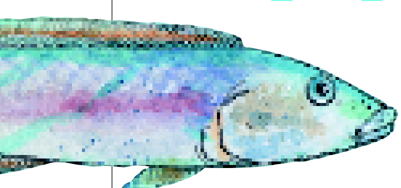
FOCUS ON RESEARCH

Phenome Fellow



Genomics research on social interactions reveals the "tremendous plasticity and potential" of individual organisms.

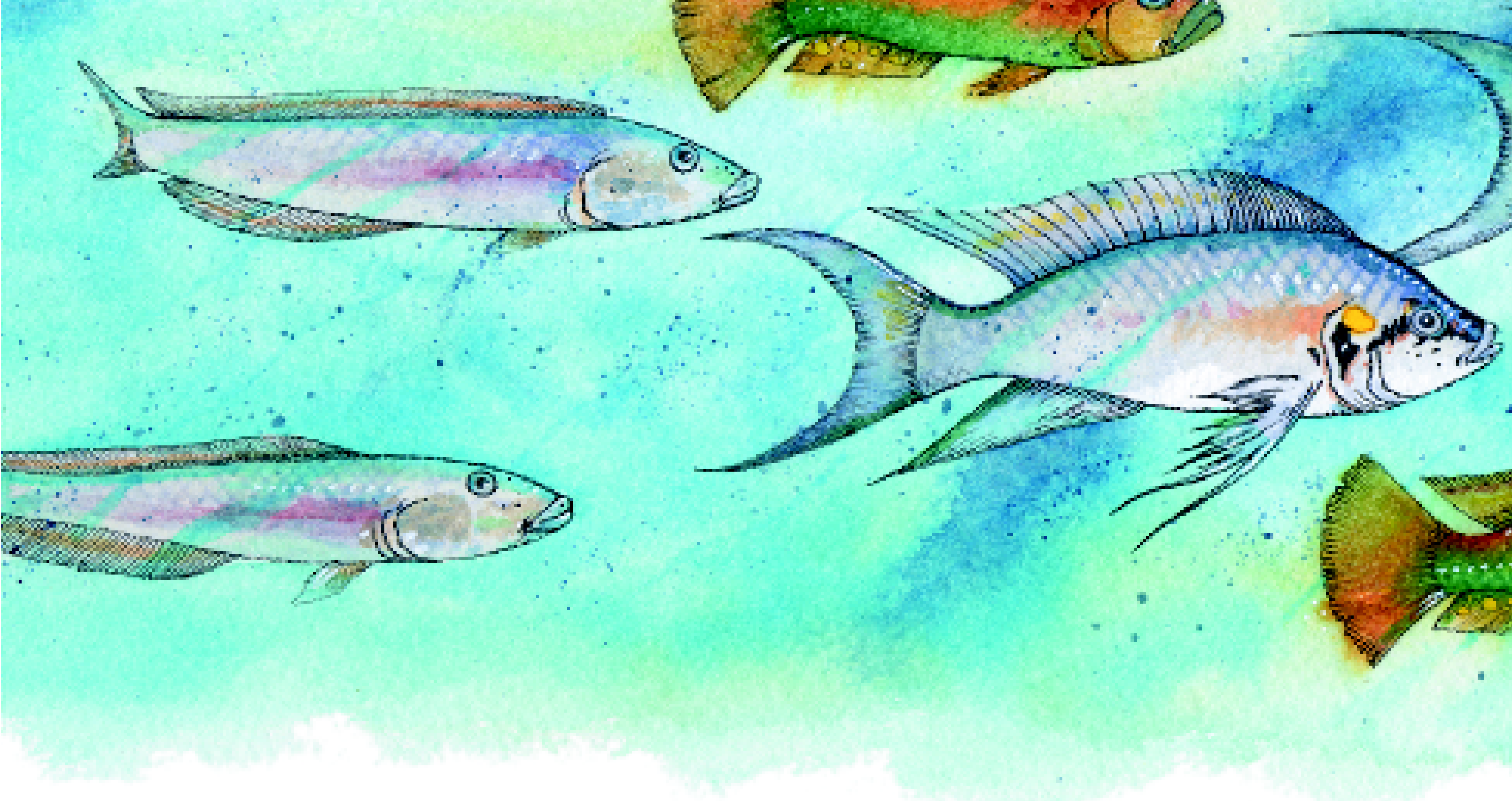
by JONATHAN SHAW

In a Marist monastery in southern Bavaria, 11-year-old Hans Hofmann began his classical education. "I studied Greek, Latin, and Hebrew," he says, "presumably so that I could read pre-modern versions of the Bible." He might have become a Catholic priest, if not for a burgeoning interest in philosophy. "If you want to become a philosopher," a mentor advised him, "you first need to learn a trade, a discipline." So Hofmann—who was raised on a farm—decided to pursue studies in biology, to the great surprise of the monks.

Like Jesuits, Marists are rigorous in their teaching, so when Hofmann left the monastery at age 20 to attend the University of W rzburg, and went on to pursue a master's degree in biology at the University of T bingen, he found himself well prepared for academic life. The emphasis on mathematical and electronic systems at T bingen, he says, proved an excellent complement to the classical analytical framework that he had learned from the Marists.

Today, Hofmann is a fellow at Harvard's Bauer Center for Genomics Research, investigating the relationship between an organism's environment and its behavior, and tracing the relative contributions of genetics and external influences. It's a line of inquiry with an analog in classical Greek tragedy: fate pitted against free will. Can mortals control their destiny, ancient philosophers asked, or is the course of life predetermined? For the ancients this was a theological debate, but in the modern scientific age we have reframed the question, either setting nature against nurture, or asking to what extent our genetic legacies—the talents, deficiencies, or predispositions to disease that we are born with—are deterministic.

In diseases like cancer, as Hofmann puts it, "the nature versus nurture debate is dead"—science has demon-



strated that both genetics and environmental factors can play a role. But we are just beginning to understand an unexpected new paradigm: certain genes that regulate phenotypes—groups of physiological traits and behaviors—are actually under social control. A genome, the complete collection of an organism's genes, is plastic, Hofmann contends. The environment—even social and cultural contexts—can switch genes on and off.

This surprising revelation is at the philosophical center of Hofmann's current research, which began with an interest in the origins of aggression. In humans, some research has suggested that serotonin, a neurotransmitter, plays a role in aggression, and Hofmann's advisers at the Max Planck Institute for Behavioral Physiology, in Seewiesen, Germany, where he was a doctoral student, suggested that he demonstrate the same in crickets. But Hofmann found this was not the case for crickets.

Crickets are, nevertheless, extremely aggressive; because they fight readily, experimenting with them is easy. So Hofmann set out to discover what *other* factors might play a role in the insects' aggression. Cricket fights follow a prescribed series of escalating behaviors (from antennal fencing to wrestling), until one of the combatants retreats. When this happens, the defeated cricket typically won't fight again for 24 hours. But Hofmann knew that fights between crickets had been staged in China for more than 1,200 years, and that Chinese cricket handlers were adept at quickly getting their crickets back into the ring. The trick, he found by reading Chinese sources, was to toss the cricket around in cupped hands, throw it in the air, and catch it again. Soon his lab was full of defeated crickets being tumbled in tubes, tossed, and forced to fly in miniature wind tunnels. With experimentation, he was able to isolate the specific mechanism for resetting aggressiveness. Flight, it turned out, whether for a few seconds or an hour, gave the crickets back their gumption.

Hofmann's discovery was significant because only rarely has a socially mediated behavior been shown to directly and immediately affect another unrelated behavior. He recognized that study of such behavioral manipulation of brain function might one day lead to insights into "how and why evolutionary adaptation has connected behaviors that were previously unrelated."

HOFMANN NOW WORKS with cichlid fish—natives of the shallow shoreline waters of Lake Tanganyika in eastern Africa—to learn more about behavioral plasticity, linkages, and evolution. Cichlids are ideal subjects for such study because they are monophyletic (descended from a single species), but have speciated rapidly from that ancestral form into an extraordinary diversity of sizes, colors, shapes, and reproductive behaviors.

In addition, cichlids' evolutionary-scale adaptability is matched by an unusual mutability during life. Males of the species exhibit two distinct, reversible phenotypes that are "directly under social control," says Hofmann. Dominant fish in the social hierarchy are territorial, solitary, sexually active, and display bright coloration. The rest of the adult male fish in the vicinity—sharing a tank with a territorial male, for example—tend to school and are reproductively inactive and dully colored. In nature, cichlid social structure is vulnerable to rapid upheaval as dominant males become food for birds or water-snakes, or their habitat is disrupted by winds or currents, the movement of a fallen banana leaf, or visits from local hippopotamuses. Any of these changes will send the formerly submissive males into a frenzy of fighting over the "new" territory, until one finally emerges the

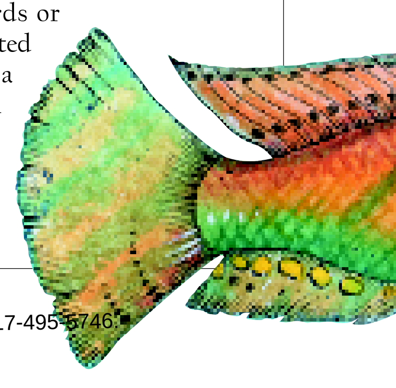
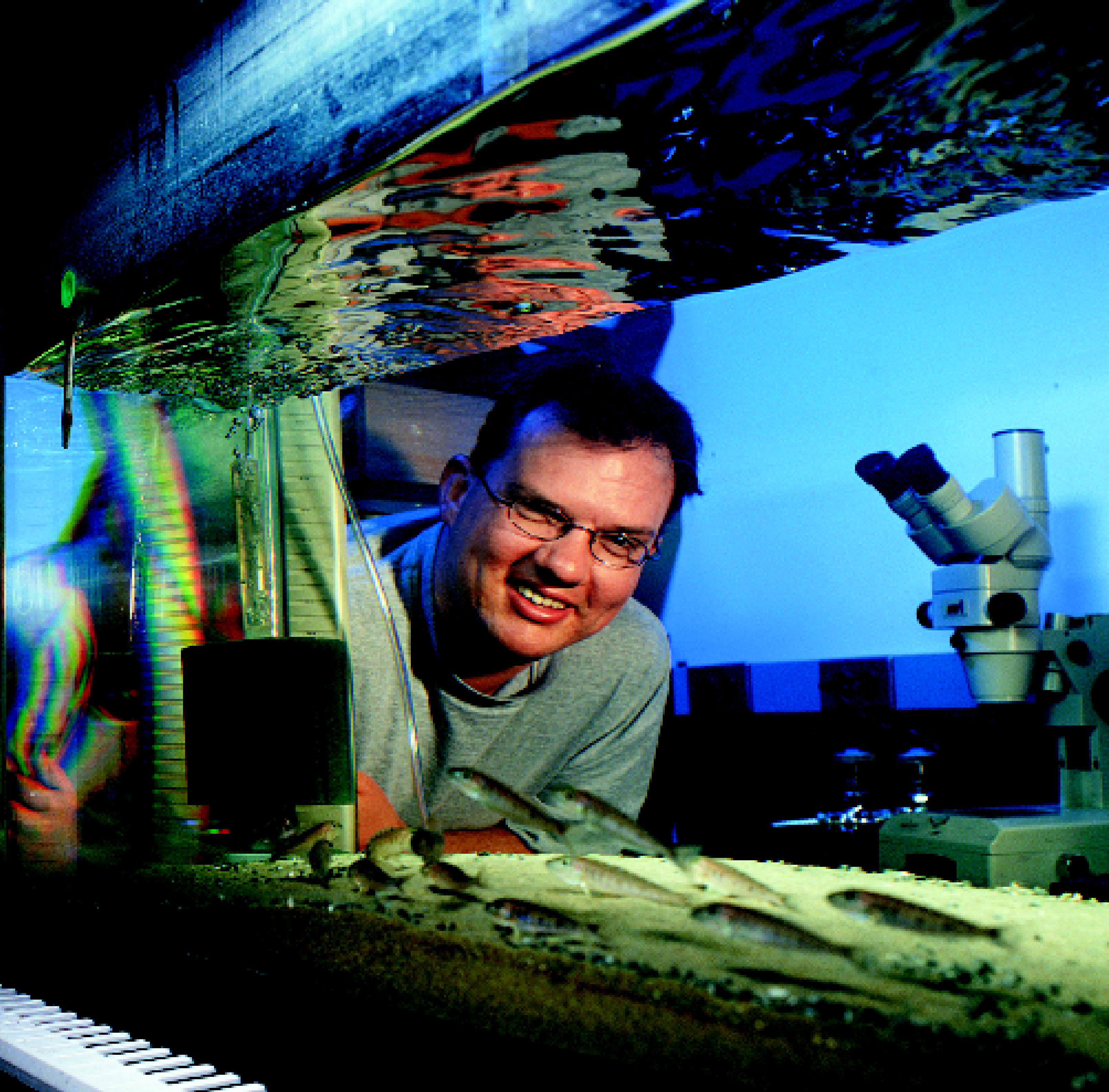
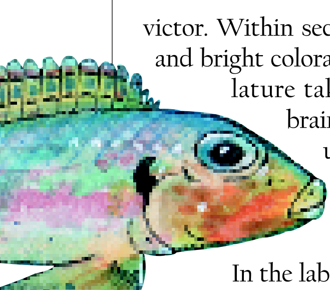


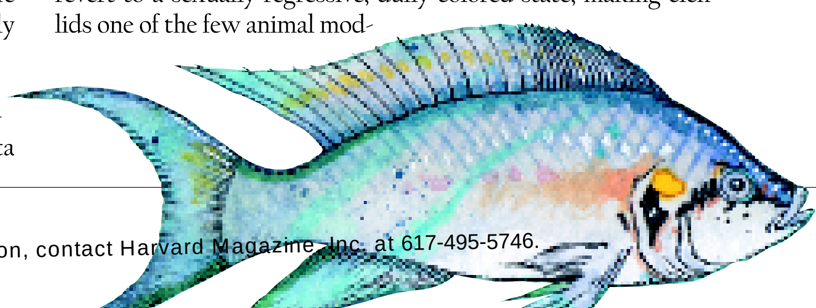
Illustration of cichlids by Mike Reagan



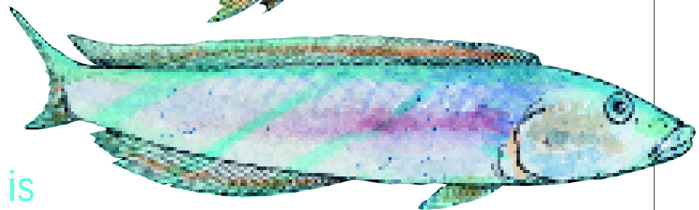


victor. Within seconds, the winning fish develops an eye stripe and bright coloration. More changes in appearance and musculature take place over the ensuing week. Within the brain, cells that produce a hormone regulating sexual development increase, and the sex organs become capable of producing sperm. The changes, while predictable, take place only after the victor has established his control.

In the laboratory, such changes can be induced when a dominant male is removed from a tank, or when Hofmann creates new territory that can be defended (by adding terra cotta pots, for example). He has shown that these transformations are not restricted to reproductive behaviors and physiology (what he calls "the reproductive axis"). "I have found them on the stress and growth axis, as well—in all, there are at least 14 phenotypic characters under social control." Dominant fish that are defeated revert to a sexually regressive, dully colored state, making cichlids one of the few animal mod-



Genomics researcher Hans Hofmann with a tank of *Enantiopus melanogenys*. The cichlid fish species he studies are descended from a common ancestor, yet are remarkably diverse in their appearance and behavior. Illustrated on these pages are, from left to right, *Xenotilapia flavipinnis, Neolamprologus brichardi, Astatotilapia burtoni,* and *Enantiopus melanogenys.*



"The idea that a gene is for one thing only is simplistic—and it misses the inherently complex system of interactions between the social environment and individual animals."

els that demonstrate this reversible pattern of dominance and sexual activity.

"We live in a time when research on the relationship between genes and their physical manifestations is suddenly possible, because of all the work that has been done on the genome project," says Hofmann. "Now that this tool has been assembled, we can do some really creative things." What he has done is link the physiological and behavioral changes he has observed back to the specific genes and molecular pathways responsible for the changes. In his first, "very preliminary," experiments, he stresses, his research group identified 96 genes that appear to play a role in the changes, and that are switched on and off by external—that is, environmental—influences. The same neural pathways used in learning and memory appear to play a role in modulating gene expression.

Because Hofmann studies neither a single animal nor a single behavior, but communities of animals and collections of behaviors, the research can seem complex. But that's the point, he says: "The whole idea that a gene is for one thing only is simplistic—and it misses the inherently complex system of interactions between the social environment and individual animals." "The hunt for disease genes has been in the news," he points out, "but you can have twins who are genetically identical, yet one has Parkinson's and the other doesn't." What accounts for the differences? "Is it diets?" Hofmann wonders. "Or whom they married, where they've lived?"

The goal of all this basic research is to contribute to an understanding of how genes interact with the environment, not only during an organism's life, but on an evolutionary scale. Hofmann suspects that the phenotypic plasticity of cichlids may have enabled the fish to adapt to new environments during evolution, resulting in the numerous species flocks found in Lake Tanganyika. By undertaking comparisons of closely related, but behaviorally diverse, species of cichlids, he plans to test this theory. The work may someday find applications in studies of human gene expression, because scientists have found that evolution tends to conserve genetic code (see "Simple Hosts," page 48). But even at this early stage, research into genomic plasticity provokes philosophical questions about human learning and behavioral modulation.

"In human society, what do you want education to be like?" Hofmann asks. "Do you want to teach a prescribed curriculum to everybody, or do you want to present people with a range of possibilities and see what they do with them? I would argue for the latter," he says. "There's tremendous plasticity and potential built into the genes of each individual."

Jonathan Shaw '89 is managing editor of this magazine. He wrote "The Great Global Experiment," the cover story of the November-December 2002 issue.

Fellow in Residence

Hofmann's goal during his five-year Bauer Center Genomics Research Fellowship is to "contribute to the creation of a conceptual framework for the study of phenotypes and genes, especially in discussions around community." The intent of the fellowship program itself is to create an ideal environment for such work. "Harvard is often seen from the outside as a conservative place, but that is not my experience of the Bauer Center," he says. "This program"—which brings people and tools from a broad range of scientific disciplines to bear on basic genetic research questions—"is an extremely bold experiment, and I am very optimistic that it will succeed. What we are doing right here," he says "may become a model for this type of research everywhere."

Photograph by Jim Harrison