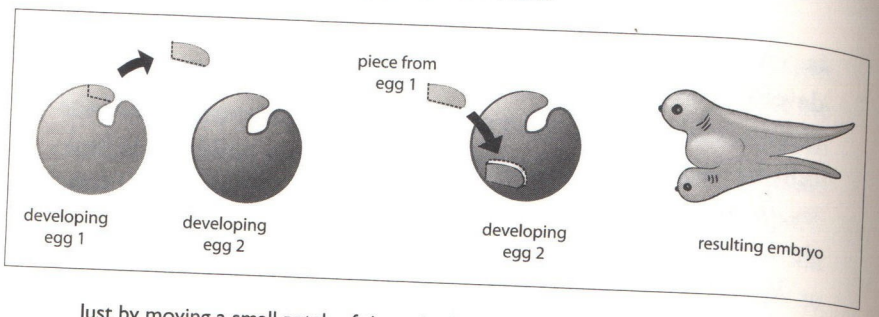


Just by moving a small patch of tissue in the embryo, Mangold produced twins.

was so skilled that the grafted embryos actually continued to develop, giving her a pleasant surprise. The grafted patch led to the formation of a whole new body, including a spinal cord, back, belly, even a head.

Why is all this important? Mangold had discovered a small patch of tissue that was able to direct other cells to form an entire body plan. The tiny, incredibly important patch of tissue containing all this information was to be known as the Organizer.

Mangold's dissertation work was ultimately to win the Nobel Prize, but not for her. Hilde Mangold died tragically (the gasoline stove in her kitchen caught fire) before her thesis could even be published. Spemann won the Nobel Prize in Medicine in 1935, and the award cites "his discovery of the Organizer and its effect in embryonic development."

Today, many scientists consider Mangold's work to be the single most important experiment in the history of embryology.

At roughly the same time that Mangold was doing experiments in Spemann's lab, W. Vogt (also in Germany) was designing clever techniques to label cells, or batches of them, and thus allow the experimenter to watch what happens as the egg develops. Vogt was able to produce a map of the embryo that shows where every organ originates in the egg. We see the antecedents of the body plan in the cell fates of the early embryo.

From the early embryologists, people like von Baer, Pander, Mangold, and Spemann, we have learned that all the parts of our adult bodies can be mapped to individual batches of cells in the simple three-layered Frisbee, and the general structure of the body is initiated by the Organizer region discovered by Mangold and Spemann.

Cut, slice, and dice, and you'll find that all mammals, birds, amphibians, and fish have Organizers. You can even sometimes swap one species' Organizer for another. Take the Organizer region from a chicken and graft it to a salamander embryo: you get a twinned salamander.

But just what is an Organizer? What inside it tells cells how to build bodies? DNA, of course. And it is in this DNA that we will find the inner recipe that we share with the rest of animal life.

OF FLIES AND MEN

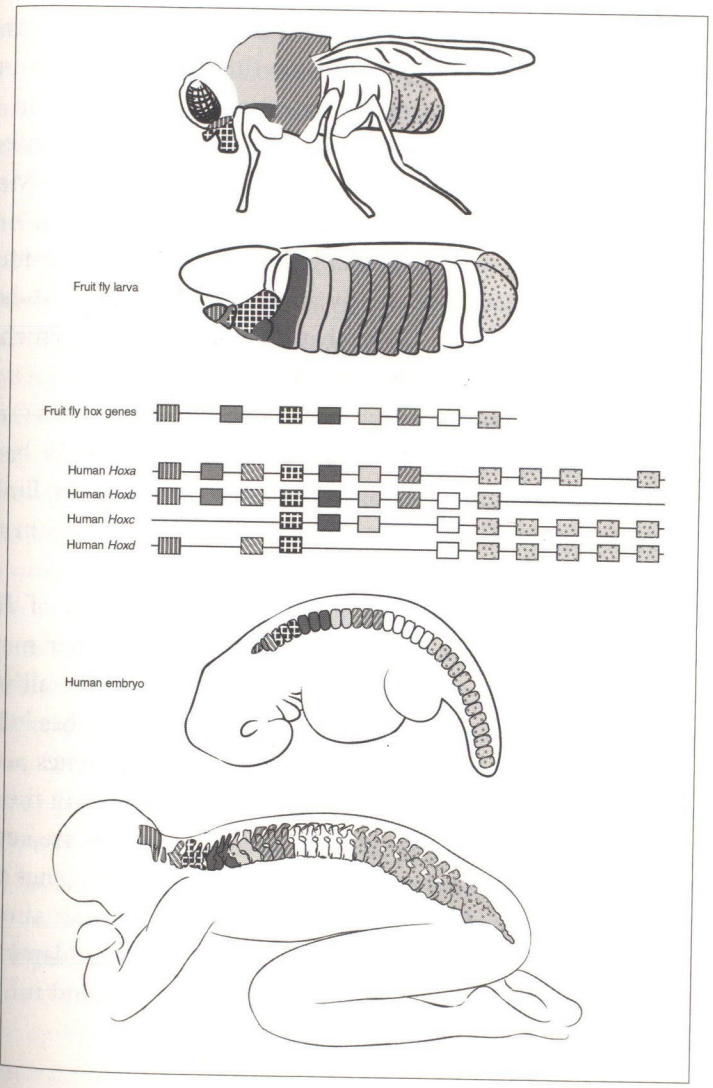
Von Baer watched embryos develop, compared one species to another, and saw fundamental patterns in bodies. Mangold and Spemann physically distorted embryos to learn how their tissues build bodies. In the DNA age, we can ask questions about our own genetic makeup. How do our genes control the development of our tissues and our bodies? If you ever thought that flies are unimportant, consider this: mutations in flies gave us important clues to the major body plan genes active in *human* embryos. We put this kind of thinking to use in the discovery of genes that build fingers and toes. Now we'll see how it tells us about the ways entire bodies are built.

Flies have a body plan. They have a front and a back, a top and a bottom, and so on. Their antennae, wings, and other appendages pop out of the body in the right place. Except when they don't. Some mutant flies have limbs growing out of their heads. Others

have duplicate wings and extra body segments. These are among the fly mutants that tell us why our vertebrae change shape from the head end to the anal end of the body.

People have been studying abnormal flies for over a hundred years. Mutants with one particular kind of abnormality got special attention. These flies had organs in the wrong places—a leg where an antenna should have been; an extra set of wings—or were missing body segments. Something was messing with their fundamental body plan. Ultimately, these mutants arise from some sort of error in the DNA. Remember that genes are stretches of DNA that lie on the chromosome. Using a variety of techniques that allow us to visualize the chromosome, we can identify the patch of the chromosome responsible for the mutant effect. Essentially, we breed mutants to make a whole population where every individual has the genetic error. Then, using a variety of molecular markers, we compare the genes of individuals with the mutation to those without. This allows us to pinpoint the region and the likely stretch of chromosome responsible for the mutant effect. It turns out that a fly has eight genes that make such mutants. These genes lie next to one another on one of the long DNA strands of the fly. The genes that affect the head segments lie next to those that affect the segments in the middle of the fly, the part of the body that contains the wings. These bits of DNA, in turn, lie adjacent to the ones that control the development of the rear part of the fly. There is a wonderful order to the way the genes are organized: their position along the DNA strand parallels the structure of the body from front to back.

Now the challenge was to identify the structure of the DNA actually responsible for the mutation. Mike Levine and Bill McGinnis, in Walter Gehring's lab in Switzerland, and Matt Scott, in Tom Kauffman's lab in Indiana, noticed that in the middle of each gene was a short DNA sequence that was virtually identical in each species they looked at. This little sequence is called a homeobox. The eight genes that contain the homeobox are called *Hox* genes.



Hox genes in flies and people. The head-to-tail organization of the body is under the control of different *Hox* genes. Flies have one set of eight hox genes, each represented as a little box in the diagram. Humans have four sets of these genes. In flies and people, the activity of a gene matches its position on the DNA: genes active in the head lie at one end, those in the tail at another, with genes affecting the middle of the body lying in between.

When the scientists fished around for this gene sequence in other species, they found something so uniform that it came as a true surprise: *versions of the* Hox *genes appear in every animal with a body.*

Versions of the same genes sculpt the front-to-back organization of the bodies of creatures as different as flies and mice. Mess with the *Hox* genes and you mess with the body plan in predictable ways. If you make a fly that lacks a gene active in a middle segment, the midsection of the fly is missing or altered. Make a mouse that lacks one of the genes that specifies thoracic segments, and you transform parts of the back.

Hox genes also establish the proportions of our bodies—the sizes of the different regions of our head, chest, and lower back. They are involved in the development of individual organs, limbs, genitalia, and guts. Changes in them bring about changes in the ways our bodies are put together.

Different kinds of creatures have different numbers of *Hox* genes. Flies and other insects have eight, mice and other mammals thirty-nine. The thirty-nine *Hox* genes in mice are all versions of the ones that are found in flies. This similarity has led to the idea that the large number of mammalian *Hox* genes arose from a duplication of the smaller complement of genes in the fly. Despite these differences in number, the mouse genes are active from front to back in a very precise order just as the fly genes are.

Can we go even deeper in our family tree, finding similar stretches of DNA involved in making even more fundamental parts of our bodies? The answer, surprisingly, is yes. And it links us to animals even simpler than flies.

DNA AND THE ORGANIZER

At the time when Spemann won the Nobel Prize, the Organizer was all the rage. Scientists sought the mysterious chemical that

could induce the entire body plan. But just as popular culture has yo-yos and Tickle Me Elmo dolls, so science has fads that wax and wane. By the 1970s, the Organizer was viewed as little more than a curiosity, a clever anecdote in the history of embryology. The reason for this fall from grace was that no one could decipher the mechanisms that made it work.

The discovery of *Hox* genes in the 1980s changed everything. In the early 1990s, when the Organizer concept was still decidedly unfashionable, Eddie De Robertis's laboratory at UCLA was looking for *Hox* genes in frogs, using techniques like Levine and McGinnis's. The search was broad and it netted many different kinds of genes. One of these had a very special pattern of activity. It was active at the exact site in the embryo that contains the Organizer, and it was active at exactly the right time of development. I can only imagine what De Robertis felt when he found that gene. He was looking at the Organizer, and there in the Organizer was a gene that seemed specifically to control it or be linked to its activity in the embryo. The Organizer was back.

Organizer genes started popping up in laboratories everywhere. While doing a different kind of experiment, Richard Harland at Berkeley found another gene, which he called *Noggin*. *Noggin* does exactly what an Organizer gene should. When Harland took some *Noggin* and injected it into the right place in an embryo, it functioned exactly like the Organizer. The embryo developed two body axes, including two heads.

Are De Robertis's gene and *Noggin* the actual bits of DNA that make up the Organizer? The answer is yes and no. Many genes, including these two, interact to organize the body plan. Such systems are complex, because genes can play many different roles during development. *Noggin,* for example, plays a role in the development of the body axis but is also involved with a host of other organs. Furthermore, genes do not act alone to specify complicated cell behaviors like those we see in head development.