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The morphogenesis of evolutionary developmental biology

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Evolution is not a speculation but a fact; and it takes place by epigenesis.
Thomas Huxley (1893) p. 202

But it has become increasingly clear from research in embryology that the processes whereby the structures are formed are as important as the structures themselves from the point of view of evolutionary morphology and homology.
Gavin de Beer (1954) p. 136

Developmental biology is experiencing a two-fold revolution. The first phase of the revolution began in the 1970s, when developmental biology began to make use of recombinant DNA technologies to explain the mechanisms by which genetic instructions specified phenotypes composed of different cell types and organs. This newly empowered science identified the transcription factors, paracrine factors, and signal transduction cascades involved in the two most central processes of developmental biology—differentiation and induction. This ongoing phase of the revolution remains one of the great projects of developmental biology.

The *second* phase of the revolution began around the same time, but grew more slowly. Developmental biology looked outward to other fields, applying these recombinant DNA techniques and even newer technologies (bioinformatics and genomics) to bring developmental biology into areas that it had abandoned during its history: evolution, ecology, and medicine. Not only are these areas being brought back into the study of developmental biology, they are forming their own links at the periphery. Ecological, medical, and evolutionary biology are becoming integrated through developmental biology. More specifically, they are becoming integrated through evolutionary developmental biology (evo-devo). If this new integration is successful, it would constitute a revolution in our way of thinking about the origins of biodiversity.

Developmental biology has had an intimate relationship with each of these fields, and this paper will outline some of those important interactions. I will try to write both about the *evolution* of the field and the *development* of the field. The evolutionary metaphor would focus on contingency and the environmental (in this case, social) factors that would select for certain interactions over others. The developmental metaphor would stress the epigenetic interactions themselves, the internal logic underlying these interactions, and the emergence of new disciplinary phenotypes from such interactions. To this end, I will therefore try to construct an outline of the *morphogenesis* of evo-devo, recognizing that evo-devo is the result of both intrinsic and extrinsic agents. Moreover, this metaphor also demands that one recognize that the surrounding contexts of ecological and medical developmental biology are critical to the eventual phenotype of evo-devo. There are many histories of evo-devo, and the following is from my perspective. I recognize that there are other important fields (e.g., paleontology, morphometrics, mathematical modeling) that have also contributed, but their contributions will have to be discussed elsewhere (e.g., Hossfeld and Olsson, 2003; Love, 2003; Vergara-Silva, 2003).

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I. Evolutionary Developmental Biology

The heritage from evolutionary morphology

Evolutionary developmental biology has its origins in the evolutionary morphology of the late nineteenth century. In 1859, Darwin had written, «It is generally acknowledged that all organic beings have been formed on two great laws—Unity of Type and Conditions of Existence.» While natural selection explained adaptation to the «offices of existence», embryonic homologies explained «unity of type.» Darwin would unite these ideas to produce the concept of «descent with modification.» By this concept, Darwin could explain the *similarities* of animal form through descent from a common ancestor, and he could explain *differences* in their forms by natural selection in different environments. Darwin was influenced by Johannes Müller's summary of von Baer's laws in 1842, and he recognized that embryonic resemblances would be a very strong argument in favor of the genetic connectedness of different animal groups (see Oppenheimer, 1959; Ospovat 1981). "Community of embryonic structure reveals community of descent," Darwin (1859) would conclude in *On the Origin of Species*. While von Baer could never accept homologies across phyla, evolutionary biology made it possible—on the principle of a monophyletic origin for the animal kingdom—to seek the links between the types (Bowler, 1996)*.

Thus, Darwin looked to embryonic and larval stages for homologies that would be obscured in the adult. In the *Origin of Species*, Darwin (1859) celebrated the case of the barnacle, whose larvae showed it was a shrimp-like arthropod, and in the *Descent of Man* (1874), he gloried in Alexander Kowalevsky's (1866) discovery that the tunicate—hitherto classified as a shell-less mollusk—was actually a chordate. It had a notochord and pharyngeal slits that came from the same germ layers as those of fish and chicks. The two great domains of the animal kingdom—invertebrates and vertebrates— were thereby united through larval homologies. "Thus, if we may rely on embryology, ever the safest guide in classification, it seems that we have at last gained a clue to the source whence the Vertebrata were derived." Comparative embryology became evolutionary embryology as questions of phylogeny and the homologies of the germ layers in various animals became paramount (e.g., Kowalevsky, 1866; Lankester, 1877; Balfour, 1880-1881; Oppenheimer, 1940).

The foundations of evolutionary embryology were built by scientists who saw evolution as the means for delineating a natural classification of the animal world (Fig. 1). To this end, homologies were critical, and Hall (2000) has identified three principles that formed the bases for evolutionary embryology. First, all animals were derived from the same three germ layers. The muscles of insects and vertebrates both arose from mesoderm. (Indeed, it was Darwin's colleague, Thomas Huxley who declared—even before Darwin's *Origin* was published—that the ectoderm and endoderm of vertebrates to be homologous with the two cell layers of the coelenterate.) Second, developmental stages were conserved. Each organism could be expected to undergo cleavage, gastrulation, and organogenesis. Third, classification could most reliably be achieved by discovering germ layer homologies between embryonic or larval organisms. Like the early germ layers, themselves, these primitive tenets were modified and elaborated in different ways by different scientists.

In Germany, Fritz Müller (1864) championed a program wherein the goal of embryology was to reconstruct phylogenetic relationships. His brief treatise, *Für Darwin*, combined natural selection and embryology to demonstrate that «Darwin's theory furnishes the key of intelligibility for the developmental history of crustaceans, as for so many other facts inexplicable without it.» He compared embryonic stages between species, believing that «above all things, a thorough knowledge of development» is critical in using evolution to construct phylogenies (p.4). Thus, he proclaimed the Nauplius larva to be the common source of all crustaceans, and he declared that its basic structure was that of the crustacean ancestor. Having such a larva became the criterion for membership in the Crustacea, and Müller showed that several parasitic animals formerly thought to be mollusks or worms were, by this criterion, crustaceans (see Tauber and Chernyak, 1991). Müller also argued for the efficacy of natural selection both in adults and in their larval stages (p.118). Therefore, since larvae, like adults, have to evolve adaptations to survive in their respective environments, one should not expect to see perfect reflections of phylogeny in the development of extant organisms. In Müller's short book, one also sees the anlagen of our current hypotheses of canalization (p. 114), developmental constraints (p. 44), and punctuated equilibrium (p. 115): «The historical development of a species can hardly have taken place in a uniform flow; periods of rest have alternated with periods of rapid progress.» Homologous larval structures indicate shared ancestry, and this book closes with a recommendation that we look for a common ancestor of the Insecta and Crustacea, perhaps «a Zoea which raised itself into a life on land.» (p. 141).

In Russia, natural selection was not considered a major part of evolution (Todes, 1999). Rather, the Russian school of evolutionary biology emphasized phylogeny and development as opposed to natural selection. (Todes [1989] has commented that the idea of competition was peripheral to early Russian evolutionary studies, even before to the influence of Kropotkin or Communism in this area). The above-mentioned A. Kowalevsky (also see Mikhailov and Gilbert, 2002) helped transform comparative embryology into an evolutionary embryology by using new histological techniques to determine homologies that might no longer be visible in the adult organism (Bowler, 1996, p. 142). These studies using cell lineage to show the homologies of the tunicate, amphioxus, and vertebrate notochords became a major support for the evolutionary theory. Haeckel introduced it in his *Natürliche Schöpfungsgeschichte* of 1868, and Michael Foster published a detailed summary of it in the *Quarterly Journal of Microscopic Science* in 1870. Darwin, himself, publicized Kowalevsky's research in the *Descent of Man* (second edition, 1874; p. 160), stating that «We should be justified in believing that at an extremely remote period a group of animals existed resembling in many respects the larvae or our present Ascidians, which diverged into two great branches—the one retrogressing in development and producing the present class of Ascidians, the other rising to the crown and summit of the animal kingdom by giving birth to the Vertebrata.»

In Britain, Francis Maitland Balfour exemplified Alfred North Whitehead's (1920) dictum that the motto of every natural scientist

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* NOTE: Interestingly, von Baer´s disagreement was with the sufficiency of natural selection, not with evolutionary ideas. He wrote to the evolutionary biologist Anton Dohrn (Beer, 1875), that development is critical for the transmutation of species: *"I cannot help but find transmutation probable to a high degree; but I cannot declare Darwin´s hypothesis of selection to be sufficient and have believed therefore that transmutation should be explained as a developmental phenomeon."*

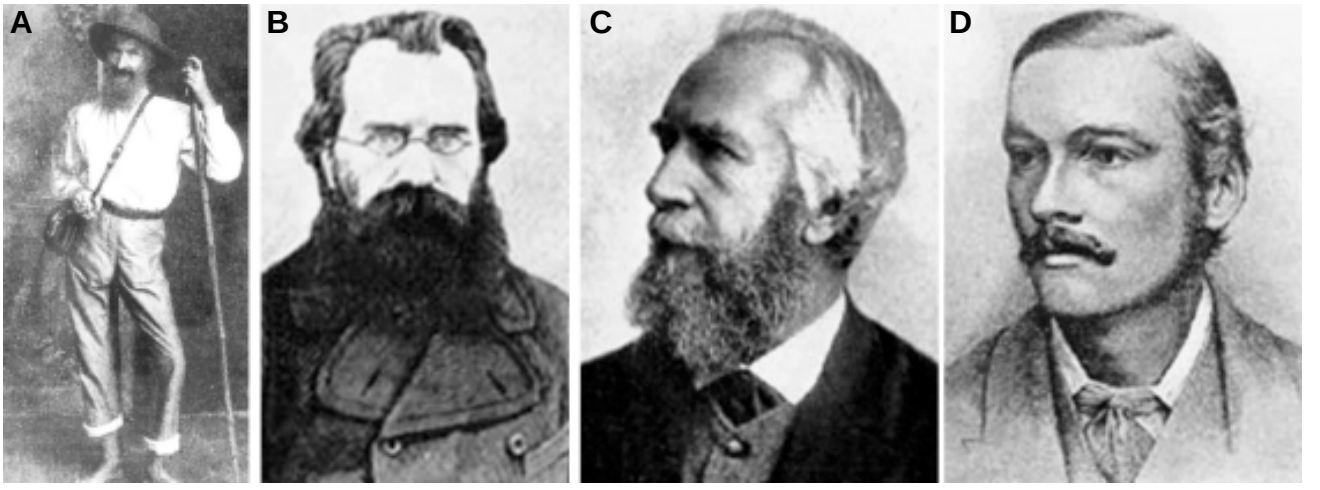

Fig. 1. Relating embryology and evolution immediately after Darwin. Four of the founders of evolutionary embryology. (A) *Fritz Müller, known primarily for his studies of mutualism and mimicry among unpalatable insects, shown here in collecting attire. An outstanding naturalist, he used crustaceans to link natural selection and embryology.* **(B)** *Alexander Kowalevsky used embryonic homologies to link the invertebrates and vertebrates.* **(C)** *Ernst Haeckel believed development to be the motor of evolution, and he fought battles with Kowalevsky over the meaning of gastrulation (while using Kowalevsky's figures).* **(D)** *Francis M. Balfour used larvae in critical ways to deduce phylogeny. His work was cut short when he died at age 31 while climbing the Mont Blanc. (Photograph A courtesy of John Longino; Photographs B-D courtesy of John Alroy).*

should be, «Seek simplicity and distrust it.» He sought embryonic and larval homologies, but, like Müller, he recognized that the early stages of development could be no less sensitive to natural selection than the adult stages. Thus, while he used cell lineage studies to show, among other things, that Hensen's node of chicks was homologous to the blastopore lip of amphibians, Balfour was suspicious of the idea that in early development one saw form unencumbered by function. Balfour sought to use embryology to reveal the ancestral forms common to all metazoa, and to see if particular embryonic or larval forms (planula larvae, trochophores, etc) represented the ancestral form of a phylogenetic group. He developed the notion that groups that share common larvae are «descended from a common stem,» and his two-volume book *A Treatise on Comparative Embryology* (Balfour, 1880 - 1881, p. 5) was written (1) to provide an embryological basis for phylogeny and (2) to provide an evolutionary context for studies of organ formation (see Hall, 2003). In this way, evolution and embryology mutually supported each other.

In the United States, there was a split on how evolution and development could be bridged. This split mirrored the arguments (see Appel, 1987) between Cuvier and Geoffroy St. Hilaire over which was more crucial for understanding animal classification—similarities or differences. E. B. Wilson (1898) favored the European program of finding embryonic homologies and using them to demonstrate shared ancestry. The homologies of spiral cleavage patterns and mesoderm-forming cells among flatworms, annelids, and mollusks demonstrated their «community of descent.» But while this tradition of evolutionary embryology used embryology as evidence for evolution and for a natural system of classification, others saw evolution as the explanation for specific embryonic stages. In the same symposium issue that Wilson used embryological *homologies* to show common ancestry, his colleague F. R. Lillie (1898) claimed that such approaches were old fashioned and that *differences* were what mattered. Also focusing on spiral cleavage patterns, Lillie showed that the alteration in cleavage needed to produce a molluscan larva that would not be swept downstream in a river current demonstrated that natural selection could take place in the embryonic as well as the adult organism.

Foremost among the investigators who saw evolution as the key to development was Ernst Haeckel. In Haeckel's view, phylogeny *caused* ontogeny (Haeckel, 1866). As historian Lynn Nyhart (1995; p. 129) concludes, Haeckel's «main concern was not to expound Darwin's own theory, but to retell Darwin's theory in terms that were peculiarly Haeckelian.» Haeckel claimed that Darwin's ideas included the progressive development of species. «Development and progress» was what characterized evolution. The explicit association of evolution with particular political, religious, and racial views became the hallmark of Haeckel's career. Haeckel proposed a causal parallelism between the embryological development and phylogeny. His «Biogenetic Law» that «Ontogeny Recapitulates Phylogeny» was based on the idea that the successive (and to him, progressive) origin of new species was based on the same laws as the successive and progressive origin of new embryonic structures. Just as the earlier stages of human development developed into the later stages, so earlier species evolved into the later ones. Natural selection would eventually get rid of the earlier species. (In the *Welträtsel*, Haeckel [1899] would also proclaim that the more evolved humans [i.e., the Aryans] would out-compete and eliminate the more primitive races.) To Haeckel, the evolution of the animal kingdom was the same as individual development not only because the laws behind each were the same but also because the entire animal kingdom was an individual. Here, he was harking back to the views of the *Naturphilosophen* of the previous century. In other words, the development of advanced species was seen to pass through stages represented by *adult* organisms of more primitive species.

Gould (1977) analyzed three principles of Haeckel's Biogenetic Law. First, there was the law of correspondence. The human zygote, for instance, was represented by the «adult» stage of the protists; the colonial protists represented the advancement of development to the blastula stage; the «gill slit stage» of human

embryos was represented by adult fish. Haeckel even postulated an extinct organism, Gastraea, a two-layered sac corresponding to the gastrula, which he considered the ancestor of all metazoan species. Second, there was the law of terminal addition. The embryo evolved new species by adding a step at the end of the previous ones. In such a view, humans evolved when the embryo of the next highest ape added a new stage. Evolution was not so much a branched chain as a ladder. Last, there was the law of truncation, which held that preceding development could be foreshortened. This law was needed to prevent gestation time from being enormous. It also was needed since embryologists did not observe all these stages in all animals. Gould argues that Darwin was far more in the spirit of von Baer than he was with Haeckel.

But at a time when there was no molecular biology that could provide mechanisms for differential gene expression, Haeckel's rules sometimes worked when von Baer's did not. Mayr (1994) points out that Balfour asked a question that von Baer's laws could not answer, «[Why do animals] undergo in the course of their growth a series of complicated changes, during which they acquire organs which have no function, and which, after remaining visible for a short time, disappear without leaving a trace?» Hypothetical adult ancestors can be used to explain gill arches and notochords in mammalian embryos; while von Baer's laws cannot. The embryonic organs are not generalized forms of later-developing organs; gill arches are not generalized middle ear bones.

Gould (1977) showed that the differences in recapitulation between Haeckel (who saw ontogeny as the recapitulation of adult forms) and von Baer (who saw ontogeny as the progressive separation of embryonic forms from a mutual origin) were extremely important. Haeckel's arguments became exceptionally popular, but they had their detractors as well. One important evolutionary embryologist who criticized Haeckel was the Russian investigator Eli Metchnikoff. Metchnikoff is now known primarily as the founder of immunology. However, he was drawn into that area by his comparative studies of mesoderm formation and function in invertebrate embryos (Tauber and Chernyak, 1991). Metchnikoff was not against recapitulation in general; but he felt that Haeckel had been mistaken in his details, careless in his reconstruction of Gastraea as the first metazoan, and backwards in his fusing evolution to Romantic *Naturphilosophie*. Metchnikoff disagreed with Haeckel over the origin of the mesoderm and over several tissue relationships that Haeckel assumed were homologous but which to Metchnikoff were problematic. Moreover, Metchnikoff (Tauber and Chernyak, 1991; p. 42) recognized that there were too many facts that contradicted Haeckel's simple recapitulationism: «Detailed knowledge about the history of animal development in no way can unconditionally support the opinion that in a history of an individual development a history of the species is repeated with just some small limitations.» Metchnikoff also appreciated that evolution consisted in changing embryonic rather than adult structures. He wrote (1891) that the first human would be viewed as a strangely monstrous ape, having altered its embryonic development.

While Metchnikoff's embryology took him off into immunology (he viewed intracellular digestion as the primary function of the mesoderm, and saw immune defense as having evolved from this property), Walter Garstang followed this idea and showed persuasively (using snail larvae) that the evolution of new features was based on changes in developmental stages, not in adult stages. He also demonstrated the incompatibility of the Haeckel's Biogenetic Law with Mendelian genetics. Garstang reversed Haeckel's relationship between ontogeny and phylogeny. In his address to the Linnaean Society, Garstang (1922; p. 724) remarked that «ontogeny does not recapitulate phylogeny: it creates it.» Garstang also renewed interest in the origin of the vertebrates, showing that tunicates were not degenerate chordates but a primitive chordate whose larvae might represent the ancestral chordate condition. In this analysis, he promulgated the idea of paedomorphosis, wherein a larval form might attain sexual maturity. Thus, the active larva of the tunicate might have become a free-living adult, setting the stage for evolutionary radiations.

The importance of heterochrony in relating evolution to embryology was stressed by one of the greatest descriptive biologists, Sir Gavin de Beer. De Beer (1954) demonstrated that characters changed their order of appearance in the ontogeny of descendent embryos compared with those of the ancestor, and that some features persist for a greater duration than others. Timing is critical, and changes in the timing of events can lead to new evolutionary features. Whether a limb is short or long, and whether a juvenile has or lacks a tail depends on the relative timing of developmental events. De Beer also updated the concept of homology. He broke from Balfour's view that the germ layer of origin was critical for assessing homology, and he pointed out that homologous structures can arise through different mechanisms. Shared germ layers (or shared genes) did not constitute proof of homology. Nor did dissimilar origins (as in the case of the gut canals in different vertebrates, and primary *versus* secondarily modes of neurulation) preclude homology.

By the end of the nineteenth century, however, descriptive embryology was waning, and a golden age of experimental embryology had begun. When Haeckel's student Wilhelm Roux announced the creation of experimental embryology in 1894, he broke many of the ties that linked embryology to evolutionary (and ecological) biology. According to Roux, embryology was to leave the seashore and forest and go into the laboratory. However, he promised that embryology would someday return to evolutionary biology, bringing with it new knowledge of how animals were generated and how evolutionary changes might occur. He stated, "an ontogenetic and a phylogenetic developmental mechanics are to be perfected." Roux thought that research into the developmental mechanics of individual embryos (the ontogenetic branch) would proceed faster than the phylogenetic (evolutionary) branch, but he predicted that "in consequence of the intimate causal connections between the two, many of the conclusions drawn from the investigation of individual development [would] throw light on the phylogenetic processes." It would take a century to fulfill Roux' prophecy.

Integrating Embryology and Evolution with Genetics

If there were to be a «Modern Synthesis», there would have had to have been some «Unmodern Synthesis» before it. This «unmodern synthesis» was this union between *embryology* and evolution. The «Modern» Synthesis would involve the supplanting of embryology by genetics, and one of Gregory Bateson's roles (in addition to naming the new field «genetics») would be to destroy the notion that embryology contributed anything to our understanding of the mechanism of evolution.

In 1894, Bateson claimed that «the embryological method has failed» when it came to determining the mechanisms of evolution. He ridiculed the debates over homologies in embryonic morphology, calling them «vain and sophistical disputes.» The time had come, Bateson wrote, to «seek facts of a new kind,» and he took pains to show that his new facts were supported by science, even if they were «made on authority unfamiliar» to the «professed morphologist.» In the preface to *"Materials for the Study of Variation"*, Bateson depicted Embryology as being blind. It just could not see variations. Embryology, Bateson later remarked (1928), had been the «readiest method» to answer evolutionary questions and had «provided us with a magnificent body of facts», but it had not done its job of showing how evolution could take place. And he wasn't alone. Sedgwick also noted that progress in evolutionary embryology was frustrated by the inability to tell whether similar structures arose through convergence or common origin. (This problem was to last a long time, and it may be no coincidence that the emergence of evo-devo was to become contemporaneous with the emergence of molecular systematics.) In his essay of 1922, «Evolutionary Faith and Modern Doubts», Bateson announced the birth of a new science out of the decay of the old, proclaiming, «Morphology having been explored in its minutest corners, we turned elsewhere...The geneticist is the successor of the morphologist.»

By the 1930s, Thomas Hunt Morgan (who had been a well known embryologist before becoming a geneticist) had formally separated genetics from embryology (see Gilbert, 1988). Each discipline had its own rules of evidence, its own paradigmatic experiments, its own favored organisms, its own professors, its own journals, and most importantly, its own vocabulary. In *The Scientific Basis for Evolution*, Morgan (1932) made the case for genetics being the sole scientifically valid approach to study evolution. His chapter on embryology is primarily given to demonstrating the inadequacies of recapitulationism. Morgan speculated that new genes might be formed that could change the patterns of late development, but by and large, he dismissed the entire embryological program, including that of heterochrony (p. 177): «It doesn't matter much, to my thinking, whether you choose an ape, or the foetus of an ape, as the progenitor of the human race.» As many scientists and historians (e.g., Hamburger, 1980; Adams, 1980; Gilbert, 1988) have noted, embryology was left out of the Modern Synthesis.

Despite the antagonism between embryology and genetics, there were some who were trying to integrate the gene, embryology, and evolution together. By the 1940s, there were at several attempts at such a synthesis. First, some of the founders of the Modern Synthesis were sympathetic to attempts to introduce developmental phenomena into it. Sewall Wright, for instance, had investigated polydactyly in guinea pigs, and he had a longstanding correspondence with Richard Goldschmidt (see Dietrich, 2000). Although there were outstanding disagreements between these two scientists, Wright and Goldschmidt made suggestions that modified each other's research. Leyland Stebbins' models of plant evolution contained numerous examples of how genes may produce selectable variation by influencing developmental physiology (Smocovitis, personal communication).

Goldschmidt, however, had his own version of evolutionary developmental biology that he called "physiological genetics." He criticized the Modern Synthesis, writing that the accumulation of small genetic changes was not sufficient to generate evolutionarily novel structures such as the teeth, feathers, cnidocysts or mollusk shells (Goldschmidt, 1940;p. 7). He claimed that such evolution could only occur through inheritable changes in those genes that regulated development, and in *The Material Basis of Evolution*, Goldschmidt presented two models relating gene activity, development, and evolutionary dynamics. In the first model, Goldschmidt argued that new species might originate as "hopeful monsters" that result from mutations in developmentally important loci ("developmental macromutations"). In the second model, Goldschmidt argued that chromosomal rearrangements («systemic mutations") would have the effect of many developmental macromutations and cause even larger phenotypic changes. Comfort (2001) has recently argued that Barbara McClintock's analysis of transposable elements represented an attempt to show that such genetic regulation was occurring and that it might be important for evolution.While Goldschmidt's view of systemic mutations did not win much favor, he did provide the influential idea that "a single mutational step affecting the right process at the right moment can accomplish everything, providing that it is able to set in motion the ever present potentialities of embryonic regulation" (Goldschmidt, 1940, p. 297). However, Goldschmidt's presentation of these ideas went against the grain of genetic science. To Goldschmidt, the gene wasn't a locus or an allele. Rather, it was a unit of development (Goldschmidt, 1940, p. 197). For Goldschmidt, the regulatory processes of development relieved the need for thousands of modifier genes, and for this reason, he attempted "to convince evolutionists that evolution is not only a statistical genetical problem but also one of the developmental potentialities of the organism." (Goldschmidt *et al.,* 1951). Indeed, in the absence of a theory of gene activity, there were several attempts (notably those of Berrill (1955) and Bonner (1958)) to bridge embryology and evolution without using genes as a common language.

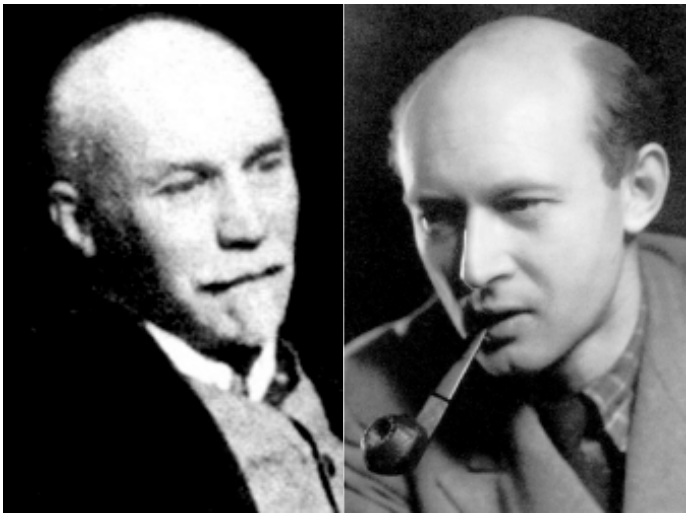

Fig. 2. Integrating developmental biology into the modern synthesis. (A) *Ivan I. Schmalhausen and* **(B)** *Conrad Hal Waddington both attempted to integrate embryology, ecology, genetics and paleontology to create a new evolutionary synthesis that included developmental aspects. They deduced similar frameworks whereby structures generated through developmental plasticity could become genetically fixed. (Photograph A courtesy of the University of Chicago Press; photograph B courtesy of Pelican Books).*

Two of the most far-reaching syntheses of evolution, genetics, and development were attempted by Ivan Ivanovich Schmalhausen and Conrad Hal Waddington (Fig. 2). Waddintgton was trained in genetics, experimental embryology, and the evolutionary biology, and he was able to appreciate the links between them (see also Gilbert, 2000; Stern, 2000). In his 1953 essay, «Epigenetics and Evolution,» Waddington analyzed the shortcomings of the population genetic account of evolution which had dominated in the Modern Synthesis. He noted (p. 187) that the genetic approach to evolution has culminated in the Modern Synthesis, but he also noticed that «It has been primarily those biologists with an embryological background who have continued to pose questions...» Waddington put forth his own critique, first noting that while the mathematics may give the Synthesis its great prestige, it had not provided any noteworthy quantitative statements about evolution of species. Other than Wright's theory of drift, Waddington found no new insights to have come from it.

Moreover, Waddington (1953a) claimed that the Modern Synthesis failed to work in at least three areas. First (as will be discussed later), much variation appeared to be non-genetic and regulated by the environment, not the inherited genotype. Second, as Goldschmidt had noted, large groups of animals differ from each other in ways not compatible with local races branching off. Accumulations of small mutations in a local group could not separate amphibians from fish or reptiles from amphibians. Waddington felt that Goldschmidt's own hypotheses were so unconvincing to geneticists that they obscured the cogency of Goldschmidt's arguments for these «unbridgeable gaps.» Third, Waddington noted the different rates of evolution seen in the paleontological record.

Waddington (1953a; p.190) claimed that in conventional studies of evolution, the animal is considered either as a genotype (and is studied by geneticists) or as a phenotype (and is studied by taxonomists). What is needed, wrote Waddington, is an evolutionary study of those processes that get the genotype to the phenotype—the «epigenetics of development.» Following Goldschmidt, Waddington (p. 190 – 191) declared, «Changes in genotypes only have ostensible effects in evolution if they bring with them alterations in the epigenetic processes by which phenotypes come into being; the kinds of change possible in the adult form of an animal are limited to the possible alterations in the epigenetic system by which it is produced.»

Waddington then launched into a critique of the notion of «random mutation,» noting that there are developmental constraints placed on what changes are possible. Therefore, «the consequential changes in the phenotype are not random, since the adult form is produced by the interaction of many genes, and only certain types of alteration of the whole system can be brought about by any conceivable alteration of a single member of the gene complex. No single mutation can produce a pentadactyl limb of vertebrate type on a *Drosophila*." Waddington distinguished here «normalizing selection» working on adults and «stabilizing selection» working during development. Waddington then showed how both normalizing and stabilizing selection can work together to produce species adapted to particular environments in a manner that can operate over a relatively short time course. To do this, he reviewed two of his fundamental concepts—canalization and genetic assimilation.

Canalization is the property of developmental pathways to produce standard phenotypes despite mild environmental or genetic perturbations. It is the buffering of development by epigenetic networks such that most mutations or environmental conditions will not deflect the genotype from realizing the appropriate phenotype of the cell (Waddington, 1942). Canalization allows mutations to build up in the genotype without their being expressed in the phenotype. Thus, it promotes cryptic genetic variation, while preserving the integrity of the differentiating cell. Such genetic variability can be made manifest by changing the environmental conditions and can be selected. (We will discuss this later in the context of genetic assimilation.) In the Soviet Union, I. I. Schmalhausen had proposed a similar idea called stabilization (1949; see Allen, 1991, Gilbert, 1994;). The canalization of development has recently been demonstrated by several independent experiments (see Gilbert, 2000).

Genetic assimilation is the process by which a phenotypic response to the environment becomes, through the process of selection, taken over by the genotype so that it becomes independent of the original environmental inducer. This idea had several predecessors, including those hypotheses of J. M. Baldwin, and is essentially the same as Schmalhausen's hypothesis of genetic stabilization. An example used by both Schmalhausen (1949) and Waddington (1942) concerns the calluses on the keels and sterna of ostriches. According to both Schmalhausen and Waddington, the genome of the ostrich has the ability to let the skin form calluses when the skin is abraded. This ability to respond is what is important. If the presence of calluses is adaptive, then that phenotype can be selected such that it forms without abrasion (and appears earlier than the abrasive stimulus). The responsive pathway leading to callus formation had been transferred from an external stimulus to a genetic stimulus.

For genetic assimilation to work, four things have to be shown.

1. The genome must be responsive to environmental inducers.
2. The competence to be induced must be transferred from an external inducer to an internal, embryonic inducer.
3. There has to be cryptic variation within a population so that the physiological induction can be taken over by embryonic inducers.
4. There must be selection for the phenotype.

Recent studies have documented each of these tenets of genetic assimilation. Numerous investigators (Waddington, 1953b, 1956a, 1957; see Gilbert 2000) have documented genetic assimilation in the laboratory, and a molecular mechanism has recently been proposed that would explain both canalization and genetic assimilation (Rutherford and Lindquist 1998). Waddington's own *Drosophila* heat-shock experiments demonstrated that traits produced through environmental stimuli can become inherited in the genome, and he concluded (Waddington 1953b, p. 198) that the unbridgeable gaps between large groups of organisms «becomes almost a necessity as soon as we think of development as a cybernetic process, involving stabilization through feed-back and other mechanisms.»

At the same time, almost identical concepts of canalization and genetic assimilation were being proposed by Ivan Schmalhausen. Schmalhausen's landmark volume Factors in Evolution (1949) was nothing less than an attempt to integrate evolutionary morphology, population genetics, experimental embryology, and ecology into a coherent framework to provide a causal theory for evolution. However, Schmalhausen was dismissed from his position at the Severtsov Institute during the

Lysenkoist purges of Soviet biology departments. Research in evolutionary biology and in embryology kept on two separate trajectories. In his extensive discussion of the relationship between ontogeny and phylogeny, the Israeli biologist and philosopher Yeshayahu Leibowitz (1962) concluded that the evolutionary synthesis was incomplete if it could not integrate the data from experimental embryology into a theory of how new phenotypes could emerge. He succinctly summarized the state of affairs:

> *"The teaching of the Neo-Darwinists gives extra emphasis to genetic factors - but the problems of experimental embryology are ignored. At present, research being conducted in ontogeny and that in phylogeny are on different tracks, with no coordination or synthesis between them."*

The conception and birth of Evo-Devo

The year 2000 might be considered the birth of evo-devo. In that year, two journals arose to publish the results of evo-devo research, and the Society for Integrative and Comparative Biology founded its section on evolutionary developmental biology. But if 2000 saw the *birth* of evo-devo as a discipline, then 1977 must have been the year of its *conception*. In that year, three publications paved the way for evolutionary developmental biology. These publications were Stephen J. Gould's *Ontogeny and Phylogeny* (1977), François Jacob's «Evolution by tinkering,» (Jacob, 1977), and Maxam and Gilbert's (1977) techniques paper for DNA sequencing. In *Ontogeny and Phylogeny*, Gould demonstrated how the Ernst Haeckel had misrepresented the field of evolutionary embryology and made it into an unscientific and racist doctrine. Indeed, the first half of this book exorcises Haeckel's ghost so that some other model of evolution and development could be put in place of Haeckel's Biogenetic Law. Jacob's paper suggested such a new and testable model, and the paper on DNA sequencing established a method that could test it. The results constitute the remainder of this volume.

As with embryos, interactions early in the course of morphogenesis have had a big impact on the discipline. In the early 1980s, John Bonner's *Evolution and Development* (1982) and Raff and Kaufman's *Embryos, Genes, and Evolution* (1983) set forth many of the paradigms that we are presently using. One of the most productive has been the developmental genetic program for evo-devo. This program has at least three extant projects. The first project focused on the similarities found in the developmental regulatory genes throughout the animal kingdom. These findings included the *Hox* genes involved in specifying anterior-posterior body axis, the *Pax6* genes that specified photoreceptor and eye development, and the *Nkx2.5* genes that instructed heart formation. The second project looked at modifications of these instructions such that clades would differ from one another. Here, the focus became genetic differences in regulatory genes, their targets, and their spatiotemporal patterns of expression. In the third project, we are beginning to look at variations of these genes and their expression within populations. This newest focus—on looking at phenotypic variation produced by mutations involving regulatory genes—promises to link evolutionary developmental biology with the more traditional areas of evolutionary biology. (Like the Hox genes, these projects are temporally nested. Right now, all three programs are in evidence).

II. Ecological Developmental Biology

So far, we have been discussing evolutionary developmental biology almost exclusively from the embryologist's perspective. But the morphogenesis of evolutionary developmental biology would be incomplete without mentioning the related morphogenesis of ecological evolutionary biology and medical developmental biology. If Leigh van Valen's (1973) oft-quoted dictum that «evolution is the control of development by ecology» is correct, then ecological considerations must be paramount to evo-devo. The ecological component of developmental biology had been a major part of the original program to introduce experimentation into the study of animal development. Nyhart (1995) demonstrated that some of the pioneering work in experimental embryology was conducted by morphologists who were interested in determining the environmentally causal factors of development. Herbst's original proposal for induction (*Auslösung*) included induction from the environment as well as from within the organism (Herbst, 1893; see Oppenheimer, 1991), and even August Weismann, the scientist most associated with the view that the nucleus was the sole source of developmental factors, did his early work in this area. He was one of the first to study phenotypic plasticity, the ability of an organism to respond to environmental conditions by altering its development. Weissman (1875) noted that certain butterflies had different wing pigmentation, depending upon the season in which they eclosed. He found that this seasonally dependent variation could be mimicked by incubating larvae at different temperatures.

However, when Weisman proposed that development was merely the segregation of entities residing within the nucleus, there was considerable reaction from other embryologists. One of the most important of these reactions came from the noted embryologist of the University of Berlin, Oscar Hertwig (1894). A thoroughgoing epigeneticist, Hertwig was fighting a major intellectual battle to maintain a middle ground between the nuclear preformationism of Weismann and colleagues and the vitalistic epigenesis of Hans Driesch and his followers. While geneticists adopted Weismann as one of their founding progenitors, it was Hertwig's «organicism» (an epigenetic materialism) that eventually was adopted by embryologists as a reasonable explanation of development (Haraway, 1976; Gilbert and Sarkar, 2000).

Hertwig's volume, *The Biological Problem of Today: Preformation or Epigenesis?*, concludes with the extension of epigenesis from interactions between cells of the embryo to the interactions between developing organisms and their respective environments. His evidence includes numerous examples of developmental plasticity. «These seem to me to show how very different final results may grow from identical rudiments, if these, in their early stages of development, be subjected to different external influences.» (p. 122). Hertwig's cases included sexual dimorphism in *Bonellia* and certain barnacles (wherein the environment regulates sex determination such that females can be over 100 times the size of the males and the two sexes have totally different morphologies), temperature-dependent sex determination in rotifers (where «by raising or lowering the temperature at the time when eggs are being formed in the germaria of the young females, the experimenter is able to determine whether these eggs shall give rise to males or to females»), the nutrition-dependent production of worker and reproductive castes in ants and bees (where «It has been

shown fully by experiment and by observation that the fertilized eggs of the queen bee may become either workers or queens. This depends merely on the cell of the hive in which the egg is placed and on what food the embryo is reared.»), and the temperature-induced wing patterns of butterflies. Thus, Hertwig (p. 132) concluded «It has been shown, I think, in these pages that much of what Weismann would explain by determinants within the egg must have a cause outside the egg.» Hertwig tried to «blend all that is good in both theories,» recognizing that both the nucleus and the environment have important contributions to make.

The idea of phenotypic plasticity was very popular in Europe (see Sarkar, 1999), especially at the Prater Vivarium in Vienna. While the environmental view became marginalized in the West by *Entwicklungsmechanik* and later by developmental genetics, this view became a major part of the Soviet program for developmental biology. In one of his last publications, Alexei Nikolaeovich Severtsov (1935), the founder of the Russian school of evolutionary morphology, wrote of the future:

«At the present time, we morphologists do not have the full theory of evolution. It seems to us that in the near future, ecologists, geneticists and developmental biologists must move forward to create such a theory, using their own investigations, based on ours…»

To Severtsov, a complete theory of evolution must causally explain the morphological changes seen in paleontology through the mechanisms of genetics, ecology, and embryology. He felt that genetics, alone, could not provide the mechanism, because it did not involve the «how» of evolution (Adams, 1980). Only ecology and embryology could do that. This integration of embryology, development, and ecology became the project of the Severtsov's Institute of Evolutionary Morphology, headed by Severtsov's student Ivan Ivanovich Schmalhausen. Schmalhausen's *Factors in Evolution* places strong emphasis on what he called «dependent morphogenesis» (i.e., that part of development which depends on its environmental context) and the norms of reaction. Norms of reaction refer to the ability of an organism to inherit a range of phenotypic potentials from which the environment elicits a particular one. The ability of organisms to inherit such norms of reaction, and the ability of the environment to induce changes in development will become essential for Schmalhausen's notion of stabilizing selection.

Despite its being translated into English in 1949 by Theodosius Dobzhansky, Schmalhausen's book had little effect on western biology. The reason is ironic. Severtsov's doctrines were being embraced by the Lysenkoists, who, in 1948, had declared Severtsov's research congruent with current Soviet biology. However, Lysenko specifically derided Schmalhausen's attempt to bring such studies in line with Mendelian-Morganist genetics (see Adams, 1980). The Lysenkoists viewed the environment as being critically important in determining phenotype, and they denounced those who thought the genome was the primary cause of phenotypes within species. It is probable that the purges of geneticists from their positions, the deportation and subsequent death of geneticists such as N. Vavilov, the exiling of geneticists such as N. Timofeeff-Ressovsky, and destruction of these people's research led to the rejection of the milder Hertwig-Schmalhausen program of ecological developmental biology. Attempts to look at non-genomic contributions to development became causualties of the Cold War (Lindegren, 1966; Sapp, 1987).

C. H. Waddington (1956a,b) tried to reintegrate ecological issues into mainstream developmental biology, but his attempts failed, partially, I believe, due to the reaction against Lysenkoism and the related fact that Waddington was well known as a left-wing scientist. It was only in the 1990s, that ecological developmental biology has regained interest. First, the field of life history strategies provided numerous examples of such context-dependent development (see Gilbert, 2001). Context-dependent sex determination was seen in turtles, lizards, and fish; nutritional polyphenisms were identified in ants, wasps, and moths; and predator-induced polyphenisms was identified not only in invertebrates but in vertebrates. Second, the mechanisms by which environmental signals can mediate differences in gene expression have been found. These include neuroendocrine mediation (Nijhout, 1999), methylation (Waterland and Jirtle, 2003) and direct induction (Hooper *et al.,* 2001). Third, developmental plasticity became a topic of great interest to evolutionary biologists; and fourth, conservation biologists needed to know about the survival and development of the embryonic and larval stages of development as well as the adult stage. Morreale and colleagues (1982), for example, showed that because they did not know how turtle sex was determined, conservation biologists were re-introducing thousands of hatchling turtles - all of the same sex. Fifth, in the late 1990s, interest surged in the possible hazardous effects that chemicals might have on embryos. Environmental chemicals which we had thought harmless (at least to adults) may be dangerous to developing organisms and may threaten the fertility of adults (Colburn *et al.,* 1996; Hayes *et al.,* 2002). Sixth, new procedures, especially the polymerase chain reaction (PCR) and microarray analysis has enabled biologists to study developmental interactions that had heretofore been inaccessible. This technique has revolutionized the study of developmental symbioses (see Hooper *et al.,* 2001).

Ecological developmental biology is interacting with evolutionary developmental biology in interesting ways. It is positioning itself to look at the proximate causes of life history strategies and to determine the epigenetic relationships between organisms. It is also forging links (see below) with medically oriented areas of developmental biology such as teratology and endocrine disruption. Most importantly for evolutionary studies, it is focusing attention on genetic assimilation as an important problem and as a mechanism for the possible morphological divergence of new species (West-Eberhard, 2003).

III. Medical Developmental Biology

As opposed to «human embryology», the application of developmental biology to medicine has not been a major part of either medicine or embryology. However, much of embryological history is rooted in the attempts to identify, classify, and treat the causes of human birth defects. As Darwin had noted, the French embryologists of the early 1800s have been identified with this program, starting with the Etienne Geoffroy Saint-Hilaire, and his son Isadore. Even Laurent Chabry's 1886 experiments on tunicate embryos (that demonstrated mosaic developmental and autonomous cell specification) were done in order to find the causes of human congenital anomalies (Churchill, 1973; Fischer, 1991).

Medical genetics has been linked to evolutionary developmental biology through the work of clinical geneticists such as John Opitz and developmental biologists such as Pere Alberch (1989)

and Brian Hall (1984). Opitz has been particularly instrumental in linking medical anomalies with evolutionary developmental biology (see, for instance Opitz, 1996; Opitz and Clark, 2000, for this evo-devo approach to syndromology), and he had been exceptionally important in retaining the notion of the developmental field in clinical research (Opitz, 1982; Opitz and Gilbert, 1982; Opitz and Gilbert, 1993). The developmental field had been one of the most crucial findings of experimental embryology for evo-devo, for it demonstrated the principle of modularity in development (see Gilbert *et al.,* 1996). The medical evidence for modularity, as shown by syndromes, was expressed in the early 1800s, by the embryologist Johann Meckel (the younger), who noted that inherited syndromes showing the same constellation of affected organs indicated that those organs shared common developmental principles. Opitz updated this concept and related it to evolutionary developmental biology.Thus, medical developmental biology is also involved in the morphogenesis of evo-devo. Since «forbidden» phenoytypes would manifest as pathologies, medical developmental biology highlights developmental constraints (Galis, 1999; Galis and Metz, 2001).

When applied to evo-devo, medical developmental biology looks specifically at two of the great questions of evolutionary developmental biology: what changes in development have generated *Homo sapiens* from the other apes, and what is the source of normal variation within human populations. The finding by Alan Wilson's laboratory (e.g., King and Wilson, 1975) that humans and apes were morphologically disparate species but had remarkably similar protein-encoding genes was one of the key elements in initiating evo-devo (and was quoted extensively by Gould and by Jacob. This research proposed that regulatory genes were critical in creating the differences within primate populations and these differences may have been critical in the origins of the human species.

These molecular differences in gene regulation are now being found. Rockman and Wray (2002) have shown that quantitative changes in the expression of regulatory genes during development are probably *the* major source of variation within humans. Moreover, ordinary small-scale mutations contribute to large variations in transcription rates across the genome and thus to human variation. For instance, Rockman and colleagues (2003) find that a single base-pair substitution in the enhancer of one regulatory gene, that encoding interleukin 4 (IL4), creates a new binding site for the NFAT transcription factor and leads to a threefold increase in IL4 synthesis. This new binding site arose by point mutation on the lineage separating humans from the other great apes, and has created a polymorphism in the human population. Its positive selection has been shaped by selective forces on the diverse roles played by this protein in the immune response. Those who carry this polymorphism are more prone to asthma, allergies, atopic dermatitis, subacute sclerosing panencephalitis, and severe respiratory syncytium virus disase (perhaps due to IL4's role in IgE production and in inducing Th2 helper T-lymphocytes). However, this allele appears to be widespread in those populations who might benefit from enhanced protection against helminthic infections (see also Bamshad and Wooding, 2003). In another instance of the interaction between medical genetics and evo-devo, the gene encoding the FoxP2 transcription factor was found to differ between humans and all other mammals (Enard *et al.,* 2002). This gene appears to be critical in the cognitive and motor skills required for speech, and mutations lead to impairment of sentence making. With its enormous databases and catalogue of clinical polymorphisms, medical developmental biology may become exceptionally important in evolutionary developmental biology.

IV. Coda

There is a new revolution in developmental biology, and this revolution is at the periphery - the meeting of developmental biology with evolutionary biology, medicine, and ecology. These areas are themselves interacting with one another to highlight questions of developmental biology that had become peripheral - genetic assimilation and life history strategies; teratology and endocrine disruption; developmental constraints and the origin of *Homo sapiens*. Together, these constitute a larger «evolutionary developmental biology» that is shifting the balance of developmental biology from the «differentiation» question towards the «morphogenesis» question. The linkage of these areas will provide the second stage in the expansion of developmental biology and its reconciliation with every other area of the biological sciences. Moreover, it has the potential to explain the proximate causation for the evolution of biodiversity. If genetics is «Darwin's missing evidence» (Kettlewell, 1959), then it must include developmental genetics as well as population genetics and molecular genetics.

J. B. S. Haldane (1953), the editor of the volume in which Waddington published his paper on the two modes of evolution, concluded that symposium by using a wonderfully apt developmental metaphor:

"To sum up, then, a number of workers are groping from their own different standpoints towards a new synthesis, while producing facts which do not fit too well into the currently accepted synthesis. The current instar of the evolution theory may be defined by such book as those of Huxley, Simpson, Dobzhansky, Mayr, and Stebbins. We are certainly not ready for a new moult, but signs of new organs are perhaps visible.»

The articles in this Special Issue represent the progress in this field precisely a half-century from that symposium. I think that not only has a new moult occurred, but that a new evolutionary developmental biology has eclosed and is ready to fly.

Summary

The early studies of evolutionary developmental biology (Evo-Devo) come from several sources. Tributaries flowing into Evo-Devo came from such disciplines as embryology, developmental genetics, evolutionary biology, ecology, paleontology, systematics, medical embryology and mathematical modeling. This essay will trace one of the major pathways, that from evolutionary embryology to Evo-Devo and it will show the interactions of this pathway with two other sources of Evo-Devo: ecological developmental biology and medical developmental biology. Together, these three fields are forming a more inclusive evolutionary developmental biology that is revitalizing and providing answers to old and important questions involving the formation of biodiversity on Earth. The phenotype of Evo-Devo is limited by internal constraints on what could be known given the methods and equipment of the time and it has been framed by external factors that include both academic and global politics.

KEY WORDS: *evolutionary developmental biology, evo-devo, evolutionary embryology, ecological developmental biology, history*

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