

Interpreting the homeobox: metaphors of gene action and activation in development and evolution

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SUMMARY Despite countless research efforts to demonstrate the precise developmental and evolutionary nature of homeobox genes, we are far from consensus on the role of this class of genes in development and evolution. This essay

attempts to clarify the debate and to nip some problematic interpretations in the bud, by exploring metaphors of homeobox gene function in development and evolution.

INTRODUCTION

The past quarter century has witnessed the discovery of the homeobox genes, a class of genes highly conserved across long-diverged phyla and believed to play a significant role in the generation and evolution of organisms from plants to people. Their discovery was heralded, in retrospect, as “one of the major scientific breakthroughs of this century” (Ruddle 1998, p. ix). Recently, sometimes outlandish but always bold claims about homeobox genes have appeared in a wide range of books and journals. Such claims have begun to excite philosophers as well (e.g., Rosenberg 1997). The scientific literature on homeobox genes ranges from experimental results and careful reviews through tracts best construed as propaganda. The philosophical and social-scientific literature too often builds on the latter, rather than the former. In this essay, I remedy this problem by exploring a full range of interpretations of the role of homeobox genes in development and evolution.

The homeobox is a sequence of 183 nucleotides encoding 61 amino acids. Identified first in the fruit fly *Drosophila*, it has now been found in a wide variety of organisms, including yeast, plants, and all animals. The homeobox, shorthand for “homeotic box,” builds on William Bateson’s 1894 notion of homeosis, according to which part of an embryo is transformed (in development) into another structure, hence, homeotic mutations such as the replacement of halteres with wings in *Drosophila*. The amino acid-specified homeodomain is a DNA-binding domain regulating specific DNA-protein interactions, thereby influencing DNA transcription. The proteins produced via homeoboxes play a variety of developmental roles, typically involving the regulation of cell pattern and the activation of other genes instrumental in the formation of basic body plans.¹ This is why homeobox genes are often referred to as

“master control genes,” setting in motion a complex of processes necessary for the formation of, for example, heads or limbs.

Of considerable evolutionary interest is what to make of the growing consensus that although vertebrates and arthropods “have strikingly different body architectures, many of the regulatory genes they use to establish their body plan are conserved” (Kmita-Cunisse et al. 1998, p. 3030; for elaboration, see Gilbert 1997; Gehring 1998; Schlichting and Pigliucci 1998; Hall 1999). That is, the “same” homeobox genes are thought to initiate vastly different *Baupläne* in vastly different species. But what exactly does it mean to say that mice, worms, fruit flies, humans, and yeast have the same homeobox genes? In the case of the homeotic complexes of *Drosophila* and vertebrates, for instance, four aspects of similarity coalesce in the judgment that homeobox genes are conserved across phyla. Firstly, the base-pair sequences of homeotic genes across taxa are remarkably alike; secondly, homeotic genes in vertebrates are present in the same chromosomal order as homeobox genes in *Drosophila*; thirdly, the expression pattern along the anterior-posterior body axis is the same in both vertebrates and fruit flies; finally, “the enhancer region of a human homeotic gene, such as *deformed*, can function within *Drosophila* to activate gene expression in the same relative position as in the human embryo—in the head” (Gilbert et al. 1996, pp. 363–364).

In this article, I explore the developmental and evolutionary inferences we are entitled to draw from the claim that develop-

¹ Sometimes very large numbers of genes are so activated. One homeobox gene, *Ultrabithorax*, may be involved in regulating the activities of as many as 170 genes in *Drosophila* (Mastick et al. 1995), which is a tiny number compared to Gehring’s estimate that 2500 of *Drosophila*’s genes are regulated, directly or indirectly, by *eyeless* (Gehring et al. 1995).

mental “cascades” in different taxa are apparently initiated by the same phylogenetically conserved genes. Though empirical considerations are of prime concern, I will consider conceptually what is so far established, in an effort to guard against certain unsavory interpretations currently in circulation.

INDIVIDUAL ONTOGENIES

It is easy to get the impression that for much of the past 80 years, it has been widely (though not universally) accepted that development is best construed as differential gene expression (e.g., Morgan 1919, p. 241). There are both strong and moderate versions of this view of development. The strong version is that DNA contains “a precise developmental program which controls ontogeny” (Gehring 1985, p. 3). Walter Gehring, one of the discoverers of the homeobox genes, subscribes to this strong thesis, holding that investigation of the homeobox has demonstrated “how much of the developmental program is written into our genes” (Gehring 1998, p. xi). For Gehring, “the genetic program” of the homeobox genes “controls development and evolution” (*ibid.*, p. xiii).

The moderate version of the ontogenetic claim is that DNA, as part of what is passed on from generation to generation (in addition to, among other things, the extranucleic elements of a structured egg), is a prime instigator of development, regulating gene and protein activities in the developing organism. On this latter view, instead of being “master genes,” homeobox genes are switches or selectors (e.g., Gilbert et al. 1996).

As for the strong version of the ontogenetic role of genes, there has long been fervent scientific opposition to such genetic determinism.² Nevertheless, notions of “genetic programs” and “genetic instructions” persist, especially in the work of geneticists studying development. I will briefly review certain well-known facts about DNA, which point out the dubiousness of the idea of a “genetic program,” and then attend to the more plausible, and increasingly widely held, weaker view of the ontogenetic role of genes.

DNA is a relatively inert molecule, requiring activation from without. In eukaryotes, DNA is coated by histone proteins and therefore not immediately accessible without cellular triage (Mahner and Bunge 1997). The function of DNA is delimited by the cellular environment in which it is embedded (Wolf 1995; Bissell et al. 1999; Hall 1999). This cellular environment is complex: in eukaryotic cells, the “ribosomal machinery itself consists of a giant assemblage of sub-units together containing

more than 80 different proteins, and RNA sequences containing more than 6,700 nucleotide bases. Without it, without the complex biochemical environment the cell provides, ‘genes’ . . . simply can’t function” (Rose 1997, p. 128).

The cellular environment of gene activation is irreducibly spatiotemporal as well, depending on the developmental history of the particular cell in which it is located—particularly, the cell’s location in the developing embryo and its time of appearance. Thus, genes are not passive providers of encoded instructions that retain their structure across generations, but, rather, “reactive complexes that are in constant and dynamic interaction with their carriers” (Plotkin 1994, p. 39). In the generation of an organism, segments of DNA interact with proteins, metabolites, nutrients, and other segments of DNA according to a structured (though flexible) schedule within specific environments, which enables such interactions and which are necessary for their occurrence (Nijhout 1990; Wolf 1995). This much is granted by all concerned, even though some researchers fail to see how the irreducibility of the developmental context challenges the notion of a genetic program for development.

But other researchers draw alternative lessons from the context dependency of gene function. Some hold, for instance, that despite the fact that certain of these complex processes appear to operate in a programmatic way, there is no evidence of a program for development encoded in the genes. Thus, “program in this context is an *a posteriori* description of a structure, and not an *a priori* instruction for generating a structure” (Wolf 1995, p. 143; see also Oyama 2000a). The same stretch of DNA can have different phenotypic effects at different times in the life cycle of the organism; moreover, which stretches of DNA count as “genes” is also dependent on spatiotemporally specific environmental conditions. Thus, “instructions” are not “just there” in the DNA to begin with, and so they are not preprogrammed; developmental information emerges during ontogenesis from cells and DNA in the developmental context described above. “The basic DNA sequence and the developmental context determine in reciprocal contingency the structure (and function) of all regulatory sequences of transcription or translation; they *co-define* and *co-construct*” (Neumann-Held 1999, p. 119; see also Nijhout 1990).³ From this perspective, there is no underlying genetic pro-

² See, e.g., Nijhout (1990) and Wolf (1995). Virtually unknown to working biologists, a useful perspective on problems with genetic determinism is that of adherents to developmental systems theory (DST), also known as developmental constructionism. The locus classicus of DST is Oyama (2000a); see also Gray (1992, 2001); Griffiths and Gray (1994); Oyama (2000b).

³ Compare also Burian (1997, pp. 259–260): “It is clear that many incredibly intricate multi-level domains, mechanisms, processes, structures, and so on enter into development. Furthermore, many of these are formed (pardon the pun) ‘on the fly’—that is, they are not laid out in advance but arise in interactions between genes and proteins that come to form a rapidly-shifting tartan of boundaries between domains and define something like morphological fields in the midst of ongoing processes of cell-type specification, tissue formation, organogenesis, etc. At any stage of development some of the relevant modules that enter into normal development preexist, others are formed in the course of events, and others will or will not be formed according to the status and condition of interacting units and modules at key moments in the processes in question.”

gram or set of instructions, but simply the deeply felt illusion of their existence (see also Dover 2000; Newman and Müller 2000).

Those persuaded of the nonexistence of genetic programs, though reluctant to let go of the idea of a program for development altogether, may find solace in the recent work of Evelyn Fox Keller (2000, 2001). Drawing on the history of the introduction of the very notion of a program in biology in the 1960s, Keller has argued convincingly in favor of a distinction between a “developmental program” and a “genetic program for development.” A genetic program is localized in the DNA (or, alternatively, the genome or the chromosomes) and putatively serves as both instruction set and builder. A developmental program, by contrast, is non-gene-centric, dispersed throughout the egg, and consists in “the interactive complex made up of genomic structures and the vast network of cellular machinery in which those structures are embedded” (Keller 2000, pp. 100–101). Gehring conflates the two notions: though he uses the phrase “developmental program,” he argues that such a program is located “in the genes.” It is important, however, to keep the two notions of program distinct, according to Keller, for if there is in fact a program for development, we have every reason to believe that it is cellular rather than nuclear.

Given these caveats, in what sense could homeobox genes—or any other genes—be master control genes in development? Gehring’s claim, as noted above, is that the homeobox genes are the first active genes leading to a particular outcome; these genes activate a series of other genes, leading eventually, in the case of the gene *Antennapedia*, for example, to leg morphogenesis. The claim breaks down at several points. First, homeobox genes are not the first active genes in the embryo—mesoderm is genetically induced at the cleavage stage, for instance, long before homeobox genes are activated. Secondly, as should be evident given the context dependency of gene activation, a large number of interacting agents and processes must be in place for *Antennapedia* to function at all, for *Antennapedia* does not arise from nowhere and operate in a precursorless (and postcursorless) void. Without the developmental system there simply is no flow of information starting from the DNA, and so no master control genes (Neumann-Held 1999).

Though we may find a gene whose product is necessary for a given developmental event to occur, it is a mistake to think that the causal pathway ends (or begins) there. “The causal pathway is endless and involves not only genetic, but manifold structural, chemical, and physicochemical events, a defect in any of which can derail the normal process” (Nijhout 1990, p. 442). Thus putative master control genes are themselves controlled, and so the strong thesis that homeobox genes contain a master program for development fails.

Antennapedia, Gehring’s gene of choice, is involved in selecting between alternative developmental pathways. Thanks in large part to his commitment to the strong thesis that a genetic program contains the entire organism in potentia, Gehring prefers the “master control gene” trope to something both

more accurate and less baggage-laden—for instance, “switch” or “selector” gene—to describe homeobox genes. Such an alternative would be in line with the recent work of many researchers; in fact, the switch or selector interpretation of homeobox genes is far more common in the literature than the master control gene notion, which tends to be expressed in more popular literature (such as Gehring 1998 and Schwartz 1999a).

Consider Gilbert, Opitz, and Raff’s (1996) framework for evolutionary developmental biology within which any talk of master genes is out of place. Significantly, though they are fully cognizant of the importance of genes and gene products in development and evolution, their perspective has its basis in developmental biology and not in genetics. A central organizing concept for Gilbert et al. is the morphogenetic field, a concept once fundamental in embryology, before the discipline was superseded by genetics. Roughly, a morphogenetic field is a bounded, modular “web of interactions” within which the functions of cells are determined by their relative positions and interrelations. Within the field, genes and gene products and other elements of the web work in concert to effect morphogenesis. As no element of the web exerts a dominating influence, there is no place for dominant “master control genes” (historically, the morphogenetic field was in competition with the gene as controller of development). But Gilbert et al. still retain a focus on homeobox genes as of crucial importance within fields. So construed, homeobox genes may be better understood as selector or switch genes, themselves regulated in initiating an effusion of interreactions.

This more moderate thesis about the role of homeobox genes in development may or may not be satisfactory. Even in the careful hands of Gilbert et al., it is possible for notions of genetic control, though not of mastery, to intervene in morphogenetic fields: they write of “genetically defined interactions among cells” (1996, p. 367), for instance. An alternative view is that cellular interactions are not determined by genes, but rather by the developmental context (of which genes are one part). From this latter perspective, “in a system in which every component, and past history, all have come together at the right time and in the right proportions, it is difficult to assign control to any one variable, even though one may have a disproportionate effect” (Nijhout 1990, p. 442). It appears as if it is this notion of “disproportionate” genetic effects that Gilbert et al. want to rescue, as opposed to other recent incarnations of morphogenetic fields within which genes are unimportant (Gilbert et al. 1996). But, there are two problems here.

Firstly, it is certainly possible to conceive of the (important) role of genes in ontogeny (and evolution) without recurring to problematic theses about genetic control. Secondly, we must recognize that whether genes have a disproportionate effect depends on the sorts of questions we are asking, the assumptions we are making, and the experiments we are running. To be sure, genetic research does not aim at the study of development as such, but rather strictly at the role that

genes play against a constant background of enabling factors (van der Weele 1999), which is then sometimes taken as a full explanation of development (e.g., by Rosenberg 1997). But these so-called background conditions are more important than is typically assumed; some may in fact be just as necessary as homeobox genes in the establishment of body plans and parts. A misexpressed homeobox gene may well lead to a new pattern ectopically, but only if the appropriate downstream targets are present at the new site. “When it comes to the downstream targets of the *Hox* genes, context is everything, in particular, which other transcription factors are present in the same cell will be a key factor determining the outcome of *Hox* gene action” (Akam 1998a, p. R678). This is the point of my earlier claim that homeobox genes do not operate, as it were, context-freely, void of postcursors.

Now, does this mean that each ontogenetic component contributes equally in development? The question is ill-formed. If the background conditions are held constant, then any variation is genetic (or epigenetic). But if the genes are held constant, then any variation will be due to other elements of the developmental context. What sense can be made of a proposal to then determine, in some global sense, the relative contributions of genes and other interactants? Whether one component or another has a disproportionate effect is fully context-dependent and will vary with time (Sober 1988).

One response could be that the genes are the hereditary material and are therefore of especial ontogenetic significance. But such an objection is disingenuous in that it ignores all else that is transmitted between generations, for instance, the complex cellular machinery containing the genes. A broader (and more accurate) conception of transmission would encompass whatever heterogeneous ontogenetic resources are reliably present in successive life cycles (Oyama 2000b). As DNA does not exhaust transgenerational inheritance, to solve for development by solving for genes is to present but part of the story—an important part to be sure, but not necessarily the most important part, and not to be mistaken for the whole truth.

Gehring is not alone in making this mistake. The philosopher Alex Rosenberg, influenced by Gehring’s work (Gehring et al. 1995) as well as that of Lewis Wolpert (1994), contends that homeobox genes build eyes by controlling downstream genes (against a constant, nonspecific background), such that the developmental geneticist may simply identify the downstream genes and thereby “‘compute’ the eye from nucleic acids and proteins alone.” There is no need, according to Rosenberg, to invoke any upper-level causal explanations (such as at the level of cell physiology), simply because in his view these upper-level structures are themselves computable from DNA. Having identified the homeobox genes controlling eye morphogenesis, all that remains in explaining development is to fill in the downstream blanks at the genetic level (Rosenberg 1997, pp. 454, 455).

Rosenberg is simply mistaken here. The development of an organism is not fully prescribed in its inherited zygotic or mater-

nal DNA. Rather, development is hierarchical, characterized by the emergence of structures and processes not entirely predictable from lower-level (e.g., genetic) properties of the embryo. For instance, how cells behave collectively during morphogenesis cannot be predicted by examining the behavior of individual cells prior to cell division, differentiation, or condensation, let alone by examining gene sequences (Hall 2000; see also Hall 1999). The very presence of the downstream targets of homeobox genes is due to the synergy of genetic, epigenetic, and environmental factors, not to genetic predetermination. Contra Rosenberg, then, developmental biologists must engage in multileveled investigation of ontogeny in order not to miss key features at micro-, meso-, and macro-levels.

The meaning and the function of homeobox genes are context-dependent. Therefore, such genes are, at most, important (though perhaps not necessary) (Strohman 1993) switches between particular pathways of organismal development. Again, though, caution is required; the metaphor of a “switch” may imply binary fixity: the switch is either on or off. But few aspects of organismal development are so inflexible. Consider Waddington’s (explicitly metaphorical) notion of an “epigenetic landscape.” An epigenetic landscape is an undulating terrain, comprising both valleys (or “chreodes”) and peaks. The chreodes are not independent but rather occasionally intersect; further, they begin as shallow indentations and gradually deepen as one moves from the top to the bottom (or as one proceeds through the ontogenetic cycle).

A ball at the top of the landscape diagram represents a system (e.g., a totipotent or pluripotent cell), and its development is represented by the movement of the ball from the top to the bottom of the diagram through the valleys (developmental pathways). Multiple pathways may lead to the same outcome, but of course not all pathways converge. A (by necessity small) lateral change anywhere along the course might (but will not often) lead to some change in outcome, as the valleys serve as buffers. Further, the likelihood of a larger change in outcome (a shift between valleys) being produced by a small lateral change may be increased if the change is early, and diminished if the change is late. Moreover, any lateral change brings with it consequences about future developmental opportunities; the possibility of achieving a particular outcome may be increased or decreased, depending on the developmental history of the cell.⁴

⁴ I take no position here on whether changes early in development are more likely to be disadvantageous for the embryo than changes late in development. Wimsatt (1986), in accord with von Baer, has long argued that changes early in ontogeny are likelier to be maladaptive, because early ontogenetic events are likelier than later ones to support a significant number of downstream effects; thus, alterations in early events will often lead to severe consequences downstream. Raff (1996) believes that there are too many exceptions to this supposed rule for it to hold true. For a recent discussion of this dispute see Sterelny (2000).

Development begins with the ball/cell proceeding downward, pushed into an initial chreode, until reaching a bifurcation point (an intersection with another chreode). Again, the ball takes one or the other course and proceeds downward until the next bifurcation point, and so on. The “decision making” at each bifurcation point is not predetermined genomically; rather, the “instantaneous epigenetic state” regulates the decision; it is determined contextually by the state of the system (M. Moss 1981).

How best to capture this notion of decision making at bifurcation points? Switching is, of course, one possible metaphor, as in a light switch. It is either “on” or “off.” But development may be less like a light switch than like a switch in a train yard (Needham 1936), selecting not between two but rather many possible tracks. And where such switches are binary, (many) switching decisions are not final, as long as the tracks intersect again. Some, such as Akam, cannot see switches as anything but binary, however. Akam has thus proposed a model of homeobox genes that “demotes” them from their status as stable binary switches somehow especially different from other genes: he reconceives homeobox genes more humbly as integrators of different types of positional information (Akam 1998b).

Contra Gehring and others, it is evident that homeobox genes are no less regulated than any other genes “by local signals, hormone receptors or any of the other stimuli that commonly mediate gene regulation” (Akam 1998b, p. 448). But homeobox genes are still very important ontogenetically, not least because in some cases they provide the best, and perhaps the only, way to channel particular developmental information from embryonic to later cells, though, contra Akam, this does not make homeobox genes “master control genes” (*ibid.*, p. 449). Drawing on the context dependency of ectopic pattern formation through misexpression of homeobox genes, Akam interprets homeobox genes as micromanagers (themselves managed), rather than switches (Akam 1998a, 1998b). Changing metaphors in this way may help to avoid misinterpretations of the evolutionary significance of homeotic mutations.

EVOLUTION BY MACROMUTATION?

There are two sets of possible implications of homeobox genes in the context of evolution. The first involves considerations about the phylogenetically widespread conservation of developmental mechanisms. The second involves claims about the nature of macromutations and the origin of species. Since the former has received more attention than the latter (Akam et al. 1994; Wray 1994; Akam 1995; Averof 1997; Purugganan 1998; Hall 1999), I will focus here only on the putative evolutionary significance of macromutations.

Homeosis has always been associated with saltationism. Bateson, who coined the term “homeosis,” “felt that he could

further strengthen Darwin’s case by exhaustively compiling the discontinuous variations that occur naturally within a species” (Lewis 1994, p. 341). One now standard and well-supported view of homeobox genes is that they are responsible (at least in part) for the evolutionary origin of body plans (Lewis 1994; Raff 1996; Gellon and McGinnis 1998). Paleontologist Jeffery Schwartz has recently taken this a step (or leap) further, invoking the role of homeobox genes in individual development as evidence of evolution by saltation (Schwartz 1999a, 1999b). Neo-Darwinians focus on microevolution, gradual evolution through the selection of minor adaptations, or what is often expressed as “the survival of the fittest.” But, we might ask, what of “the arrival of the fittest” (Gilbert et al. 1996)? While the neo-Darwinian contention is that incremental micromutations add up and eventually produce new species, Schwartz holds that macromutations, generated through changes in homeobox gene activity, offer a better explanation of the origin of new species.

Schwartz’s interpretation of ontogeny is *Hox*-genocentric. He suggests that in the production of feet and brains and “completely useful and fully formed eyes,” “*all that is necessary* is that homeobox genes are either turned on or they are not” (Schwartz 1999a, pp. 362, 368–369; italics added).⁵ It is worth noting briefly that this position is not quite the same as Gehring’s, for Schwartz emphasizes the timing of homeobox gene activity, not the activity as such; if timing is what matters, and timing is decided beyond the genome, then the “programmed in the genes” line may perhaps be sidestepped. Even so, Schwartz claims that “when particular genes are turned on for certain lengths of time and in certain regions, a worm may emerge. If the same or other genes are expressed for different lengths of time and in different regions, a more complex organism may develop” (Schwartz 1999a, p. 342). Such a suggestion is plainly false: worms do not produce frogs, no matter how many experimental manipulations of homeobox gene timing one performs. Worms produce worms. Although we may induce species *X*-specific structures in an organism of species *Y*, this is a long way from *X*s birthing *Y*s thanks to small changes in the timing of gene expression. For there is much more to development than the expression of homeobox genes—the whole of organismal reproduction, for instance.

Notwithstanding these difficulties, Schwartz postulates that homeobox genes “control everything” and “run the whole show.” Therefore, “since the morphologies that make up an organism ultimately derive from the turning on and off of homeobox genes, you would expect that evolutionary novelty would emerge abruptly, rather than through the accretion of

⁵ Presuming that the apparent sensitivity to light of ectopically induced eyes is enough to substantiate a claim to “functioning” (Gehring et al. 1995), the question of the usefulness of such homeotic mutations remains unresolved.

minute building blocks to make a whole structure.” Homeobox gene activity is thus construed as sufficient for speciation. According to Schwartz, “timing is everything,” making the difference between eels and elephants, or between stable lineages and hopeful monsters (Schwartz 1999a, pp. 36, 34, 44, 380): a recessive mutation in a homeobox gene will eventually become fixed in a population; when it reaches homozygosity, a number of monsters will be produced and mate among themselves, thereby beginning a new species.

If Schwartz were alone in holding such a position, toppling his radically unorthodox interpretation would be neither scientifically nor philosophically impressive. But aside from his mistaken sense that homeotic mutations are the only difference there is between fish and fowl, his notion of evolutionarily significant macromutations generated by homeobox genes is not completely far-fetched. In fact, it might simply follow from the idea that homeobox genes are binary switches and can induce ectopically. In other words, our metaphors of gene action in ontogeny may generate inappropriate interpretations in both developmental and evolutionary realms, and especially where they intersect. As Akam notes, “if selector genes work as stable binary switches, their role cannot change in small steps. They must be either ‘on’ or ‘off.’ Any mutation that alters the regulation of a selector gene will be a mutation of major effect, a ‘hopeless monster’ that is unlikely to be tolerated by natural selection” (Akam 1998b, p. 445). Schwartz may be said to have taken the (switch and) bait. Given the switch and master gene metaphors, others may be similarly inclined.

I have already identified some caveats about gene activation that generate significant problems for Schwartz’s view of homeobox genes. One I have not mentioned involves the heuristic role of particularly dramatic experiments. Sometimes, we overestimate what our experimental results actually show, or we generalize inappropriately. L. Moss has suggested that the persistence of the notion of a genetic program may be due in part to drawing unjustified inferences from viruses as model organisms. The attribution of agency to genes is facilitated by the dramatic evidence of the formidable effects that the introduction of a virus can have on an organism. The penetration of viral DNA (or RNA) can have a drastic impact on the behavior of an infected cell, and the observation of this impact may have led investigators to overestimate the agentic role of DNA in ontogenesis. But as Moss points out:

What becomes easy to overlook in the midst of such apparent power and efficacy is that viruses are molecular parasites whose ability to act entirely presupposes a living system, in relation to which the virus is a kind of trigger or perturbant. Shooting DNA constructs into a cell and shouting “Now dance!” does not constitute an explanation of the mechanisms by which “the genetic program informs and instructs ontogeny” or “supervise[s] its own precise replication and that of other living systems such as organelles, cells, and whole organisms” (even if the cell dances).

[L. Moss 1992, pp. 340–341; the embedded quotations are from Mayr 1982]

Something similar may be true in the case of interpreting the ontogenetic and evolutionary roles of homeobox genes. Instructive in this regard is Smith and Schneider’s (1998) reassessment of *Hox*-knockout experiments believed by many (e.g., Mark et al. 1995; Martin et al. 1995; Matsuo et al. 1995; Qui et al. 1995) to provide evidence of evolutionary reversals or atavisms in the first arch of mice. Matsuo and colleagues (1995), for instance, have studied the effects of failing to express *Otx-2* in mice. They interpret the results of their experiment as providing evidence of an atavistic palatoquadrate (an element of the upper jaw in nonmammalian vertebrates), and as suggestive of *Otx-2*’s possible evolutionary significance in establishing the neurocranium and key elements of the masticatory apparatus.

Smith and Schneider (1998) dispel claims about atavisms in the first arch in all the studies they review, demonstrating misinterpretations of morphology and homology and also failure to apply appropriate criteria for identifying atavisms. But Smith and Schneider also note the tendency of the investigators to interpret gene knockouts as evidence that, if the knockout produces a mutant phenotype, then the knocked-out gene is (fully?) responsible for the normal phenotypic trait. The mere experimental absence of a particular homeobox gene says nothing about the actual developmental mechanisms involved in the evolutionary modification (Smith and Schneider 1998). Moreover, genes do not produce traits directly; rather, they produce, in an appropriate, resourceful developmental context, still further developmental resources to be integrated into various ontogenetic pathways.

Smith and Schneider offer an alternative interpretation of the ectopic generation of cartilage in the mouse jaw. Drawing on the work of Hall and Miyake (1992, 1995), they suggest that cell condensations must meet a critical threshold in order to produce cartilage; whether that threshold is breached determines whether cartilages form. When development is disrupted in any number of ways, additional mesenchyme may collect, breaching the threshold, and so creating a cartilage where cartilage does not normally appear—without any recourse to explanation in terms of loss of *Hox*-gene function (Smith and Schneider 1998).

Below, I will provide an alternative hypothesis about homeobox genes in evolution to counteract Schwartz’s saltation scenario, just as Smith and Schneider have done with ectopic cartilage formation. My contention is that, even were Schwartz right about development, problems with his evolutionary interpretation would remain. Firstly, although he provides a possible evolutionary scenario, he provides no evidence whatever that speciation has in fact occurred through homeotic saltations. Secondly, the homeotic saltation scenario ignores the other morphogenetic transformations required for a change in the timing of homeobox gene expression not to be deleterious. Consider the feeding appendages of crustaceans; these are intricate, integrated units, as are all organis-

mal features. If it were shown that an alteration in the timing of homeobox gene expression results in a homeotically transformed feeding appendage, an outstanding problem may well remain, namely that of “the integration of the new morphology into the functional complex that is an animal as a whole”: not only would the new appendage need to be integrated with the other feeding appendages, but alterations in muscles and in the nervous system would be similarly required. Or consider that bithoracic fruit flies (that is, flies with an extra pair of wings) are nonetheless incapable of flying, and this for two reasons: the musculature of the fly is not accordingly altered homeotically to accommodate the extra wings and, more basically, the body plan of the fly is not aerodynamically suited to two pair of wings, but only to the usual single pair (Budd 1999).

Budd offers a hypothesis about homeobox genes in evolution that is vastly different from Schwartz’s. Budd’s evolutionary suggestion is that morphological change of evolutionary significance is not initiated or driven by changes in homeobox gene expression. Given that homeobox genes offer an efficient way to channel developmental information and build particular body plans, Budd’s notion of “homeotic takeover” suggests that homeobox genes are employed after the fact to streamline developmental processes once gradual (micromutational) morphological change has occurred (Budd 1999).

Budd notes that homeotic takeover is related to Waddington’s notion of genetic assimilation, whereby, over time, nongenetically (e.g., environmentally) induced aspects of morphogenesis may be assimilated into the genome (Budd 1999; Waddington 1961). I suggest that homeotic takeover is a token of Weiss and Fullerton’s more general notion of “phenogenetic drift” (also clearly related to genetic assimilation). Phenogenetic drift refers to the process of different genotypes being associated, over time, with the same phenotype, through genetic substitution. Since selection acts on phenotypes (not genotypes), these different genotypes will be indistinguishable to natural selection. Weiss and Fullerton propose, as against Dawkins-style neo-Darwinism, that “genes may be better understood as having a phenotypic *raison d’être*” (Weiss and Fullerton 2000, pp. 188, 189, 188). Perhaps the same is true of homeobox genes.

Consider Newman and Müller’s (2000) idiosyncratic but ultimately very useful interpretation of the relationship between genetics and epigenesis. Waddington coined the term “epigenetics” to marry genetics with the ancient but updated notion of epigenesis, the view that organismal development involves an increase in complexity over time (as against preformation, the idea that individual development just is the growth of a preformed miniature without an attendant increase in complexity).⁶ Recently, “epigenetics” has been used to refer to mechanisms of gene regulation; epigenetic mech-

anisms thus include DNA methylation, genomic imprinting, and chromatin restructuring (Peterson and Sapienza 1993; Jablonka and Lamb 1995; Riggs and Porter 1996).

Newman and Müller, however, invoke a “pre-Mendelian” (or pregenetic) interpretation of “epigenetic mechanisms” whereby these are “conditional, non-programmed determinants of individual development” such as tissue-environment (both exogenous and endogenous) and tissue-tissue interactions (Newman and Müller 2000, pp. 305–306). For Newman and Müller, “as evolution proceeds, genetic change that favors maintenance of morphological phenotype in the face of environmental or metabolic variability co-opts the morphological outcomes of epigenetic processes, resulting in the heritable association of particular forms with particular genealogical lineages.” On this alternative interpretation of epigenetics, “the correlation of an organism’s form with its genotype, rather than being a defining condition of morphological evolution, is a highly derived property” (2000, pp. 306, 304).

As morphological change proceeds gradually and epigenetically (in Newman and Müller’s sense), homeotic takeover, as an instance of the more general phenomenon of phenogenetic drift, provides a model for homeobox genes as efficient micromanagers advantaged by natural selection.

Of course, although these alternative models count against the homeobox theory of evolution by saltation, they do not by themselves disprove saltationism. Budd (1999) knows this, and therefore marshals additional arguments against the latter position. Meanwhile, Schwartz does not himself dismiss altogether the import of microevolutionary processes, though he is at a loss as to how to explain the origin of species in strictly gradualist terms (Schwartz 1999a). There certainly is something to the suggestion that the neo-Darwinian view of evolution is incomplete (Arthur 2000), but investigating what is missing is a task best left for another occasion. It is sufficient for now to have shown that (1) the identification of changes in homeobox gene expression does not (ultimately or otherwise) explain development, but only, at best, provides insight into gene activation, which is a subsidiary question;⁷ and (2) the ontogenetic activity of homeobox genes is not evidence that evolution has proceeded via homeotic mutations of major effect.

CONCLUSION

Homeobox genes certainly are important in evolution and ontogeny, but not for some of the usually cited reasons. The

⁶ See Thom (1989) and Hall (1992); see also Pinto-Correia (1997) for a fascinating history of preformation.

⁷ Whether they even explain gene activation is unclear, given the linearity and unidirectionality of models of developmental “cascades” as against more adequate models of (nonlinear, multidirectional) feedback elements of morphogenetic fields or networks; see, e.g., Freeman (2000), Keller (1999, 2000), and Solé et al. (2000).

conservation of the same homeobox genes across distantly related phyla surely has evolutionary implications, even if not in the ways some have imagined. And while homeobox genes are not master control genes, they are nonetheless crucial interactants in development. My twin conclusions are that we should consider the possibilities that homeobox genes have played a derived, not a driving, role in evolution; and also that homeobox gene action, like all gene action, is deeply embedded in the developing organism, itself deeply historically and ecologically embedded.

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