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Letter

The Generation of Novelty: The Province of Developmental Biology

In his op-ed piece, "Forty years a philosopher of biology: Why EvoDevo makes me still excited about my subject," Michael Ruse (2006) presents a tamed version of EvoDevo which will trouble no waters and which would integrate easily into the existing framework of evolution proposed by the population geneticists of the 1930s. In that paper, and even more explicitly at the conference "The Making Up of Organisms" (Ecole Normale Supérieure, Paris, June 8–10, 2006), Ruse opined that natural selection alone has the power to create evolutionary novelty. In both instances, he cited our 1996 paper (Gilbert et al. 1996) and quoted the following paragraph from it:

> The homologies of process within morphogenetic fields provides the best evidence for evolution—just as skeletal and organ homologies did earlier. Thus, the evidence for evolution is better than ever. The role of natural selection in evolution, however, is seen to play less an important role. It is merely a filter for unsuccessful morphologies generated by development. Population genetics is destined to change if it is not to become irrelevant to evolution as Newtonian mechanics is to contemporary physics.

Strong words. But I would contend that the past decade has proven those words remarkably accurate. Ruse, on the other hand, declares them to be "hogwash." "Hogwash" is a technical term in American rural philosophy, meaning "I don't have the data, but I know it to be wrong." Taking a leaf from the Creationists' instruction manual (e.g., Wells 2005), Ruse then portrays the EvoDevo statement as being anti-Darwinian, continuing, "I think that Charles Darwin himself would be incredibly excited by the findings of EvoDevo—he was ever fond of embryology—and argue that EvoDevo will complement natural selection, not contradict it." Michael, the supplementation of natural selection is precisely what EvoDevo is trying to do. Take for instance the question of how novelties of the arthropod body plan arose. Hughes and Kaufman (2002) begin their study, "To answer this question by invoking natural selection is correct—but insufficient. The fangs of a centipede . . . and the claws of a lobster accord these organisms a fitness advantage. However, the crux of the mystery is this: From what developmental genetic changes did these novelties arise in the first place?" Even in the 1996 paragraph quoted above, we merely thought to give natural selection a less important role, not abandon it. Similarly, in all of my writings on EvoDevo (e.g., Gilbert 2003, 2006), I have stressed the complementary nature of the population-genetic approach and the developmental-genetic approach. However, where we differ is that I think that natural selection has to relinquish its claim to being the sole (or even the major) mechanism for generating diversity. Natural selection oversteps its bounds when its advocates claim that it both generates and selects variation. Generating variation is the province of development.

The notion that natural selection could create variation exists because until recently the only genetics available to explain evolution was population genetics. Genetics was (as Kettlewell would claim), "Darwin's missing evidence." But both *population* genetics and *developmental* genetics have to be recognized. Darwin did not have a theory of variation. The genetics of the 20th century gave an inkling of what might be involved. Gray moths could become darkly peppered moths when exposed for generations to a darkened habitat. Those moths that had more cryptic coloration and could avoid predators survived to mate and their descendents had the more protective wings. Was natural selection creating novelty? Only by expanding the definition of natural selection *to include* development. Mutation and recombination were invoked as mechanisms by which genes could be altered to generate evolutionary innovations. But this really isn't "natural selection," it's more of a general statement about some unknown set of mechanisms active in development.

Darwin (1859) realized that selection could not act upon traits that had not yet appeared, noting that "characters may have originated from quite secondary sources, independently from natural selection." He continued this line of reasoning in his book on variation and domestication (Darwin 1883: p. 282), where he admits, "the external conditions of life are

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quite insignificant, in relationship to any particular variation, in comparison with the organization and constitution of the being which varies. We are thus driven to conclude that in most cases the conditions of life play a subordinate part in causing any particular modification." At best natural selection "creates" novelty by preparing a permissive environment for it. Thus, if variant A is more likely to arise from variant B than from variant C, then if the environment selects for B, the appearance of A is more probable. But this says nothing about the generation of A and why such generation is more likely from B. The mechanisms allowing B (but not C) to give rise to A are part of development (indeed, the "classic" area of developmental constraints).

Developmental genetics now has such a theory of evolutionary variation (reviewed in Carroll et al. 2005; Gilbert 2006). The tenets of these theories involve transcription factors and paracrine factors, concepts that were unknown to Darwin and to the architects of the Modern Synthesis. First, there are two major preconditions for developmental alterations that can generate morphological change. The first is *gene duplication* wherein genes can make copies of themselves and the sister genes mutate independently to assume different functions. Entire families of genes (*Hox* genes, *globin* genes, *cadherin* genes, *TGF-β* genes) have been produced this way. The second precondition is *modularity*. Modularity pervades development (Raff 1996; Schlosser and Wagner 2004). This means that a change can occur in one area of the body and need not affect another. Indeed, one of the most important aspects of EvoDevo is that not only are the *anatomical* units modular (such that one part of the body can develop differently than the others), but the DNA regions that form the *enhancers* of genes (telling the gene when, where, and how much it can be transcribed) are also modular. Thus, if a particular gene loses or gains a modular enhancer element, the organism containing that particular enhancer allele will express that gene in different places or at different times or different amounts than those organisms retaining the original allele. These changes can cause different morphologies to develop (Sucena and Stern 2000; Shapiro et al. 2004; Maas and Fallon 2005). Modular units allow certain parts of the body to change without interfering with the functions of other parts.

The importance of enhancer modularity in evolution has been dramatically demonstrated in three-spine stickleback fishes. Freshwater sticklebacks evolved from marine sticklebacks about 12,000 years ago, as the marine populations colonized the newly formed freshwater lakes at the end of the last ice age. The marine sticklebacks have a pelvic spine that serves as protection against predation by other fish. It lacerates the mouths of those fish who would try to eat it. The freshwater sticklebacks, however, do not have these pelvic spines. This may be because they lack the predators that the marine fish have and the predators of the freshwater sticklebacks are invertebrates that capture them by grasping onto such spines. Thus, the freshwater populations of this species have evolved a pelvis without such lacerating appendages.

To determine which genes might be involved in this difference between marine and freshwater populations, David Kingsley's laboratory (Shapiro et al. 2004) mated individuals from certain marine populations (with pelvic spines) and freshwater populations (without spines). The resulting offspring were bred to each other and produced numerous progeny, some of which had pelvic spines and some of which didn't. Using molecular markers that could identify specific regions of the parental chromosomes, they found that nearly all the fish with pelvic spines had a portion of chromosome 7 from the marine parent, while nearly all the fish that lacked pelvic spines obtained this region from the freshwater parent. This genetic region contained the gene-encoding transcription factor Pitx1.

When they compared the amino acid sequences of the Pitx1 protein between marine and freshwater sticklebacks, there were no differences. However, there was a critically important difference when they compared the *expression patterns* of the *Pitx1* gene between these species. In both species, *Pitx1* was seen to be expressed in the precursors of the thymus, nose, and sensory neurons. In the marine species, *Pitx1* was also expressed in the pelvic region. But in the freshwater populations, the pelvic expression of *Pitx1* was absent or severely reduced. Since the coding region of *Pitx1* is not mutated (and since the gene involved in the pelvic spine differences maps to the site of the *Pitx1* gene, and the difference between the freshwater and marine species involves the expression of this gene at a particular site), it is reasonable to conclude that the *enhancer region* containing the information to express *Pitx1* in the pelvic area no longer functions in the freshwater fish. Thus, the modularity of the enhancer has enabled this particular expression domain to be lost, and with it the loss of the pelvic spine. No other function of *Pitx1* had to be disturbed.

In addition to the two preconditions for evolution by changing development, EvoDevo has also recognized four mechanisms of *bricolage* which are responsible for producing these variations (Arthur 2004; Gilbert 2006):

– heterotopy (change in location)
– heterochrony (change in time)
– heterotypy (change in kind)
– heterometry (change in amount).

Although these mechanisms can be employed at any level of development, I will focus on the level of transcription, since investigations have focused on this area and because it is the most gene-oriented. References to the papers here can be found in Gilbert (2006).

Heterotopy of gene expression involves changing the types of cells expressing a particular gene. Heterotopy of *Fgf10* expression in the turtle dermis may explain the formation of

the carapace (Cebra-Thomas et al. 2005). Gremlin expression in the interdigital web of the duck hind limb (where it is not seen in the chicken or mouse) goes a long way to explaining how ducks got their webbed feet. Indeed, Gremlin inhibits the signal for programmed cell death, and if Gremlin protein is added to embryonic chick foot webbing, the chick foot becomes webbed, too. The different expression patterns of the *Ubx* and *Abd* genes between lobsters and shrimp explain the divergence of the animals in our seafood platters, and the difference in the epidermal expression of *BMP2* and *Shh* genes explains how feathers may have evolved from scales. Indeed, the proximate cause of the Genesis curse against snakes is the heterotopic expression of the *Hoxc-6* gene during snake embryonic development, where altered expression prevents limb development.

Heterochrony of gene expression involves the timing of gene expression. The origin of the vertebrate jaw comes, in part, from heterochronic gene expression (Shigetani et al. 2002), as does the elongation of the bat digits necessary to produce the wing (Sears et al. 2006). In this latter example, the gene encoding the paracrine factor BMP2 is expressed in the digital mesoderm for a longer period of time compared to that of other mammals. *Heterotypy* concerns changing the actual protein that is being made. Heterotypy of the gene encoding the Ultrabithorax (Ubx) transcription factor may explain why insects have just six legs, while other arthropod groups (think of spiders, millipedes, centipedes, and shrimp) have many more. The *Distal-less* gene in arthropods is essential for leg formation. Throughout most families of the arthropod lineage, Ubx protein does not inhibit the *Distal-less* gene. However, in the insect lineage, a mutation occurred in the *Ubx* gene wherein the original 3′ end of the protein-coding region was replaced by a group of nucleotides encoding a stretch of about ten alanine residues. This polyalanine region functions as a repressor of *Distal-less* transcription. When a shrimp *Ubx* gene is experimentally modified to encode this polyalanine region, it, too, represses the *Distal-less* gene. The ability of insect Ubx protein to inhibit *Distal-less* thus appears to be the result of a gain-of-function mutation that characterizes the insect lineage.

Heterometry involves changing the amount of gene expression. Evolution only rarely proceeds by total loss of function. Rather, the alterations of the amount of function can give different phenotypes. One way of providing such variations is to alter the amount of gene transcription. Indeed, some of the best examples of heterometry in action are Darwin's celebrated finches. Systematists have shown that these species evolved in a particular manner, with one of the major separations being between the cactus finches and the ground finches. The ground finches have evolved deep, broad beaks that enable them to crack seeds open, whereas the cactus finches have evolved narrow pointed beaks that allow them to probe cactus flowers and fruits for insects and flower parts. Developmental research demonstrates that species differences in the beak pattern are caused by changes in the growth of the neural crest-derived mesenchyme of the frontonasal process (i.e., those cells that form the facial bones). Abzhanov and his colleagues (2004) found a remarkable correlation between the beak shape of the finches and timing and amount of BMP4 expression. No other paracrine factor showed such differences. The expression of BMP4 in ground finches started earlier and was much greater than the expression of BMP4 in cactus finch beaks. In all cases, the BMP4 expression pattern correlated with the broadness and deepness of the beak. Experimentally adding BMP4 will deepen chick beaks.

Another example of heterometric variation involves the evolution of the *IL4* gene in human populations. Most of human variation (both pathological and nonpathological) does not come from changes in the structural genes. Rather it arises from mutations in the *regulatory regions* of these genes (Rockman and Wray 2002; Rockman et al. 2003). A single base pair mutation in the enhancer of the *IL4* gene creates a new binding site for transcription factor NFAT, a more rapid transcription of IL4 and higher levels of that protein. Moreover, population genetic studies show that this regulatory allele has been positively selected in particular populations and not others. Having this allele appears to be advantageous in those populations exposed to intestinal helminth parasites. However, this is not an exonic mutation in the actual protein; rather, it is an enhancer of the gene encoding this regulatory protein.

Recent research in developmental biology has also shown that in addition to producing new evolutionary variants, these four mechanisms also explain such evolutionary phenomena as parallel evolution (which has been used to justify the notion that natural selection is itself "creative"). Comparative developmental studies of the insect eye (Oakley and Cunningham 2002), stickleback fish armor plates and spines (Colosimo et al. 2004, 2005), as well as avian and *Drosophila* pigment patterns (Gompel et al. 2005; Mundy 2005) show that parallel evolution results from the independent recruitment of similar developmental pathways by different organisms. Thus, the loss of the pelvic spines in other stickleback species appears to be caused by independent losses of the Pitx1 expression domain mentioned earlier (Colosimo et al. 2004). Instead of extrinsic selection pressures being thought to play a dominant role in such phenomena, intrinsic developmental factors are now seen to play a critical role in producing these parallel variations (Hall 2003; Rudel and Sommer 2003; West-Eberhard 2003).[1]

What we see here is variation caused by developmental mechanisms. I have emphasized those involving gene transcription because these are the mechanisms closest to the genes themselves. These four mechanisms each involve changes in gene transcription during embryonic development. They

each involve the signaling molecules whereby cell fates are determined—transcription factors and paracrine factors. They change the way the embryo is constructed and thereby change the phenotype in ways that natural selection can then test. Natural selection alone generates neither novelty nor variation. Development does. Natural selection can clear the area so that these new variants can spread through a population, and it can promote an environment permissive for such change. But the motor of evolutionary innovation is not natural selection; it is development. Biodiversity can be explained only when population genetics and developmental biology complement each other; but this can happen only if the proponents of natural selection allow developmental biology its proper place as an explanatory agent. Darwin originated much of evolutionary theory; but he lacked a theory of variation. His colleague Thomas Huxley (1878/1896) was more of an embryologist than Darwin, and he intuited that variation must be caused by inherited alterations of development. "Evolution is not a speculation but a fact;" he wrote, "and it takes place by epigenesis."

Note

1. Indeed, in some of these papers (especially Colosimo et al. 2004, and 2005 and Rockman et al. 2003) one sees precisely the critical importance of the population genetics of regulatory alleles, as mentioned in the paragraph that so offended Ruse.

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