The Ghost of Geoffroy Saint-Hilaire

Frog and fly genes revive the ridiculed idea that vertebrates resemble upside-down insects

By JOHN TRAVIS

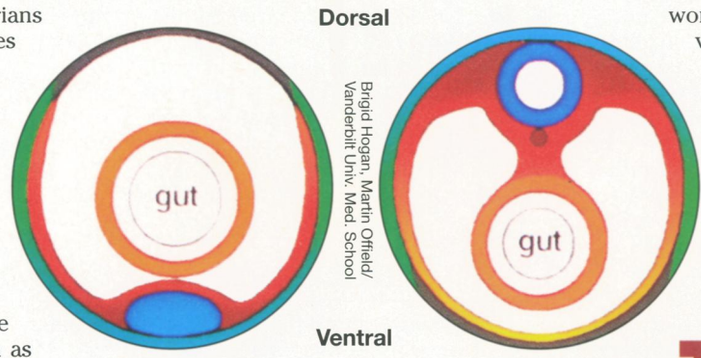
The year was 1830, the place Paris, and revolutionary ideas filled the air. To most historians, that setting recalls the troubles of Charles X, the French king forced to abdicate the throne in August. But to historians of science, it evokes memories of one of the greatest scientific debates of all time—the clash between eminent French zoologists Étienne Geoffroy Saint-Hilaire and Georges Cuvier.

In 1822, decades before Darwin propounded his theory of evolution, Geoffroy Saint-Hilaire wrote a provocative essay in which he linked the body plan of vertebrates such as humans to that of arthropods, a class of invertebrates that includes insects, crustaceans, and spiders. He noted that in vertebrates, some organs, such as the heart, lie in the belly, or ventral side, while other features, such as the spinal cord, reside in the back, or dorsal region.

Yet in the arthropods he studied, Geoffroy Saint-Hilaire observed that the location of comparable organs is reversed. For example, the arthropod's nerve cord, its version of a spinal cord, rests in the ventral side. "He dissected this famous lobster and turned it upside down," says Eddy M. De Robertis, a Howard Hughes Medical Institute investigator at the University of California, Los Angeles.

Geoffroy Saint-Hilaire consequently proposed that the vertebrate's body plan was a flipped-over version of the arthropod's. "If you lay down on your back and waved your arms, you would be doing what insects do when they walk," says Thurston C. Lacalli of the University of Saskatchewan in Saskatoon, chuckling over an image that has either amused or outraged scientists for more than a century.

Among the outraged was Cuvier, who led the opposition to Geoffroy Saint-Hilaire's underlying idea of a *unité de plan.* Geoffroy Saint-Hilaire theorized that all animals share a fundamental body plan upon which nature has imposed dramatic variations. At one point in their 1830 debate at the Academy of Sciences in Paris, Cuvier attacked his fellow zoologist, ticking off a list of differences between a duck and a squid that far surpassed a tally of similarities.



Brigid Hogan, Martin Offield/ Vanderbilt Univ. Med. School

A dorsal-ventral inversion can be seen in these idealized cross sections of the developing embryos of an arthropod (left) and a vertebrate (right). The embryonic regions that will generate the central nervous system (blue) and other major body systems are flipped.

Historians still discuss whether Geoffroy Saint-Hilaire battled Cuvier to a standoff. Clearly, however, most investigators of Geoffroy Saint-Hilaire's time rejected his ideas, including the notion of a dorsal-ventral inversion between animals with backbones and those without. Every few decades, a researcher or two would revive aspects of the *unité de plan,* only to be beaten down by the majority of scientific opinion. Embracing Geoffroy Saint-Hilaire even damaged the careers of some scientists. "This has been one of the untouchable things in zoology. Science is very unforgiving," says De Robertis.

Geoffroy Saint-Hilaire may have the last laugh, however. Researchers comparing the genes that turn on and off early in the development of frog and fly embryos made a surprising discovery recently. Genes with apparently equivalent functions in the two species work in opposite (that is, dorsal versus ventral) regions of their respective embryos.

"My guess is there really was an inversion. . . . It's a hypothesis that I find very attractive at the present time," says developmental biologist Edwin L. Ferguson of the University of Chicago.

To formulate his radical ideas, Geoffroy Saint-Hilaire examined adult organisms. His supporters today look at embryos, in which they believe it is easier to see similarities. "In adults," explains De Robertis, "the great changes in morphology mask any commonality."

Despite vast differences in their adult forms, frogs and fruit flies start off similarly. A sperm fertilizes an egg, forming a cell called a zygote. This initial cell then begins a series of cleavages that creates a ball of cells known as the blastula. (In the fruit fly, the blastula is actually considered one large cell, even though it contains more than one nucleus.)

Next comes gastrulation, the crucial step in which the blastula rearranges itself into three populations of cells: a surface layer, the ectoderm; a middle layer, the mesoderm; and an inner layer, the endoderm. From the ectoderm will eventually spring the skin and the nervous system, whereas the endoderm gives rise to the lungs and parts of the gut. The mesoderm completes the picture, producing muscles, the heart, reproductive organs, and other tissues.

In the last decade, researchers have

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discovered that components of the genetic machinery establishing the embryonic body plans of vertebrates and invertebrates are similar. For example, in species ranging from humans to mice to fruit flies, the homeobox genes, a collection of genes that guides the development of the embryo by turning on other genes, help distinguish the animal's eventual head from its tail—and all points in between.

In addition to defining the anterior and posterior of the embryo, genes apparently help divide the mesoderm, ectoderm, and endoderm into regions that will generate dorsal or ventral structures. In the fruit fly, a key gene called *dpp* directs the synthesis of a protein secreted by a select population of embryonic cells. Early in development, this protein somehow activates other genes necessary to the formation of dorsal structures. "Different levels of the protein specify different cell fates," explains Ferguson.

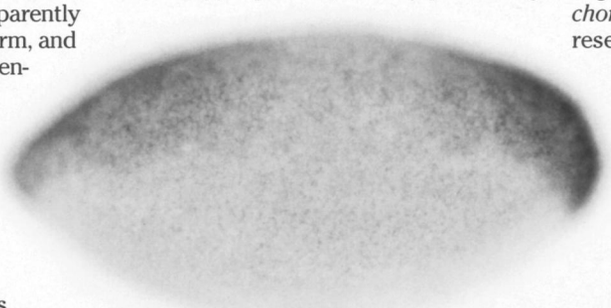
Researchers believe that *dpp*'s protein also prevents normally ventral insect structures, such as the fly's nervous system, from developing in the portion of the embryo that makes dorsal structures. "It actively suppresses neurogenesis," says Ethan Bier of the University of California, San Diego.

The attempt to find *dpp*'s equivalent in vertebrates eventually led to the revival of Geoffroy Saint-Hilaire's idea of a dorsal-ventral inversion, says Ferguson. The counterpart turned out to be *bmp-4*, a gene that operates in the ventral region of the frog embryo. Though researchers cloned *bmp-4* a number of years ago, "people just didn't make the connection," says Ferguson.

At least, not until last year. Then, two German researchers noted in a letter published in the Sept. 1, 1994 NATURE that the two genes act in opposite areas of embryos but appear to perform similar functions. They suggested that, not long after the primitive versions of vertebrates and insects diverged on the evolutionary tree, the vertebrate line experienced a dorsal-ventral inversion. "We propose that the longitudinal nerve cords of insects and vertebrates derive from one and the same centralized nervous system in their common ancestor," wrote Detlev Arendt and Katharina Nübler-Jung of the Albert Ludwigs University in Freiburg.

A few years ago, researchers exploring the dorsal-ventral patterning of fruit fly embryos also became intrigued by a gene called *sog*. The gene appeared to counteract the influence of *dpp* and allow ventral structures such as the fly's nervous system to form. After researchers cloned *sog* last year, they discovered that the gene generates its protein only in the ventral part of the embryo. As result, the presence of *sog*'s protein seems to define a region where *dpp*'s protein will not work.

"You need *sog's* protein to keep *dpp*'s from leaking out of the dorsal region," says Bier, a member of one of the three groups that independently cloned the *sog* gene last year. Investigators are not certain how *sog*'s protein accomplishes that task, however. It may, for example, simply bind to *dpp*'s protein, thereby preventing the dorsally made protein from turning on genes.



Ethan Bier/Univ. of California, San Diego

In this developing fruit fly embryo, biologists have used different stains to highlight the presence of two proteins, sog (dark area) and dpp (light area). Sog defines the ventral portion of the embryo, dpp the dorsal.

Recently, while studying the development of frog embryos, investigators inadvertently unearthed one of *sog*'s vertebrate relatives—and, bringing a smile to Geoffroy Saint-Hilaire's ghost, it guides dorsal development. In the Dec. 2, 1994 CELL, De Robertis and his colleagues reported isolating a gene called *chordin*.

Chordin's protein is normally found in the dorsal regions of an embryo, where the frog's nervous system forms. But De Robertis' group forced other regions to make the protein by injecting into embryos *chordin* messenger RNA (mRNA) a DNA-derived molecule that contains the instructions for building the gene's protein. As a result, embryonic regions that would normally generate ventral structures began producing dorsal structures.

Once researchers cloned *chordin,* they quickly linked it to *sog.* In the Jan. 12, 1995 CELL, Bier and his colleague Vincent François analyzed the sequence of amino acids that makes up the proteins encoded by *sog* and *chordin*. Despite some differences in their sequences and the fact that they operate in diametric regions of the embryo, the two proteins appear homologous, which means they probably perform the same tasks in their respective embryos. "We don't believe there's any difference in how *sog* functions in flies and *chordin* functions in frogs," says Bier.

A dramatic series of experiments, detailed in the July 20 NATURE, supports that conclusion. The fly protein encoded by *sog* and the frog protein encoded by *chordin* can be substituted for one another in developing frog and fruit fly embryos, reports a collaboration of groups headed by Ferguson, De Robertis, and F. Michael Hoffmann of the University of Wisconsin Medical School in Madison.

The investigators injected *sog* mRNA into frog embryos and observed that it promoted the maturation of dorsal structures, just as *chordin* normally would. *Sog*'s protein behaved entirely like *chordin*'s, says Ferguson. And when the researchers injected *chordin* mRNA into fruit fly embryos, it induced ventral development, as *sog* normally does.

From these and other experiments—*dpp* mRNA, which promotes dorsal development in flies, induces ventral development when injected into frogs—researchers conclude that *sog* and *dpp* have the same roles in the developing fly as *chordin* and *bmp-4*, respectively, have in frog embryos. But, as Geoffroy Saint-Hilaire might have predicted, the locations in which the equivalent genes act are inverted.

Though many researchers are now more willing to discuss Geoffroy Saint-Hilaire's ideas, most remain cautious about accepting his conclusions. Considering the historical opposition to the proposal, they stress the need to discover and compare more genes involved in patterning the embryo, including genes from a greater variety of species.

"When the body plan is so different, one pair of genes won't do it. How much do we need to convince people? Do we have to know how 100 genes interact or 10?" wonders Nicholas D. Holland, a developmental biologist at Scripps Institution of Oceanography in La Jolla, Calif.

In addition to settling the Geoffroy Saint-Hilaire–Cuvier debate, researchers note, unearthing the genes that forge the body plans of diverse species will reveal which developmental genes all vertebrates and invertebrates share. That, in turn, should provide insight into the primitive organism that gave rise to both.

"We're trying to weave a picture of how the common ancestor looked. We're getting there," says De Robertis.

With the tools of modern genetics, developmental biologists have resurrected Geoffroy Saint-Hilaire's idea that vertebrates are arthropods walking on their backs. "You could have been laughed out of science the last 150 years for suggesting this. But the question is now alive again," says Holland. "Maybe he wasn't as wrong as we thought." □