admitting the existence (and importance) of such complexity.

There are abundant examples of hedgeless hedging in biological research. Elisabeth Lloyd has explored a curious phenomenon, one that she refers to as 'ritual recitation' (my 'reflexive refrain'), whereby investigators favourably cite the papers of those who have challenged the investigators' theoretical framework, perhaps to demonstrate awareness of the ideas of detractors, but then proceed as if there are in fact no problems with the framework. According to Lloyd, there is 'a peculiar disconnect between what the authors explicitly acknowledge as serious theoretical and evidential problems, and how they actually theorize and evaluate evidence' (Lloyd 1999: 225).

In illustrating this claim, Lloyd discusses the emerging field of evolutionary psychology. According to Lloyd, central texts in evolutionary psychology are rife with footnotes citing, for instance, Gould and Lewontin's paper on the limits of adaptationism (Gould and Lewontin 1979), indicating awareness of problems of panadaptationist evolutionary theory, and sometimes acknowledging the need to avoid committing the errors Gould and Lewontin warn against. But, as Lloyd shows, these citations are smuggled into monographs

expressly giving adaptation by natural selection an exclusive role in the evolutionary origin of phenotypic traits. Accused of naive adaptationism, the authors may simply point to the references as putative evidence of their innocence. The issue here, as elsewhere, is 'a matter of the *actual weight given in practice* – not in lip-service' to the *B* term of the HHH (Lloyd 1999: 226).[1]

HEDGING ABOUT THE HOMEOBOX

Ritual recitation as an instance of hedgeless hedging is evident in philosophical commentaries on biology as well as in actual biological practice. But philosophers tend to go beyond ritual recitation in their application of the hedgeless hedge, building more sophisticated safeguards into the heuristic. Consider Alex Rosenberg's use of this heuristic in his critical analysis of physicalist antireductionism. Rosenberg defines physicalist antireductionism as the coupling of two theses: 'physicalism – the thesis that biological systems are nothing but physical systems, with antireductionism – the thesis that the complete truth about biological systems cannot be told in terms of physical science alone' (Rosenberg 1997: 446). He identifies this sort of coupling as a consensus view amongst philosophers of biology, and he interprets recent findings in developmental molecular biology as a substantive challenge to physicalist antireductionism.

Following Lewis Wolpert, Rosenberg asserts that, from 'the total DNA sequence and the location of all proteins and RNA' (Wolpert 1994: 571), we could predict the development of an embryo or, alternatively, compute, or even construct, the embryo.[2] Of course, as will be demonstrated in the paragraphs that follow, genetic research does not aim at the study of development as such, but rather strictly at the role that genes play against a constant developmental background (van der Weele 1999: 24); but Rosenberg takes the additional, unwarranted step of interpreting the genetic research as providing a complete explanation of development.

Rosenberg is interested in a class of genes known as the 'homeobox genes'. Widely, though problematically, referred to as 'master genes', the homeobox genes are often interpreted as crucial developmental switches which 'trigger' large numbers of downstream genes in the generation of complex structures, such as eyes (Robert 2001a). Rosenberg asserts the 'computability' of the embryo from a small number of 'stock elements', particularly DNA, RNA, and proteins, as directed by members of the class of homeobox genes. To avoid triviality, Rosenberg places what he takes to be a necessary constraint on the computability claim, namely that a computable algorithm must not advert to

any cellular structures 'not themselves "computable" from the nucleic acids and the proteins that compose the fertilized egg' (Rosenberg 1997: 450). That said, he asserts that the essence of developmental molecular biology is to assume certain constant factors (e.g., inherited cellular structures and environmental context) and then to explain the whole of development 'without adverting further to ineliminable cellular physiology' (p. 455).

In defending this claim, Rosenberg ritually recites what he takes to be a truism, namely that 'the molecular developmental biologist cannot simply build an eye, still less an animal *in vitro*, by combining the right macromolecules in the right proportions in the right sequence, in the right intervals' because 'the cellular milieu in which these reactions take place is causally indispensable' (Rosenberg 1997: 454). Rosenberg thus subscribes to the interactionist consensus. So committed, he proceeds to interpret the role of the *Eyeless* gene and its homologues in eye morphogenesis against such a supportive background. He makes the claim:

> one of the most complex of organs is built by the switching on of a relatively small number of the same genes, across a wide variety of species, and that the great differences between, say mammalian eyes, and insect eyes, are the result of a relatively small number of regulatory differences in the sequence and quantities in which the same gene products are produced by genes all relatively close together on the chromosome, and that these genes build the eye without the intervention of specialized cellular structures beyond those required for any developmental process. Identifying the other genes in the cascade that produces the entire eye should in principle be a piece of normal science, which will enable the developmental geneticist to 'compute' the eye from nucleic acids and proteins alone. For if switching on *Eyeless* can create the eye, surely its creation is 'computable' at least in principle. (Rosenberg 1997: 454)

As there is no room in this story for causal explanations above the molecular level, physicalist antireductionism falters.

The in-principle computability of the embryo from a description of DNA, RNA, and proteins (the *A* term in the HHH) is by definition set against a constant background of supporting factors (the *B* term). If challenged, Rosenberg may point to his admission of their importance as evidence that he is guilt free. Rosenberg hedges here by defining core elements of the constant background, notably cell structures and activities, as themselves computable in the same way the rest of the embryo is. He does this in order to avoid triviality, as already noted. However, if we grant him this move – and we should not – then his conclusion follows necessarily.

Rosenberg attempts to defend the controversial move in two ways. First, he asserts that 'cellular structures only come into existence through the molecular processes that precede them. There is in developmental molecular biology therefore no scope for claims about the indispensable role of cellular structures in these molecular processes. The future cannot cause the past' (Rosenberg 1997: 455). Of course, no one is claiming that causation works against the arrow of time; but even if molecular processes do indeed occur before (and concurrently with, and after) cellular processes, it is an open question whether cellular processes and structures are in fact explicable (or even predictable[3]) from a description of molecular processes and structures. Rosenberg forecloses the question by sleight of hand in requiring that cellular structures be computable; momentarily, I will show that this foreclosure is suspect.

Rosenberg's second strategy is to claim that the very possibility of ever explaining development turns on the particular features of the computability claim he endorses: 'unless the vast diversity of form is . . . explainable from a tractable base of a relatively small number of regulatory and structural genes (and their protein products) combined by a similarly small number of combination rules, *we can surrender all hope* of any completeness and generality in the [sic] understanding how diversity in development is possible, let alone actual' (Rosenberg 1997: 451). Thus either we succumb to Rosenberg's conclusion or give up on understanding development altogether.

Most developmental biologists would, with justice, take issue with this putative dilemma. Developmental biologists almost uniformly hold that development is hierarchical, characterised by the emergence of structures and processes not entirely predictable (let alone explicable) from lower-level (e.g., genetic) properties of the embryo. A leading example of the fact that the development of an organism is not fully prescribed in its inherited zygotic or maternal DNA is cellular behaviour during morphogenesis. Despite Rosenberg's admonitions, cells' collective behaviour during morphogenesis simply cannot be either predicted or explained by examining the behaviour of individual cells (or, for that matter, DNA) prior to cell division, differentiation, or condensation (Hall and Miyake 1992, 1995, 2000; Hall 1999, 2000a). This is because the formation of cell condensations is contingent not on the directives of some imagined genetic programme but rather on the spatiotemporal state of the organism and its constituent modules. Developmental biologists, therefore, hold to a kind of physicalist antireductionism, offering the methodological advice that we must engage in multileveled investigation of ontogeny in order not to miss key features at microlevels, mesolevels, and macrolevels. Moreover, and again despite Rosenberg's

admonitions, these biologists *qua* physicalist antireductionists are not confined to providing mystical pseudo-explanations; even a cursory look at the field of developmental biology today provides striking evidence that the quest to understand development beyond the genome is progressing apace. In other words, Rosenberg's preferred vision of developmental biology is not the only one – let alone the best one – available.

Rosenberg implausibly contends that a full explanation of development will have 'no room' for any reference to cell physiology, or anything else above the level of 'the molecular processes that subserve development'. He argues that, 'just as cell–cell signaling is ultimately to be cashed in for a chain of molecular interactions that extend from one stretch of nucleic acids to another across several lipid bi-layers (the cell membranes), all other cellular structures implicated in the machinery of differentiation will eventually have to be disaggregated into their molecular constituents, if development is fully to be explained' (Rosenberg 1997: 455, 454). However, it is not clear that such disaggregation constitutes an adequate explanation at all, though Rosenberg assumes that it does, for a microreduction may be no more explanatory than a macroreduction, especially if we do not adequately understand the mesolevel phenomena.

We cannot assume, as Rosenberg would have us do, that the background factors are computable as imagined. As this assumption is a hedging tactic to avoid triviality, we need not grant Rosenberg's conclusions about physicalist antireductionism, the prospects for explaining development, or the wondrous powers of the homeobox genes. (I return to the homeobox genes in Chapter 2.)

BEYOND THE HEDGE

The difficulty with the HHH in the context of development is that it amounts to paying lip service to development rather than taking it seriously. But what would it mean to take development seriously? I suggest that what we need is a better, less suspect variant of a context simplification heuristic, a more honest one, one more adequate to investigating biological reality, and one less likely to yield inference to an inappropriate conclusion about development. Following J.H. Woodger (Woodger 1952), I refer to this alternative interpretation of the second premise as the 'constant factor principle' heuristic (or CFPH).

Writing a half-century ago, Woodger noted the importance of heuristics in biological experimentation. For Woodger, as for others, the assumption

of constant factors is often a useful simplifying strategy in order to achieve experimental tractability. In attempting to understand how genes function, for example, we may assume that the environment is a constant factor; against a constant environmental background, we may then solve for phenotypic differences by exploring the genotype, that is, the variable factor (Woodger 1952: 186). Where such differences are found, we may account genetically for the existence of variations. The heuristic assumption of constant factors is methodologically commonplace, but it is by no means infallible, as should be evident from the discussion thus far. Nonetheless, I will urge here that Woodger's 'constant factor principle', interpreted as an heuristic, works against the particular biases of the HHH and so is a more legitimate simplification heuristic and a more appropriate interpretation of our second premise.

Considering Woodger's own example permits a further bias of context simplification through holding factors constant to emerge. The strategy of solving for genes by holding the environment constant presumes that there are only two sources of variation: genetic or environmental. However, other potential sources of variation are stochasticity and epigenetic interactions, neither of which is, strictly speaking, genetic *or* environmental – they result from development as such. Especially instructive is the work of Gaertner, who, over a period of thirty years, developed *genetically identical* strains of laboratory mice and rats and reared them under *identical environmental* conditions – and yet the mice and rats were, nonetheless, phenotypically *non-identical*, thereby demonstrating the existence of a source of ontogenetic variation that was neither genetic nor environmental (Gaertner 1990; Molenaar et al. 1993). Thus, phenotypic differences against a constant environmental background may not legitimately be presumed to be genetically based (or environmentally based), even though some versions of context simplification heuristics simply do not guide us to investigate alternative possibilities.

But the most encompassing problem with simplification heuristics, especially as instantiated in hedgeless hedging, is the tendency to downplay or simply neglect the causal significance of those factors held constant. Consider loss-of-function experiments. A typical loss-of-function experiment is one in which, against a constant background, a particular gene is manipulated so that it is not expressed at the right time and place; the investigators then observe the phenotypic outcomes and conclude that the outcomes are caused by the misexpressed gene. However, often investigators will, in the absence of a complementary gain-of-function experiment, draw an additional, unwarranted conclusion, namely that the gene, when properly expressed, is itself causally responsible for the correct phenotypic outcome. This latter inference