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Profile: Hopping Mad
by Kerry Tremain

A frog biologist battles an agrichemical giant

A blow-up of a Gary Larson cartoon signals that I've found the right steel door. It depicts a nightclub where a frog is croonin' the "greens" he's got so bad: "My baby's just left my lily pad, my legs were both deep-fried; I eat flies all day and when I'm gone, they'll stick me in formaldehyde." Below, in large block letters, a sign reads, "Hayes Lab."

Tyrone Hayes, the renowned biologist whose experiments have linked the nation's most widely used herbicide to deformed sex organs in male frogs, waits at the door. He greets me brightly but briefly, and then starts speed walking down a long hallway at the University of California at Berkeley. He's lugging the suitcase he carries everywhere containing his two computers and his data. Despite being a foot taller, I struggle to keep up.

It's only when we climb into an elevator next to a student balancing a pint jar of tadpoles that I get a good look at this man who four years ago went to war with, as he puts it, "the number-one-selling product of the largest agrichemical company in the world, sold to the largest agricultural economy in the world and sprayed on its largest crop to kill the most common weed in the world." That product is atrazine, produced by the Swiss chemical giant Syngenta. Beyond defects in frogs, atrazine has been linked to human infertility as well as to muscular degeneration, heart disease, and cancer in animal studies. The European Union banned atrazine last year, but roughly 75 million pounds are sprayed in the United States annually, mostly on corn crops.

In the last month, Hayes has flown to four cities to give lectures to sanitation managers, water-quality specialists, herpetologists, and integrated pest managers to speak about his frogs, atrazine, and human health. Tonight, it's a breast cancer group in San Francisco. His inexhaustible cheer and energy make me wonder if he's undergone some Spider-Man-type lab accident. Although he whisks around the lab in running sweats (he jogs or bikes at least ten miles a day), he wears a suit to his lectures.

The one he's wearing now is black, with a black shirt and a very wide electric-blue tie. His hair is parted into two pigtails, each tied with a lime-green band. He has four ear piercings, two per ear, and each represents one of four values he's assigned them: independence (pierced on his first day at Harvard University), perseverance (pierced on Halloween 2002, when the prestigious journal Nature published his paper on hermaphroditic frogs), prudence (pierced in sympathy with his daughter after he botched her ear piercing), and balance (pierced, well, to balance out the other earlobe).

In recent years, Hayes has called heavily on those values as he endured a high-profile attack on his work and character by Syngenta. Although he's a wunderkind among biologists—at 36 he has an endowed chair at Berkeley and publishes in the top scientific journals—Hayes says the dispute is not about science. "When I began my studies, I learned that science was about finding truth," he says. "Now science is being done to undo science." Attacks that might have felled others have invigorated Hayes. He has intensified his frog experiments.

His lab is breaking new ground in understanding the combined hormonal effects of multiple chemicals—experiments that make current limits on toxic substances look woefully inadequate. He has also metamorphosed into a kind of public scientist, taking his findings out

of the cloistered world of professional scientists and explaining their relevance for human and environmental health to the wider world. As a biologist, Hayes once spoke mostly to endocrinologists and herpetologists. "Now," he says, "I get the opportunity to talk to broader audiences and be what some would consider more political. It's not really political, though. It's bringing science to people who might not otherwise have access."

Tyrone Hayes grew up in a neighborhood built on a drained marsh in Columbia, South Carolina. After heavy rains the area would flood, filling his backyard with snakes, turtles, and frogs. From the first, he was hooked. "You can watch a newly fertilized egg; you can see the cleavages as it divides and becomes multicellular," Hayes says. "In a stage called morulation, the animal develops an inner core and becomes a living, breathing organism. These processes occur in everything from fish on up to mammals, but they're often behind eggshells or inside moms. I could watch these things happening in the frogs in my backyard."

Hayes's parents encouraged his interest. His mother had one rule: no frogs in the house. So he raised them on the porch, and collected grasshoppers in cages to feed them. As a high school freshman, he got interested in what caused certain lizards to change color. He kept them in the dark in a doghouse on the porch, and then shined lights on them. He heated them with blow-dryers to see if temperature made a difference. He woke them at varying hours.

The doghouse and grasshopper cages drew the derision of neighborhood toughs. But Hayes's wife, Kathy Kim, says he's never backed down in the face of attacks. "His mother and father told me he always stood up for kids in the neighborhood who were unpopular or poor and were being bullied." Asked about it, Hayes says, "Yeah, well, I got my ass kicked a few times."

After scoring high on his SATs, Hayes was courted by several colleges, but applied only to Harvard. Acclimating there was difficult. "I came from an all-black neighborhood to a place where there was only a tiny percentage of African Americans," he says. Hayes found a home at Harvard in Bruce Waldman's amphibian lab and then met Kim. They married two days after his graduation with departmental honors, in 1989, and moved to Berkeley for graduate school.

Hayes finished his PhD work in three and a half years, at 24. "He'd already started some frog research as an undergrad at Harvard, so when he came to Berkeley he hit the ground running," says Paul Licht, a comparative endocrinologist who became Hayes's dean, professor, and friend during his doctoral studies. "We clicked. We both wanted to study endocrinology in an environmental context—real animals in the real world."

Since childhood, Hayes had dreamed of going to Africa, and after finishing his doctorate, he made the trip. There he encountered a frog that changed his life, Hyperolius argus, an African reed frog. The male and female of most frog species share the same coloration, but in Hyperolius the genders are different: The female is spotted, the male is plain. Hayes hypothesized that this quality might make them ideal for testing the effects of chemicals that stimulate estrogen. He was right.

Increased estrogen produced spots in male frogs. He also discovered that increasing testosterone caused female voice boxes to grow, and increasing thyroid hormones sped up the metamorphosis of tadpoles to frogs. This African reed frog, in other words, offered a quick way of testing endocrine disruption—hormonal malfunctioning linked to birth defects and cancer in lab animals and humans.

Back from Africa, Hayes told his wife about his test, and Kim suggested they patent it. With help from UC Berkeley, where Hayes had been hired as an assistant professor, they did, calling it the Hyperolius Argus Endocrine Screen test, or HAES test. The HAES test soon caught the attention of other scientists, including a Syngenta-funded panel of researchers called Ecorisk.

In 1999, Ecorisk asked Hayes to examine the effects of atrazine on frogs as part of the chemical company's reporting requirement to the EPA. Years earlier, a television reporter had asked Hayes if someday some company might shake in its boots over whether his reed frog changed sexes. "I told him that if a big company had a chemical that was potentially harmful, I would think they would be happy to get the data," Hayes says. "That's how naive I was."

What he found was that at doses as low as one part per billion (or 1ppb), atrazine shrank the larynges of male frogs—an animal that uses vocalization to mate. EPA rules put the safe level of atrazine in drinking water at three times that level, or 3ppb—and many water systems in the Midwest exceed even the EPA standard.

In follow-up experiments, Hayes found a still more shocking effect. At levels one-tenth the rate of the earlier study, or 0.1ppb, atrazine turned significant numbers of male frogs into hermaphrodites. Multiple nonfunctioning ovaries and testes appeared in the same frogs. Male testes produced eggs rather than sperm.

When Ecorisk failed to report his data to the EPA and dragged its feet on funding new studies to confirm the results, Hayes grew concerned. Like amphibian biologists everywhere, he knew that frog populations were declining or disappearing worldwide. Could endocrine disruption caused by pesticides be part of the explanation? Although toxicologists traditionally worry about high doses of chemicals, endocrinologists know that hormonal effects can occur at low doses; birth control pills, for example, contain minuscule amounts of estrogen.

By late 2000, Hayes became convinced that Ecorisk was burying his findings. He quit the panel and pursued the experiments independently. It was then, Hayes says, that Ecorisk's Ron Kendall offered him $2 million to do the studies "in a private setting"—meaning one where Ecorisk and Syngenta could control the release of the results. Hayes refused; Kendall denies it happened at all.

But Syngenta then funded Ecorisk to perform over a dozen studies to discredit Hayes's data, all of them, according to Hayes, badly or even ludicrously conducted. In one, frogs were left in open tanks, leaping freely among tanks containing atrazine and those without. But the result, that the study "did not support Hayes findings," was dutifully reported to the EPA and the press.

The EPA acknowledged the Ecorisk studies were flawed. Nonetheless, in a decision last October, the agency put no new restrictions on atrazine use. The ruling called only for Syngenta to monitor the herbicide's levels in drinking water, a project that could trigger regulatory action if levels rose. And it called for more studies. "Who's going to do those studies?" Hayes asks. "Syngenta."

But so is Tyrone Hayes.

Above one of Hayes's lab tables, a series of 20-foot shelves is stacked with green slide boxes from recent experiments. Others are stored downstairs. In a rough count, I calculated those shelves hold 3.6 million tissue samples. Hayes sits at a small table and sink nearby where he uses a single-edged razor to dissect each frog. "I've looked at tens of thousands of animals. And at least three people read every one of these slides," he says. "I don't publish a paper unless I'm sure."

To care for and study the frogs, Hayes attracts and rigorously trains teams of student lab assistants, most of them undergrads. Each one completes an SOS—a semester of service—that requires a 4 a.m. wake-up to feed the frogs and change their water on a three-day cycle. Still, competition for the lab slots is fierce. Hayes runs a lab known for its diversity of students—not only in racial or ethnic terms, but also in scientific interests.

Remembering his own tough years at Harvard, he also picks one student each year who struggles in his endocrinology class. "I look for how eager they are, not their SATs," he says. "When people rub me the wrong way, I take them. They help correct my biases."

Come summer, the team hits the road to collect frogs and water samples. Their surveys are extraordinarily ambitious. Gathering frog and water specimens every ten miles down the entire North Platte River, which runs from Colorado through Wyoming to Nebraska, Hayes's team and a scientist from the U.S. Geological Survey are comparing atrazine levels with levels of hermaphroditism.

One of Hayes's students, Virginia Ngo, calls him a good candidate for Survivor. Barefoot much of the time, he would wake up at 4 a.m. to run, then get the students up an hour later for breakfast so they'd be collecting frogs by six. He sometimes caught fish for dinner, once frying a carp in a sputtering campfire skillet in the rain.

Used to treating his team almost like family, Hayes grows angry when talking about students elsewhere who get caught in the middle of unethical relationships between industries and university professors. "In one study a PhD student killed 90 percent of her frogs due to bad husbandry, but her advisor, who works for Ecorisk, submitted it to the EPA anyway." To Hayes, that's not only bad science, it's educational malpractice. "Or look at this one!" he says one day while we're sitting in his lab.

The study, sent to the EPA by Ecorisk, claimed to find hermaphroditic frogs in both corn-growing and non-corn-growing regions in South Africa, supposedly disproving that atrazine causes the effect. But in the "control" region that didn't grow corn, the water contained more atrazine than Hayes uses in his experiments. "I'm reviewing this paper next to my ten-year-old—and granted I think he's a very special ten-year-old—and he says, 'Dad, they don't have any controls.' If my ten-year-old knows they are doing bad science, so do they. But they're pushing it with their students' names on it. They're throwing their students' futures away."

Watching him speak to the breast cancer organization's attentive members in San Francisco, it occurs to me that Hayes, who won Berkeley's Distinguished Teaching Award, is simply expanding his classroom outside the university. He guides the group through a dazzling amount of information, seamlessly combining data from molecular biology, endocrinology, population ecology, and public policy. At one point, he asks the group members to close their eyes and "imagine there's a potent chemical that disrupts hormones."

Hayes prepared them by explaining how atrazine turns on an enzyme called aromatase that stimulates estrogen production, a process shown to occur in frogs, reptiles, rodents, and human tissues. He tells them that one study found an increase in breast cancer in women whose drinking-water systems are contaminated with atrazine, and that another study in the Midwest associated poor semen quality with atrazine contamination.

He continues, "Then I want you to imagine what the world would be like if the EPA required these companies to report these effects, so it could make regulatory policy based on the science. And now I want you to open your eyes and I want you to join me in reality."

In the real world, Hayes says, Ron Kendall was working for Syngenta and running Ecorisk while chairing a scientific advisory panel to the EPA. He was also editing the only journal to publish a paper challenging Hayes's findings, by one of Kendall's colleagues at Texas Tech University who was under contract to Ecorisk.

According to Hayes, industries sponsor studies that go on for years but aren't reported to the EPA because they're "unfinished." That way, if they find something bad, the company buys time to look for a replacement product.

Hayes also explains to the group that while the EPA regulates toxics based on a safe dose for individual chemicals, his findings question whether a safe level exists if several chemicals are interacting in the environment at once. "We've found that frogs are counting the number of chemicals in the water. If you expose them to two chemicals, there's a slight delay in metamorphosis; if you expose them to ten, there's even more of a delay. No single compound will do this."

With drugs for humans, that's a routine assumption: You know not to take a dose of aspirin, ibuprofen, and acetaminophen at the same time. If this routine assumption were applied to toxics, the traditional framework for regulating them could collapse.

For such a revolutionary shift to occur, it will take more than scientists debating among themselves. On the way to San Francisco, Hayes had told me about an epiphany he'd had. When his paper on hermaphroditic frogs was published in Nature, he'd called his mom to tell her. The next day, she called back and said, "Honey, I don't want to hurt your feelings, but I went down to the Barnes & Noble and they've never heard of that magazine."

"She made me realize that the things that counted the most for me—getting tenured and published—are the least relevant," Hayes says. "Here you have this important information, but so very few people have access to it." In his new role as a public scientist, he wants to change that. He speaks to groups all over the country and beyond—his recent favorite was the Used Oil and Household Hazardous Waste Conference.

"Look, the people who we're poisoning are our country; they're our economy. They're paying my salary. But they're not at that EPA hearing. They're not invited to any scientific conferences." So this summer, he's planning a scientific conference on atrazine that will include farm laborers and others directly affected by the herbicide.

Academics are known for narrowing their vision to a tiny field of study, but Hayes has expanded his fascination with frogs into a window on the world. "I like frogs, but amphibians are a marker," he tells the breast cancer group. "Living organisms are all connected to the environment, the water especially. We're using an animal that develops in an aquatic environment to tell us something about another animal that develops in an aquatic environment." As Hayes speaks he points to a slide of a human fetus in the womb.

"I don't know why we're continually surprised that pesticides, which are designed to take away life, create these kinds of effects," says Hayes. "It's not just that environmental health is related to public health. They are one and the same."