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The Interpretation of Genes

The "expression" of a genome is best understood as a dialogue with an organism's environment. That dialogue, not the genes alone, determines which ant becomes a queen, which fish becomes a male.

We sometimes think of the environment as "out there," a place separate from us, a place we can enter and leave at will. But the environment is, quite simply, the context for all of life; it is what makes us what we are. Plants in dry soil grow deeper roots than those in wet soil. Turtle eggs become male or female depending on temperature. A fish may become female in one social environment, male in another. Genes not only direct, they also take orders. In a sense, our genes are the means by which the environment regulates our development.

Everything about us--from the shape of a toe to the shape of a protein, from the year we enter puberty to the amount of stress hormone we release when another car gets our parking space--is a manifestation of an ongoing conversation between genome and environment. This conversation started billions of years ago, when life began, and goes on every minute of our lives. Yet, strangely, it's a conversation to which most biologists turned a deaf ear for decades, starting in the 1940s, when the focus of biological research became overwhelmingly genetic. We've all read or been told repeatedly that genes provide a "blueprint" for the body, that genes "program" development, that we are "products of our genes." A 1996 introductory biology text used by more than half of all college biology majors in the United States asserts: "An organism's development is largely determined by the genome of [the fertilized egg] and the organization of the cytoplasm of the egg cell." No mention is made of any influences outside the egg.

How did biologists come to snub so thoroughly one partner in the developmental conversation? The answers lie deep in the political and scientific history of biology. Decades before the advent of genetics in 1900, biologists sought to understand heredity by studying development, the process by which organisms take shape from seemingly formless fertilized eggs. Indeed, for the first experimental embryologists, the most obvious place to look for answers to the mysteries of heredity was not deep in the genome--an entity whose existence they barely suspected--but within the environment of the embryo. During the latter half of the nineteenth century, biologists showed, for example, how different color morphs of the same butterfly species resulted from changes in temperature. Others examined the effects of ion or nutrient levels on development or looked at how environmental factors such as

temperature could determine sex.

Then, in the early twentieth century, a confluence of discoveries and new technologies turned the attention of most biologists to genetics and physiology. Increasingly, in the West, biologists saw every individual as a self-contained unit whose study could answer virtually every biological question. Developmental biologists focused their attention on laboratory experiments in which the role of the environment was deliberately eliminated.

In the Soviet Union, however, biologist Trofim Lysenko believed that environment determined phenotype--that is, all of an organism's observable attributes, both structural and functional. As a student, Lysenko had been laughed at by geneticists; once he rose to power, he denounced old acquaintances and even mentors. Under Stalin and Lysenko, an entire generation of Soviet geneticists was exiled or murdered. Those who survived fled to Europe or to North or South America.

Biologists in the West recoiled violently from Lysenkoism. Many had lost personal friends in the purge or were themselves expatriate Soviets who had fled. The very idea that the environment influences phenotype became associated with the worst aspects of Stalin's bloodthirsty reign, with Communism, and with left-wing politics in general--but not with science.

In the 1940s and 1950s, a handful of Europeans and Americans attempted to reintroduce environmental considerations into developmental biology but met with little success. The molecular genetics revolution of the 1960s swept up many of the brightest young minds. Throughout the 1960s and 1970s, biologists interested in the effects of environment on development, survival, and reproduction worked primarily in ecology, agriculture, conservation biology, and related fields.

As developmental biologists increasingly focused on how genes "determine" phenotype, they turned to just a handful of "model" organisms that would reproduce rapidly and easily, primarily in the laboratory. Studies of the development of six animals-nematode worms, Drosophila fruit flies, zebra fish, African clawed frogs, domestic chickens, and house mice--formed the basis for nearly all we know about the genetics of development in animals. All six share certain traits, such as rapid development and early sexual maturation, that tend to minimize the effects of environment.

Jessica Bolker, an evolutionary developmental biologist at the University of New Hampshire, has argued that biologists, in choosing organisms little affected by the environment, have unwittingly reinforced assumptions about the primacy of genes. All six of these lab organisms give molecular genetics the answer it expects, namely, that genes rigidly program development, independent of the environment of the embryo. As Bolker says, "Most of our models are small and fast and hardwired .... And so we think of development as being hardwired."

But in the past decade biologists have come to realize that development is far from hardwired; instead, organisms show enormous developmental plasticity. Very recently, a new field of study--called ecological developmental biology, or eco-devo--has emerged. Eco-devo examines how developing individuals integrate environmental and genetic information, as well as how this process of integration influences the direction of evolution.

A basic tenet of eco-devo is that individuals with the same genes can turn out differently, depending on the environment in which the embryos find themselves. This plasticity, however, is not a general trait covering everything an organism does and is. Instead, plasticity itself varies across traits and species.

Sonia Sultan, of Wesleyan University in Middletown, Connecticut, has studied plasticity in four closely related species of buckwheat in the genus Polygonum. One of the four produced different-size leaves in response to changes in light intensity, whereas another species did not adapt to light at all. Sultan has also shown that a species that is plastic with respect to one trait, such as leaf size, may show little plasticity with respect to another.

Her four species of buckwheat differed in the magnitude, direction, and timing of plasticity in traits as varied as leaf size, root length and form, and rate of photosynthesis. These differences corresponded roughly to the ecological distribution of the plants. For instance, the generalist species Polygonum

persicaria was quite plastic. It reproduced well in poor conditions (doubling its leaf tissue in low light, for instance) but did better than the other three species in environments rich in light, water, or nutrients. By contrast, P. hydropiper, a more specialized species, showed far less plasticity. In poor, shady conditions it increased leaf tissue very little, and it only slightly increased its reproductive output--as measured by the number and size of its fruits--even in the most resource-rich environments. The species apparently could not take advantage of a bonanza.

Clearly, the environment somehow influences the genetic pathways that guide the development of the phenotype. British biologist C.H. Waddington considered how that might happen. He found that two distinct triggers--one environmental and one genetic--can activate the same molecular pathway during development. In the 1940s he was struck by the fact that ostriches hatch with calluses on their chests and abdomens, in just those places where contact with the ground later abrades the skin. Skin that is rubbed regularly becomes thicker and tougher as skin cells proliferate, as a glance at our heels and toes will confirm. But our own calluses are triggered by the abrasion itself. Waddington suggested that in ostriches, the trigger for making calluses had been transformed from an environmental switch to a genetic one--a process he called "genetic assimilation."

Such developmental switches can be found anywhere in the network of genes involved in the formation of a trait. Ehab Abouheif, now at the University of Chicago, has demonstrated this idea beautifully in wingless ants. Most ant species have several castes. Pheidole morrisi has four: two with wings (queens and males) and two wingless (soldiers and workers). The network of six genes that regulates wing formation in these ants does the same thing in fruit flies (Drosophila melanogaster). And the winged ant castes express the six genes controlling wing formation in almost exactly the same way as fruit flies express them. These genes constitute a sort of gene "cascade," with one gene coding for a protein that in turn regulates the next gene. In soldiers, the first five genes are expressed normally, `just as in the winged queens', but the most downstream gene in the cascade is not. So at the last moment, genetically speaking, the soldier ants shut off wing formation. In the workers, wing formation is interrupted farther upstream in the gene cascade.

Sisters in an anthill are 75 percent genetically identical. But whether they become soldiers, workers, or queens depends not on any differences in their genes, but on a set of environmental switches. At the first switch, the right light and temperature cause the ant embryos to release a burst of juvenile hormone, setting them on the path to becoming queens. Otherwise they become soldiers or workers. At a second switch, a protein-rich diet can trigger another pulse of juvenile hormone, turning the embryos into soldiers; on a poorer diet, they become workers. Both switches operate by means of a hormone, but the triggers that throw the switch--food, temperature, and light--are purely environmental.

In three other ant species, Abouheif found, wing formation was interrupted at a different point in every caste. He concludes that although the network of genes for wing formation is evolutionarily stable--conserved in various insects over some 300 million years--ants can turn off wing formation anywhere in the network. Making wings is a conservative process, but not making them is a flexible one. Abouheif hypothesizes that such evolutionary flexibility may be a general characteristic of organisms that have more than one form.

The idea that traits can be controlled by multiple triggers, both endogenous (originating within the organism) and exogenous (originating outside it), is generalizable and useful. The more medical investigators understand the triggers that instruct 'juvenile brain cells to multiply and form healthy new brain tissue, for example, the more success they may have turning on this activity in adults whose brains have been damaged (ultimately, with a drug that mimics the endogenous trigger). And understanding exogenous triggers in development can help identify which synthetic compounds are likely to wreak havoc on humans and other organisms when released into the environment.

The mechanisms for these triggers will almost certainly lie among the signaling molecules (hormones and neurotransmitters, for instance) that cells use to talk among themselves. Signaling molecules appear to be the means by which an organism converses with its environment, both during early development and throughout life. Other molecules called "heat-shock proteins" also seem to act as switches that can decrease or increase plasticity, especially when an organism is under stress.

As we have seen, signals from the environment can be physical: temperature, light, pressure, abrasion. They can also be molecular (when, for example, a compound that mimics a hormone alters gene expression) or social. Social milieus can induce many fish to change from male to female and back again. Take the Japanese goby Trimma okinawae. If the resident male in a group leaves or dies, one of the group's females can become a male. But if a larger male then shows up, the recently remodeled "he" reverts to a "she." Such transformations can take place in as little as four days.

The development of some animals is influenced by predators. A substance released by predatory dragonfly larvae causes wood frog (Rana sylvetica) tadpoles to grow smaller than usual and to develop a deeper tail musculature (which seems to enable faster swimming and sharper turns). To effect these changes, the dragonfly larvae need only be in the water; they needn't actually be attacking the tadpoles. Similarly, the tiny water flea (Daphnia cucullata) develops a large protective "helmet" when predaceous larvae of the Chaoborus fly are present in the water nearby. And Daphnia is a predator in its own right, capable of inducing changes in its prey: green algae. Chemicals released by grazing water fleas cause the algae to give up the single-celled life and form colonies.

Relations between symbiotic bacteria and their hosts are another major strand of the eco-devo tapestry. The most detailed work in this area comes from the laboratory of Margaret McFall-Ngai at the University of Hawaii, where biologists study codevelopment in the squid Euprymna scolopes and the luminescent bacterium Vibrio fischeri. The bacterium guides normal development of the squid's light organs, which illuminate the squid's body so that it does not appear to predators as a conspicuous dark silhouette against the brightly lit surface of the ocean.

The immature light organs of a young squid develop a field of ciliated cells, which help draw Vibrio in from ocean water, as well as a series of deep pockets, or crypts, in which these bacteria will live. Within just a few hours, the new arrivals induce the cells of the light organs to swell and to grow tiny, hairlike microvilli. These changes help the bacteria flourish within the light organs. Young squid raised experimentally in water without Vibrio don't receive the right molecular signals and thus fail to go through normal development.

Invertebrates aren't the only organisms to have coevolved with bacteria. Mammals and other vertebrates are walking ecosystems. We humans normally carry hundreds of kinds of bacteria in our mouths alone. And these symbiotic organisms are not merely the inevitable result of living in a microbe-ridden world. Colonizing the body soon after birth, they are in fact essential for normal development, as has been shown in laboratory studies of mice raised in sterile environments. Development of nearly all the major organ systems is aberrant in these "germ-free" mice, says McFall-Ngai. The lining of the intestines, for instance, appears to have evolved to interact with bacteria. A few days before mice are weaned, when bacteria normally first appear in the gut, the intestinal cells cover themselves with a sugar called fucose, on which some symbiotic bacteria can live. If none of the right bacteria show up, the fucose disappears. But if the right ones do show up, they induce the gut cells to make more fucose. "The host tissues," writes McFall-Ngai, "are poised for interaction with the symbiont." Germ-free mice, which never encounter their coevolved symbionts, need 30 percent more calories to live than do mice with a full complement of gut bacteria, because vertebrates generally depend on such bacteria to help digest food and even to synthesize vitamins.

One of the best-known examples of how environment can influence development comes from research on endocrine disrupters--molecules in the environment that bind to receptors that normally link to the body's own hormones. Some of these molecules are natural substances, such as the plant estrogens in soy-based baby formula and other soy products. Many others are human made, including the plastic stabilizers in baby bottles, pacifiers, dental sealants, plumbing pipes, and gallon milk jugs, not to mention dispersants used to spread pesticides or to keep the spots off dishes in dishwashers.

Some of the most disturbing news on endocrine disrupters recently emerged from the laboratory of Tyrone Hayes, a developmental endocrinologist at the University of California, Berkeley. Hayes's lab showed that minute amounts of atrazine, a nearly ubiquitous herbicide, can derail reproduction in natural populations of leopard frogs by causing males to make eggs (see "Another Silent Spring?" page 56).

Why is the study of eco-devo blossoming now? One reason is concern over the increasingly obvious effects of endocrine disrupters. Another, say several investigators, is the infectious zeal of developmental biologist Scott Gilbert, who in the past two years added a chapter on eco-devo to his bestselling developmental biology textbook. Gilbert recently published an influential review article in the journal Developmental Biology describing and naming the new field, and organized, with Jessica Bolker, a symposium on the subject. Converts to eco-devo, who come from every area of biology, are extraordinarily enthusiastic.

All the enthusiasm in the world wouldn't have sufficed, however, without the major advances in genetics of the past decade. Abouheif's research on developmental switches in wingless ants is a good example of how developmental genetics (including the many studies already done on fruit flies) provided the basis and tools to do eco-devo. The new tools--which include polymerase chain reaction, a technique for multiplying traces of DNA, and microarray analysis, a method for simultaneously studying the expression of tens of thousands of genes--are enabling scientists to ask and answer whole new sets of questions. Many bacteria that live in animals, for instance, cannot be cultured in the lab, and they occur in numbers too low to detect by conventional methods. Only recently, with the advent of microarray analysis, have biologists been able to sample and characterize whole communities of microorganisms, whether in the mouth, the gut, or the soil.

Just as important as the new technologies is an increasing emphasis on cross-disciplinary work. Hayes recalls that when he was in graduate school, biologists knew everything about me genetics of Xenopus laevis, the African clawed frog, but little about the animal itself. "Everything was so specialized" he says. Now he sees entire fields as tools to ask larger questions: "I used to think of endocrinology as a field, and now I think of it as a tool to understand something else, to understand biology."

Ecological developmental biology may lead to fundamental changes in the way biologists think. For example, an assumption of standard evolutionary theory has been that genetic differences rigidly determine the relative success or failure of organisms. But phenotypic plasticity implies a degree of play, or looseness, in selection processes. Biologist Philip Yund, of the University of Maine, says that when biologists better understand how environmental information is incorporated into developmental processes, they will have a much more sophisticated understanding of how selective pressures form the phenotype over evolutionary time.

Hayes points out that leopard frog populations have now been exposed to atrazine for some forty years, long enough for selective forces to have changed their biology. "Effectively, we've done a pretty awful experiment," says Hayes, who speculates that a population of frogs living in a pond with high levels of the herbicide might evolve toward early metamorphosis and delayed sexual maturity. If they can get out of the pond soon enough, he reasons, their gonads could complete development away from the influence of the atrazine. In the future, Hayes will be looking for signs that leopard frogs are evolving in response to this herbicide.

Just as our environment is the context for how we become who we are, we are also the context for the development of other organisms--a conversation of which we are only now becoming fully aware.

Another Silent Spring?

That frogs are disappearing all over the world is hardly news. But that minute amounts of a common herbicide can demasculinize frogs was front-page news for days last spring, thanks to the work of developmental biologist Tyrone Hayes, of the University of California, Berkeley. Atrazine, considered harmless because it breaks down in a few days, is the most commonly used herbicide in the world. Farmers make up for its rapid breakdown by applying it in huge quantifies. In the United States alone, farmers spray more than 60 million pounds of it each year, on corn, soybeans, and other crops. Rivers and streams in agricultural areas may contain 100 to 2,300 parts per billion (ppb). The ubiquitous herbicide even falls in rainwater--1 ppb in non-agricultural areas and up to 40 ppb in agricultural areas.

Early laboratory studies showed gross malformations in amphibians exposed to atrazine, but this effect occurred only at concentrations that animals in the wild would rarely encounter. Investigators did not look for subtler effects, so atrazine was declared safe for the environment, and the safe level for

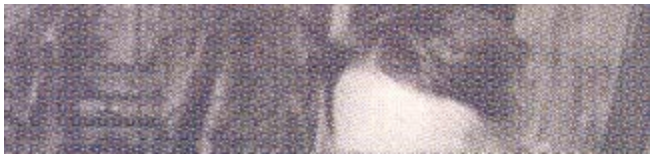
drinking water was set at 3 ppb. But Hayes's lab has shown that doses as low as 0.1 ppb turned male Xenopus laevis tadpoles into hermaphrodites, with three ovaries and three testes; doses of 1 ppb reduced the size of muscles of the larynx, which frogs depend on to call and attract their mates.

Hayes and his coworkers backed up their lab study with a dramatic field study of leopard frogs (Rana pipiens). Starting in California, the biologists drove east across the United States, collecting tadpoles and water samples from Utah to Illinois. The wild frogs were being hit even harder than their lab cousins: nearly fully formed eggs containing large amounts of yolk were found in the testes of male tadpoles. (Normally, eggs do not develop in tadpoles of either sex.) And the more atrazine in the water, says Hayes, the worse the malformation.

How can a chemical manufactured to kill plants by interfering with photosynthesis have such profound effects on animals? Atrazine is a potent endocrine disrupter because it boosts levels of an enzyme that normally transforms testosterone into estrogen. The result in male tadpoles is dramatically reduced testosterone levels and elevated estrogen levels, an effect Hayes and his colleagues measured in both R. pipiens and X. laevis.

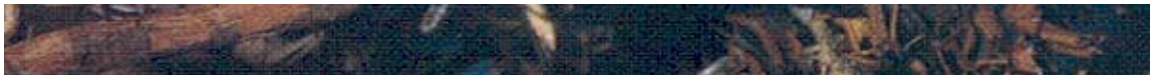
Biologists have known for years that amphibian numbers are dropping precipitously, with populations winking out one by one. Yet no single cause seemed to explain more than a few regional declines. Hayes's work suggests a major contributing factor in the eighty countries that use atrazine. Beyond that, his work suggests the importance, when evaluating potentially harmful molecules, of looking at the internal morphology of developing embryos. Endocrine disrupters may be capable of destroying entire populations and species, but such compounds will not necessarily reveal their effects through extra legs or other malformations obvious to a layperson.

Leopard frogs (Rana pipiens) in duckweed. The common herbicide atrazine causes eggs to develop in the testes of mate tadpoles of the species, making them incapable of reproducing.



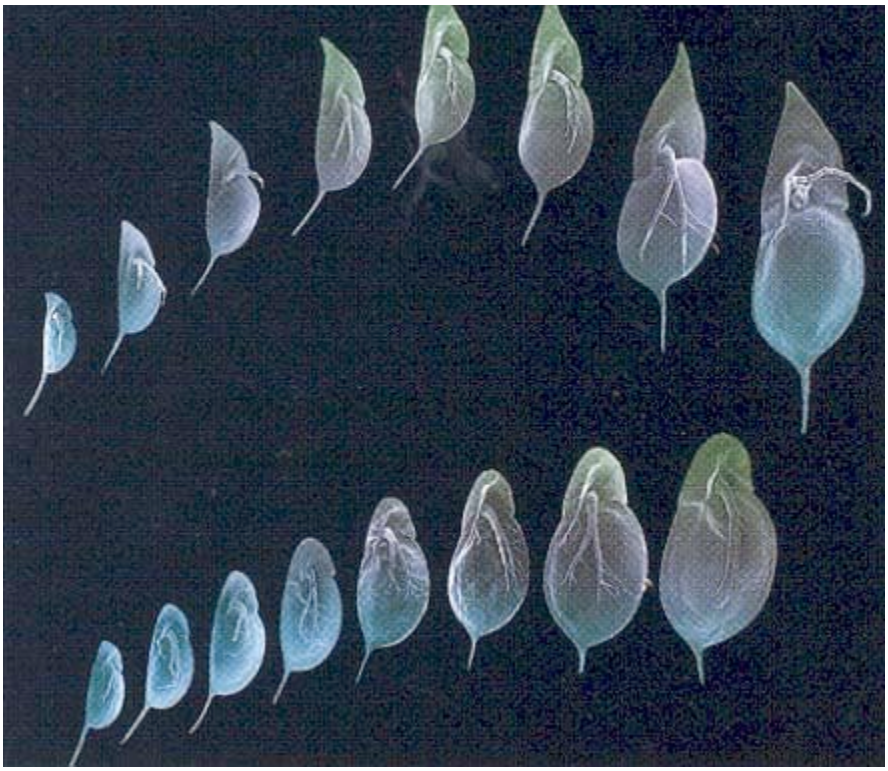
Soviet biologist (and Stalinist ideologue) Trofim Lysenko, above, thought the environment alone shaped an organism.

Western scientists held a view just as extreme: their experiments with phenotypically inflexible organisms--fruit flies, below, among others--led them to virtually ignore developmental plasticity in all species.



The desert "plague" locust has two environmentally influenced forms. At low population densities the insect is green, with small wings and legs; at higher densities its colors become mottled and brighter, and its appendages larger.

When a species of social wasp attacks red-eyed tree frog eggs, some of the eggs save themselves by hatching prematurely.



Left: Predatory midges alter the development of the water flea Daphnia cucullata. In the top sequence, a water flea exposed to these predators develops a long, pointed "helmet" and a spiky tail; in the bottom sequence, a water flea grows in the absence of predators.

S (COLOR): As the caterpillar Nemoria darwiniata feeds, it adopts the color of its host plant. The white

insect, far Left, is feeding on the pate flowers of Ceanothus velutinus, an evergreen shrub in the buckthorn family; the same caterpillar turns purple-red, Left, when it enjoys Amelanchier alnifolia, a relative of apples and roses.

When a school of scalefin anthias (Pseudanthias squamipinnis), above, tacks a male, the dominant female turns into one (mauve fish with yellow franks).

Right: The queen and worker ants shown here are sisters and 75 percent genetically identical Their obvious differences arise out of differing diets, which lead to a cascade of genetic effects.

Calluses usually form only when external abrasion turns on the right genes, but ostriches hatch with calluses on their abdomens and chests. Evolution can "genetically assimilate" an environmentally induced trait.

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By Jennie Dusheck

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