Article

How Did We Get Here?

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Summary

From the inheritance of acquired traits to natural selection to evo devo, evolutionary theory has itself evolved.

Today's evolution is not your grandfather's evolution. Molecular biology and genetics, crucial to our current understanding of evolution, didn't even exist as scientific disciplines during Charles Darwin's life. In fact, Darwin's evolution was not even *his* grandfather's evolution.

Erasmus Darwin published *Zoonomia* in 1794, an early attempt to provide an evolutionary account for life. He and Jean-Baptiste Lamarck thought that traits acquired during the lifetime of an animal could be inherited by the next generation. An extreme example disproves this notion: if the three blind mice lose their tails to the knife-wielding farmer's wife, the mice's offspring would nevertheless have tails. (On the other hand, if the mice were blind because of an inherited genetic mutation, the offspring may indeed be blind.)

Erasmus Darwin and Lamarck were wrong about the mechanism for evolution. But, in contrast to most of their contemporaries, who believed that each species was independently created by divine fiat and remained immutable, they were right in perceiving that evolution had occurred. That majority view still held in the middle of the 19th century, and anyone sympathetic to the notion of evolution was stymied by uncertainty about if-and total cluelessness about how-it happened. Then came Charles Darwin, who started with the simple philosophy that "something might perhaps be made out of this question by patiently accumulating and reflecting on all sorts of facts which could possibly have any bearing on it."

After more than 20 years of such patient accumulation and reflection, Darwin published *The Origin of Species* in 1859. He accomplished two vitally important things. He documented vast amounts of evidence to support the fact that evolution had occurred. He also provided the first plausible mechanism for evolution: natural selection.

Pigeon breeders, through selective breeding, could mold their stocks in just a few years by mating birds with characteristics the breeders liked. So, thought Darwin, why couldn't nature exercise a similar selective process? Geologists had realized that the earth was far older than had been previously thought. Over exceedingly long periods of time, Darwin realized, nature itself could mold organisms. Individuals with certain advantageous traits, such as thicker fur in cold climates or the ability to run faster when chased by predators, were more likely to survive and thus pass on those traits. Given enough time, entire new species could gradually come into being.

Darwin prosecuted his case so powerfully that within a few years of the publication of *The Origin of Species,* evolution was widely accepted in the scientific community. But natural selection as the mechanism was on less sure footing. What exactly was the source of the variations that natural selection was supposed to choose from? And then there was the fundamental problem with "monsters," the occasional freaks of nature.

**Freaks and Flies**

Gregor Mendel's now famous genetics research on pea plants, done in obscurity and virtually unread for decades, clearly showed how heritable traits made their way from one generation to the next. The work was published in 1865, but failed to attract attention until it was finally discovered by the biological community in 1900. Shortly thereafter, naturalist William Bateson became a passionate advocate of Mendel's laws of heredity. Bateson was also aware of monsters: "Insects with legs in the wrong place, crabs where a claw was transformed into a leg, pythons with extra ribs, frogs with extra cervical vertebrae, all these sorts of things," notes HHMI investigator Sean Carroll, professor of molecular biology and genetics at the University of Wisconsin-Madison. Bateson subscribed to Darwinian selection-but not too much. "We must relegate Selection to its proper place," he said in a 1909 essay commemorating the 50th anniversary of *The Origin of Species.* "Selection permits the viable to continue and decides that the nonviable shall perish.. Selection determines along which branch Evolution shall proceed, but it does not decide what novelties that branch shall bring forth."

For Bateson, big biological innovation required big mutations rather than the fine tuning associated with Darwinian gradual change. Biologists formed rival camps of mutationists and selectionists. The battle was at times unpleasant, in large part because of Bateson's caustic personality. The cure for all this contention, as usual, turned out to be more research.

The fabled labs of Thomas Hunt Morgan at Columbia University went through millions of tiny fruit flies to track heredity in the 1910s and 1920s. All those insects proved without a doubt that genes mapped to chromosomes and that mutations occurred in genes: heredity had a physical basis. Then, in the 1930s, mathematicians and biologists showed that it made sense to consider evolution as changes in the frequencies of particular genes in populations. The combination of Darwinian natural selection, Mendelian genetics, and "population genetics" seemed to many to account for all aspects of evolution. This second evolution revolution became known as the modern synthesis.

Ronald Fisher, one of the founders of the synthesis, argued that mutations with large effects were usually negative. He believed that most evolutionary change therefore had to result from the rise and subsequent spread of mutations that each had only tiny effects. So-called micromutation, which fit nicely with Darwin's view of slow, gradual change, became a key aspect of the modern, or neo-Darwinian, synthesis. With natural selection working on micromutations, selectionists and mutationists seemed to have made their peace. Scars from the battle, however, would have repercussions for almost the entire remainder of the 20th century.

"I think Bateson's strong personality and argumentative and dismissive tone about the role of Darwin's gradualism had a lot to do with the subsequent strong defense of micromutation that was incorporated in the neo-Darwinian synthesis," says HHMI investigator David Kingsley, a professor of developmental biology at the Stanford University School of Medicine. "Emotions ran so high on this issue that neo-Darwinians were also willing to overlook or try to dismiss evidence for large mutations." What possible survival advantage could a fly have with legs where its antennae should be? Large mutations, however, would continue to raise their literally ugly heads, and other body parts.

Darwin himself suspected that understanding the process of development would have great implications for understanding evolution. In development, a single fertilized egg grows into a complex complete organism. In evolution, a single ancestor species may give rise to a diversified set of species. The connections between evolution and development had thus long intrigued researchers. German anatomist Ernst Haeckel famously hypothesized that "ontogeny recapitulates phylogeny," meaning that an egg developing into an organism, ontogeny, went through all its ancestral forms, phylogeny, during gestation. But Haeckel's conjecture went too far.

"We've been trying to kill that idea for a long time," says Carroll. "I'd say that ontogeny and phylogeny are really interesting, and now let's figure out their relationship." Research in the second half of the 20th century revealed that development and evolution were indeed intimately connected-genetically based changes in the programs for development have huge implications for evolution. This third revolution in evolution is thus known as evo devo, for evolution of development. It started small, with two high school students.

**Weaving Evo Devo**

In the mid-1930s, teenagers Edward Lewis and Edward Novitski saw an ad in a magazine offering a batch of fruit flies for a dollar. They bought a starter set and began doing their own experiments. Later, they wrote to Calvin Bridges, a former Morgan student. Bridges, who had carefully bred and preserved lines of *Drosophila* with particularly interesting mutations, sent Lewis and Novitski some choice ones, as well as written notes on how to breed them.

Bridges had spotted an odd fly in 1915 that he bred to keep the mutation around for further study. Normal fruit flies have one pair of wings, behind which sit a pair of halteres, tiny club-shaped organs that improve fly flight. The mutant had another set of wings where the halteres should be, and thus was dubbed bithorax (because it looked like it had an extra thoracic segment). In fact, the insect's entire third body segment was transformed into a repeat of the second, winged, body segment.

"This was a largely normal body part, but in the wrong place," notes Carroll, author of *Endless Forms Most Beautiful*, about evo devo. "You have not just changed the coloration," notes Carroll. "You've changed the entire architecture." This kind of huge mutation, in which a body section is transformed into another section, is known as homeotic.

A few other homeotic mutations were discovered by the time Lewis joined the Caltech faculty in 1946. Lewis was particularly interested in how new genes arose. He thought that random gene duplications might be one of evolution's most potent tools. If a mutation changed the function of a crucial gene, the animal probably died. But with the gene there twice, one copy could carry on its normal, vital function, while the other was free to mutate and perhaps come up with something that made the animal even fitter. He therefore set out to study what appeared to be the repeated genes involved in the bithorax mutation.

The work took three decades. Meticulous research with millions of flies ultimately revealed that the entire Bithorax gene cluster was involved in the basic organization of the fruit fly's body, specifically the back half of it. When one of these genes mutated, the result was far more complex than a change in eye color; the very way the fertilized egg developed into a fly changed. Lewis shared the 1995 Nobel Prize in Physiology or Medicine for this fundamentally important work with Christiane Nüsslein-Volhard and Eric Wieschaus, who also identified key genes necessary for normal fruit fly development. (Novitski also made key contributions in his scientific career.)

In the 1970s, Thomas Kaufmann at Indiana University discovered another gene cluster, whose primary member was called *Antennapedia.* The Antennapedia complex governed the development of the fruit fly's front half, and homeotic mutations here led to flies designed by Rube Goldberg in collaboration with Hieronymus Bosch: legs where the mouth or antennae should be, mouth parts where legs belong, and other structural calamities. These homeotic mutations in effect take development down an alternate path-they act as master regulators that choose between alternate developmental fates.

Less monstrous are the alternate paths taken during normal development in related species. Numerous creatures have similar-sized genomes composed of virtually identical genes: the human and chimp genomes are more than a 98 percent match. Even a mouse's genome does not differ in size or content that much from our own. During development, however, genes are switched on and off in a symphony of expression. Just as two symphonies use notes and instruments in completely different ways, two species may use similar genomes in completely different ways during development. All animal species develop according to the control exerted by an unexpectedly small number of genes-a few hundred in the fly and only two to three times that many in us-that perform fundamental tasks, such as guiding the early decision of one part of an embryo to be the front and the other to be the back.

How crucial are these master control genes? Every animal has them. "And there's only one inescapable conclusion you can draw from that," says Carroll. "If all of these branches have these same genes, then you have to go to the base, the last common ancestor of all animals. You deduce that it must have also had these genes. So the whole radiation of animals, the whole spring of animal diversity, has been fed by essentially this same set of genes." And mutations or duplications in the master control genes give development whole new areas to explore, in turn helping drive evolutionary change.

"This means that in some sense, evolution is a simpler process than we first thought," says Carroll. "When you think about all of the diversity of forms out there, we first believed this would involve all sorts of novel creations, starting from scratch, again and again and again. We now understand that, no, evolution works with packets of information and uses them in new and different ways, in new and different combinations, without necessarily having to invent anything fundamentally new but new combinations."

Darwin dismantled the commonly held assumption that individual species were each created fresh and remained immutable. But, in an ironic recapitulation of that old error, even scientists believed for much of the 20th century that evolution freshly created the genetic programs for different organisms. As Carroll says, it's actually simpler than that-variations in the application of common genetic programs account for much of the differences in animal species. In the last paragraph of *The Origin of Species*, Darwin wrote, "There is grandeur in this view of life." Darwin's aesthetic appreciation of evolution seems ever more warranted.