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Lewis I. Held, Jr
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Introduction

Ever since Aristotle called insects "bloodless" [149] and Linnaeus banished them to a separate class that we now call the phylum Arthropoda [1329], we have had little reason to view insects as anything but alien lifeforms. After all, they have compound (vs. simple) eyes, six (vs. two) legs, and a chitinous (vs. calcified) exo- (vs. endo-) skeleton . . . plus they're so tiny that many escape our notice completely.

Our age-old chauvinism ended in 2001 when the genomes of humans and fruit flies became available for comparison [105,143,1946], and we could fathom the large (~50%) overlap of the respective gene repertoires [180,2486,2549]. Even our smug predictions of having many more genes were dashed [1905,2199]: we have ~22,000; they have ~15,000 [1771], though we can still cling to the slight excess to salvage some shred of superiority. As Gerry Rubin put it, flies turned out to be just "little humans with wings" [71].

The egotistical wall separating us from insects may have crumbled in 2001, but it had been badly cracked by unsettling findings on several earlier occasions. Those episodes are worth recounting, at least briefly, because they convey the thrill that scientists often feel upon discovering heretical facts that challenge a prevailing paradigm before it finally topples. To allow readers to experience these epiphanies in their purest form, the leading pioneers are quoted in their own words.

In 1822 the first hint of a similarity between vertebrate and arthropod body plans came to light when Étienne Geoffroy St.-Hilaire described his dissection of a crayfish (≈ lobster) [486,787]. He was startled to find that crayfish – and, by inference, insects as well – have the same strata of organs as vertebrates, though the layers are inverted. That is, the back of a crayfish corresponds to the belly of a vertebrate, and vice versa (boldface added):

> Je viens de trouver que tous les organes mous, c'est-à-dire, que les organes principaux de la vie sont reproduits chez les crustacés, et par conséquent chez les insectes, **dans le même ordre, dans les même relations et avec le même arrangement que leurs analogues chez les hauts animaux vertébrés** . . . **Quelle fut ma surprise**, et j'ajoute, de quelle admiration ne fus-je pas saisi, en apercevant une ordonnance qui plaçoit sous mes yeux tous les systèmes organiques de ce homard dans l'ordre où ils sont rangés chez les animaux mammifères? Ainsi sur les côtés de la moëlle épinière, je vis tous et chacun des muscles dorsaux; au-dessous étoient les appareils de la digestion et les organes thoraciques, plus bas encore, le coeur et tout

> le système sanguin, et plus bas enfin formant la dernière couche, tous et chacun des muscles abdominaux. [740][1]

The idea that a lobster is essentially an armored, upside-down mouse sounds as absurd today as it did then, but Geoffroy defended his theory by pointing out that the flatfish embodies an equally absurd, but undeniably real, instance of postural shift relative to other fish – albeit a rotation of 90°, versus the 180° he envisioned in the crayfish case. His analogy, clever though it may have been, failed to convince his colleague Georges Cuvier, and these titans of the French academic elite clashed in a historic debate (1830, Paris) that was widely deemed to have been won by Cuvier [74]. It took 172 years for Geoffroy's inference of an inversion to be vindicated by evo-devo research [83,1654]. The story of that redemption will be recounted in Chapter 1.

In 1915 the neuroanatomist Santiago Ramón y Cajal charted the wiring of neurons in the optic lobes of the fly brain [303]. He had wanted to understand the vertebrate brain but was daunted by its complexity, so he had sought a simpler nervous system that he could analyze in order to figure out the basics of the circuitry, with the intention of going back and applying what he learned to vertebrates. Surely, he thought, the fly must have a simpler visual system. But he found that, on the contrary, it is just as intricate, and it even operates in a similar way [1976]. Some of those similarties are covered in Chapter 3, and the chiasms to which he refers ("cruces intra-retinianos") are treated in Chapter 2 (boldface added):

> Confrontando esta retina ideal del insecto con la de los vertebrados (figuras 82 y 83), todas las dudas se disipan *in continenti*, imponiéndose imperiosamente las homologias esenciales sugeridas por Kenyon, Cajal y Zawarzin. Y todavia se acentuaria el parecido si se hubiera prescindido de los dos cruces intra-retinianos, que constituyen una de las originalidades más notables de la retina de los articulados . . . **Con todo lo cual no pretendemos afirmar que la retina de los insectos deje de ofrecer algunos rasgos de organización originales, especificos ó poco ó nada representados en los vertebrados.** [303][2]

In 1917 the embryologist Ross Harrison described extra legs that sprouted after he transplanted leg rudiments to ectopic sites on the opposite flanks of host salamanders [880]. Occasionally, the operations produced triplicated legs, and those

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[1] I just discovered that all the soft organs, as in the main organs of life, are found in crustaceans and consequently in insects **in the same order, with the same relations, and with the same arrangements as their analogs in the higher animals, the vertebrates** . . . **What surprise** and, might I add, what admiration came over me when, before my eyes, I saw a prescription that placed all the organic systems of this lobster in the same order in which they are arranged in mammals! On the sides of the dorsal cord, I saw each and every dorsal muscle; beneath them were the digestive and thoracic organs, under them the heart and the entire circulatory system, and finally beneath those, the abdominal muscles formed the last layer.

[2] All doubt is dispelled when comparing this ideal retina of the insect with the one of vertebrates (figures 82 and 83). The essential homologies, already suggested by Kenyon, Cajal and Zawarzin, become evident. If they lacked the two intra-retinal crossings, which is one of the most notable originalities of articulated organisms, their resemblance would be even more obvious . . . **With this being said, we do not try to claim that the retina of insects no longer offers original organizational characteristics, which may or may not be represented in vertebrates.**

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legs obeyed the same rules of symmetry that William Bateson had formulated in 1894 for triplicated legs of abnormal arthropods (insects and crustaceans) [160]:

> There may be further reduplication [of salamander legs], so that more or less complete triple limbs may result. The three limbs then have approximately the same relations as found by Bateson, especially in arthropods. [880]

In 1976 the notion that arthropods and amphibians regenerate their appendages by similar rules resurfaced [278], when the developmental biologists Vernon French, Peter Bryant, and Susan Bryant proposed a unifying model to explain how triplications occur at the cellular level (boldface added):

> The results of the contralateral grafts [of salamander leg blastemas] are **exactly analogous to those obtained with cockroaches** and can be explained in the same way. The handedness and axial orientation of the supernumerary limbs are the same as those of the stump. [673]

Their model has since been supplanted by alternative explanations [309,923], but the similarity of the underlying mechanisms upon which it was based has been confirmed genetically. The evidence for a common appendage algorithm in arthropods and vertebrates is presented in Chapter 6.

In 1978 the fly geneticist Edward Lewis echoed another theme (aside from limb triplications) from Bateson's 1894 classic *Materials for the Study of Variation* [160,1297]. In Bateson's vast collection of aberrant animal specimens there were many cases where one organ had been converted into the likeness of another – e.g., an antenna that developed as a leg instead. Bateson coined the term "homeosis" for such transformations.

Lewis studied homeotic mutations – the most famous of which, *bithorax*, converts the tiny third thoracic segment into a larger second thoracic segment, yielding a four-winged fly with two thoraxes [911]. His 1978 paper summarized his genetic dissection of this part of the fly's third chromosome, and it set forth a model for how the "Bithorax-Complex" (BX-C) dictates identities of body segments [1296]. Lewis's model was wrong in the number of genes expected for the BX-C (9 vs. 3) [1974], but it was right in the colinearity predicted between chromosomal loci and the segments they control [1218,1460,1461].

In 1984 a 180-base-pair motif was identified in the homeotic genes of both the BX-C and its sister "Antennapedia-Complex" (ANT-C) by Matt Scott's lab in the USA and Walter Gehring's lab in Switzerland [1463,1899,2037,2039]. It was named the "homeobox" [731] and the genes in these complexes, which specify consecutive groups of body segments, came to be called *Hox* genes [298]. The homeobox encodes a DNA-binding domain that allows proteins to regulate target genes by binding their *cis*-enhancers [1751]. Homeoboxes were subsequently found throughout the animal kingdom [509,732,972] (boldface added):

> The discovery of the homeobox . . . enforced the idea that evolutionarily distant organisms might share common developmental pathways and common genetic circuits. This idea is now taken for granted in all current genomic approaches, and today it seems strange that **it was completely unanticipated in 1980 at the beginning of the cloning era.**
>
> — Eric Wieschaus [2431]

> It is difficult to understand now how surprised people were by the finding of vertebrate cognates of *Drosophila* homeotic genes; it was quite amazing.
>
> — Denis Duboule [1899]

In 1988 mice were shown to have *Hox* complexes homologous to the combined BX-C and ANT-C of flies [2021], and in 1989 the order of genes in those clusters was found to be colinear with the order of body zones along the head–tail axis [552,790]. Why should flies and mice be using the same system of "area codes" to subdivide bodies that have overtly different metameric units – ectodermal segments versus mesodermal somites, respectively [430]? Evidently, *Hox* complexes act like abstract yardsticks to mark locations [31,1462] without regard to embryological origin (ectoderm or mesoderm) or histological character (segments or somites) [2114]. This ancient system of axial zonation is discussed in Chapter 1.

> Today we take the colinearity and clustering of vertebrate *Hox* genes for granted, and everyone thinks that it was a logical step after cloning *Drosophila* homeobox sequences in 1984. But it wasn't, mostly because our minds were not prepared for this.
>
> — Denis Duboule [1899]

In 1994 Geoffroy's old hypothesis of dorsal–ventral inversion was confirmed at the molecular level [83]. Vertebrates were shown to use the same signaling molecules as insects along their dorsal–ventral axis but to do so with inverted polarity. The inversion event itself was later traced to the base of the chordate phylum [1356]. The evidence that led to this conclusion is considered in Chapter 1.

In 1995 the fly's *eyeless* gene was shown to be capable of inducing extra eyes when it is artificially misexpressed at ectopic locations [844]. The spectacle of flies with eyes on their legs, etc., was shocking enough, but what startled the research community even more was the ability of the mouse's orthologous *Pax6* gene to elicit extra fly eyes in the same way. Could the same "master gene" be regulating the assembly of a compound eye in an insect and a camera eye in a vertebrate [732]? Evidence for and against this idea is presented in Chapter 3, along with an assessment of the many other parallels between the eyes of insects and those of vertebrates.

In 1996 this fast-moving field was codified by Rudy Raff, a tireless champion for evo-devo in the USA, in his monograph *The Shape of Life* [1847]. A sampling of his chapter titles conveys the scope of his synthesis: "Deep time and metazoan origins, The developmental basis of body plans, Building similar animals in different ways, Developmental constraints, Modularity, dissociation, and co-option." In the following passage from his preface, Rudy alludes to the progress that had been made since he and Thom Kaufman first laid the foundations for evo-devo with their seminal 1983 book *Embryos, Genes, and Evolution* [1848]:

> Over a decade has passed since *Embryos, Genes, and Evolution*, and an experimental discipline that integrates developmental and evolutionary biology has begun to coalesce. Most important, the whole emphasis of work on development and evolution has shifted to new ground due to the transformation of our understanding of the genes that regulate development. [1847]

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In 1999 Rudy founded the journal *Evolution and Development*, together with other leading lights (Wallace Arthur, Sean Carroll, Michael Coates, and Greg Wray). It quickly became the premier outlet for evo-devo researchers to publish their findings and has remained so ever since.

In 2000 the DNA sequence of the fruit fly genome was published [105], with the human genome following shortly thereafter. The expectation had been that the number of human genes would dwarf the number of fly genes [1373], but this prediction proved to be misguided [1771]. Indeed, the more that these two genomes have been compared, the more similar our "operating systems" appear to be, despite the differences in the anatomical "apps" that they control (boldface added):

> The remarkable similarity of the genetic regulation of development in distant organisms has heralded a new conception of evolution. It was a big surprise when evolutionary conservation of the Krebs cycle, the genetic code, and classes of structural proteins was extended to regulation of development. **The diversity of organisms had fooled everyone into thinking that the evolution of completely different regulatory processes, or at least completely different uses of the same genes, was likely to be responsible for evolutionary change.**
>
> — Matt Scott [2036]

The primary aim of the present book is to survey those unexpected similarities. Admittedly, these revelations are still so fresh that it is hard to know what to make of them. For that reason this book will inevitably be disappointing, since it cannot reach any firm conclusions based upon the piecemeal nature of the evidence. Even so, for those of us who happen to like Swiss cheese with our ham, we can still savor the taste in spite of the holes.

Aristotle was the first author ever to mention the fruit fly *Drosophila melanogaster* [801,1780,2204] (though it had no such name then) when he described a "gnat" emerging from vinegar slime in *History of Animals*, *c.* 350 BCE (Book 5, part 19, line 552b5) [149]. If he were alive today, he would surely be a card-carrying evo-devotee – surfing the internet databases to study the history of animals from a modern genomic perspective. There is also little doubt that he would be as amazed as the rest of us to see how much we resemble the little vinegar gnat when, like the mythical Orpheus – or better yet like Lewis Carroll's Alice – we descend into the hidden world beneath our superficial differences.