DROSOPHILA ENVY

A maverick scientist is risking all to study the behavior of fruit flies, convinced that they have much to teach us about the evolution and neurobiology of emotions.

BY JEFF MILLER • PHOTOGRAPHS BY MISHA GRAVENOR

"SCIENTISTS ARE REWARDED FOR

their conventional ways," says HHMI investigator David J. Anderson, "for making a continual set of contributions to one problem." But Anderson, a neurobiologist at the California Institute of Technology, who admits to being "occasionally crazy and easily bored," has chosen a different course.

He traded continued success studying the biology of neural stem cells for the uncharted world of fruit fly emotion. Anderson likens his path to the one pursued by Caltech colleague Seymour Benzer. "Starting out in solid-state physics, he switched to molecular biology, then made a 180-degree turn and founded the field of neurobiology and neurogenetics," says Anderson, with obvious admiration.

Benzer is motivated by the answer to a single question. "Isn't it more crazy not to follow the driving force of your curiosity and passion?" he asks, rooting for Anderson. "David has the courage, energy, and intelligence to make a go of it."

Although Anderson has an obvious love of risk, he has certainly shown himself capable of playing by the usual rules. After completing his postdoctoral studies in the Columbia University laboratory of HHMI investigator Richard Axel (2004 Nobel Prize winner, and his mentor), Anderson spent more than 20 years helping to pioneer the study of the developmental biology of stem cells in mice.

"He made seminal contributions to our understanding of neural development," says Sean Morrison, an HHMI investigator at the University of Michigan who was a postdoctoral fellow in Anderson's lab from 1996 to 1999. "He discovered many of the genes that regulate neurogenesis. And his lab is the place where neural crest stem cells were identified and characterized."

Anderson's discovery of three classes of master genes inside neural stem cells—genes that give rise to neurons and related cells that insulate nerve fibers—was one of the first to answer the larger question of how stem cells differentiate. He also discovered some fundamental properties of angiogenesis (the formation of blood vessels)—namely, that arteries, but not veins, are aligned with nerves in embryonic skin and that the nerves are required for arterial differentiation.

But Anderson needed a change.

Was it the typical lag time of 12 to 18 months between testing a hypothesis in mice and getting a result that agitated him? "I can get very impatient," he concedes.

Was it the need to recharge his research batteries by challenging himself? Yes, he agrees. "One of my biggest self criticisms is that I tend to identify problems and get into areas a little too early—which is also good because I'm ahead of the pack."

Or was it the thrill of the hunt, the same feeling that once tempted him toward archaeology when he was a boy? Perhaps. "The happiest moments of my scientific life have come when I've made that initial discovery and I suddenly glimpse something about nature that, at that moment, no one else knows."

There was something else, too, Anderson acknowledges. *Drosophila* envy. "I've had it my whole career. Fruit flies are such a powerful system, and they are simpler. You can understand mechanisms that govern processes more easily than you can in mice."

Other scientists have broken ranks before, of course. "But what makes Anderson's move more unusual is that he moved out of a very active field of which he was a leader," says Gerald M. Rubin, HHMI vice president and long-time *Drosophila* researcher.

And he did it just a few years before California voters agreed to spend $3 billion to underwrite stem cell research. That a tiny fruit fly proved irresistible to Anderson just as support for his core area of research was mounting illuminates another of Anderson's key beliefs. Put simply, packing up the furniture—if not exactly chopping it into kindling—is sometimes necessary to break new scientific ground, especially when herds of fellow scientists begin warming themselves at your campfire.

Morrison was just finishing his postdoctoral work when Anderson began to talk about shifting to studies on the molecular regulation of behavior. "My reaction was that it sounded like a really hard problem that was obviously of great interest to solve," he recalls, "but I worried how much headway they'd be able to make experimentally."

Anderson's the kind of standout scientist, though, who picks problems that everyone agrees are important but no one else knows how to solve, just like Richard Axel and his olfactory research, Morrison says. "Everyone else looked at the problem and agreed it would be cool to understand how we smell, but no one knew how to tackle it."

Given Anderson's success in the five years since he began his scientific walkabout, few would now call him shortsighted. Morrison calls the move heroic. "As this new line of work matures in his lab, it will be a force in shaping our understanding of how behavior is regulated."


"David Anderson sets a great example for the people who train in his lab—it's not about ego or reputation, it's about getting to the truth," says Sean Morrison.

THE SMELL OF FEAR?

Anderson expects to learn from his mistakes more rapidly and less expensively in fruit flies than he would in mice. But since he longs to get inside a fly's head to study the connections between neurons, genes, and behavior—Anderson's current passion—he'll need to be patient too. After all, he says, "It is extremely difficult for all but the most talented electrophysiologists—such as my Caltech colleague Gilles Laurent—to stick an electrode into a fly's brain and measure the electrical activity of its neurons."

Researchers can alter flies genetically, however, and use various imaging techniques and special microscopes to see which brain cells fluoresce or react in response to different stimuli or during various activities. Such processes, Anderson says, are not only informative but downright thrilling. "It's like flying over a city at night and watching the lights of the houses go on and off."

But, he cautions, "Just because there is a correlation between neurons and an activity doesn't mean those neurons alone are responsible for the behavior. To test that hypothesis, you have to turn off the neurons, and see if the behavior goes away." Using one such genetic technique, Anderson, with a team including Axel and Benzer, was able to engineer temperature-sensitive neurons that shut down at 90°F. In a series of experiments that pivoted around this temperature sensitivity, they discovered that "traumatized" fruit flies emit a stress odor containing carbon dioxide, repelling other flies, and that a single type of neuron in the nose of the fly is responsible for detecting the noxious gas.

Were the normal flies reacting to a "smell of fear"? Maybe, and maybe not, says Anderson. What he learned in additional experiments—that the target olfactory neuron is both activated by carbon dioxide and necessary for the response to carbon dioxide—still did not prove what actually triggered the avoidance behavior. So in a clever case of genetic manipulation, Anderson added a bit of algae DNA to the fruit fly's carbon-dioxide-sensitive neurons: specifically, an ion-channel gene that is activated by blue light.

The next step was to put these altered flies into an apparatus and give them a choice between flying into an empty tube or one illuminated with blue light. "We wanted to know if flies exposed to this light would think they smelled carbon dioxide and act to avoid it," Anderson explains. Sure enough, when he flicked on the switch, the altered flies shunned the blue light, proving the primary link between neuronal activity and behavior.

In comparable research with mice, Anderson has also narrowed the search for genes that control whether a stressed mouse freezes or flees when hearing the mouse version of an alarm bell. But be they fruit flies or mice, is their behavior *emotional* behavior, and if so, so what?

INSPIRATION AND DARWIN

Anderson's knowledge is encyclopedic, according to Morrison. "He has a truly remarkable ability to bring together diverse facts from different areas and synthesize them into incredibly creative ideas." That brainpower may come from Anderson's parents. His father is a retired theoretical astrophysicist, who lettered in chess at the University of Chicago. Every year, he traveled the family from Teaneck, New Jersey, to Woods Hole, Massachusetts, because he was interested in learning more about fluid mechanics. Anderson's mother, a professor of Latin American literature, still teaches at New York University.

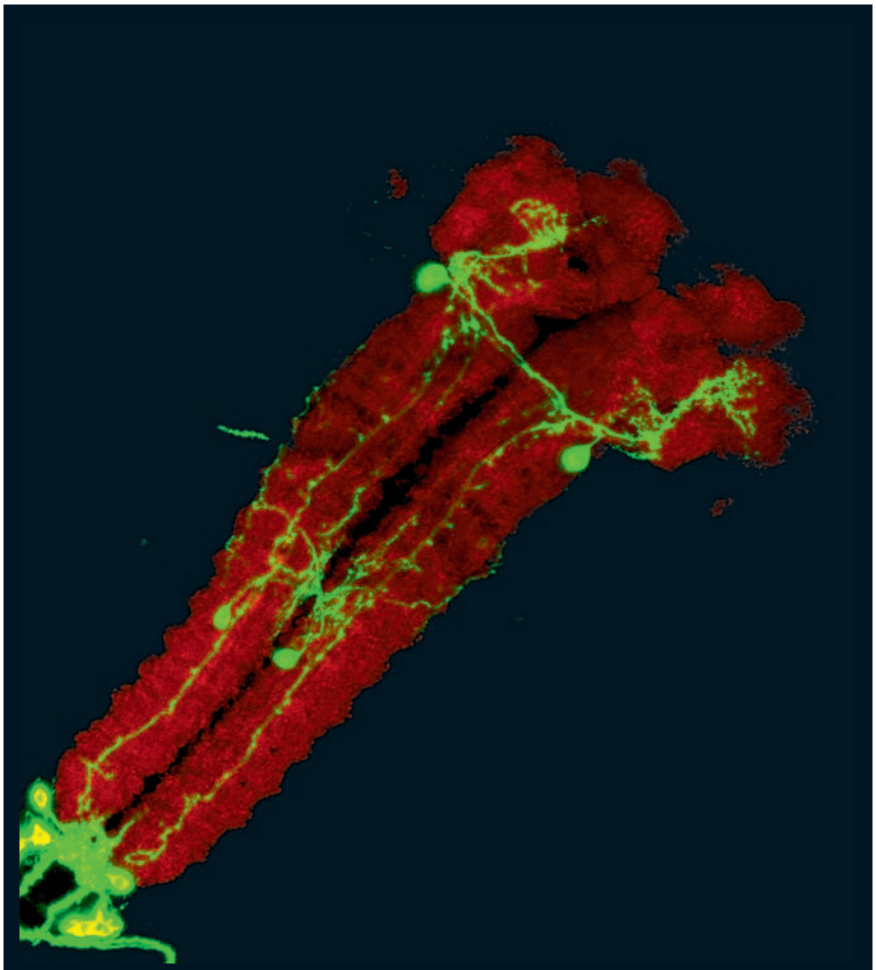
The younger Anderson says he takes inspiration from many sources, among them Charles Darwin's 1872 monograph, "The Expression of Emotion in Man and Animals." This dense work, overshadowed by Darwin's writings on natural selection, asks why emotions take on physical expressions—why people smile when they're happy or cringe when they're afraid. Darwin posited that opposite emotions produce opposite behavioral manifestations, as well: a smile will turn up the corners of the mouth; a frown will turn them down.

ALONE WITH THE FLIES

For most principal investigators, the moments for real science are crowded by constant meetings and nagging administrative duties, articles to read, lab notes to review, grants to write, and both scheduled and unscripted mentoring moments.

Anderson loves his time with students and colleagues—"I would not do well in a scientific monastery"—but he also has a deep longing for his lab bench, where he can work alone, dirty his hands, and fill his own lab notebook with observations and results. In early 2006, he got his wish, taking a six-month sabbatical at Germany's University of Würzburg.

In Germany, Anderson was able to immerse himself in the lives and biology



In this larval fly nervous system, major structures are stained red and neurons expressing a specific neuropeptide are stained green. In the mammalian brain, many neuropeptides are produced in the hypothalamus to play a role in the control of emotional behaviors. Of the approximately 100,000 neurons in the fly's nervous system, only about 10 express this neuropeptide, suggesting that they have a very specific function.

Anne Hergarden and Timothy Tayler

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of fruit flies. Period. There were leads to ponder, behavioral experiments to design, and always a single question to answer: "How can we determine in an objective way whether flies have emotions or not?"

The problem was—and remains—vexing. For example, when flies scatter as a shadow passes over them, are they truly afraid?

Of course, to detect an emotion requires first defining the term, a task that Anderson agrees can be subjective, if not downright emotional. His choice? Emotion is something that places value on behavioral options and that reveals itself in grades of intensity and that produces internal states with similar ranges—from mild apprehension to terrorizing fear, for example.

Studying fruit flies long enough and hard enough, as Anderson did in Germany, enables one to detect some intriguing emotion-like clues, he contends. During courtship, for example, male fruit flies extend their wings horizontally as they sing to their mates. Flies engaged in aggressive behavior, on the other hand, elevate their wings straight up in the air.

"When you look at their wings and the two perpendicular axes associated with two activities of opposite emotional valence, it makes me wonder," says Anderson. "Maybe the wings of the fly are the best way to read its internal state."

Adding weight to his hypothesis is work by Axel and others that has found a similar structural scheme in both mice and fruit flies. In short, all neurons that express a common olfactory receptor in these creatures have axons that converge on a single point in the brain.

"In over 400 million years of evolution, the same neural circuit organization has been conserved, even when the molecules themselves have not," Anderson relates with genuine awe. And if this circuitry has been conserved, perhaps emotional responses have been as well.

Rubin, for one, already is convinced that flies have emotions. "What is not clear is how analogous fly 'fear' and human 'fear' are in the way the fly or human feels them and responds behaviorally."

Answering that question could lead to novel antidepressants with, for example, fewer side effects. But these would be consequences, Anderson insists, not objectives. Indeed, he is openly scornful of the current funding fashion that dresses up the "best" and most attractive scientific research as "translational." Scientists need to be free to follow their curiosity, he believes, even when any ultimate application is not yet evident and even though they essentially have to start their careers all over again. HHMI enabled that freedom, Anderson says. "Its financial support has made everything I've done possible."

STAYING THE COURSE Not surprisingly, support and understanding from many of his peers has been grudging, Anderson confesses. He had little formal training in *Drosophila* neuroanatomy and, when he started, precious little intuition about the most productive experiments that such training and experience provide. "I basically had to teach myself," he acknowledges. "I felt like a graduate student again."

Moreover, the switch in research direction from development of the nervous system to behavior—"like turning around an oil tanker"—jolted the academic lives of the graduate students and postdocs who had allied themselves to his previous scientific interests. Neglect was never an issue, however. In each case, Anderson stayed the course, supervising experiments in angiogenesis, and teaching, guiding, and mentoring until the cycle of students and fellows could finish their work and move on with their careers.

What stirs Anderson now is to nail down, once and for all, the genetic controls and neuronal circuitry behind fear and anxiety in fruit flies, no matter that these creatures lack an amygdala and hippocampus and no matter the ultimate relevance to human health.

Where his present research will lead is unclear, although, in one experiment, when he put a black patch on the surface of their vial, the flies congregated under it when a shadow was passed over the vial. They appeared, at least superficially, to be hiding—as if from a predator.

"If an animal suddenly becomes, say, very aggressive, what's going on in its brain—and where—to make it act that way?" Anderson asks. Wouldn't it be great, he adds, if it were possible to derive certain universal rules that could definitively link a particular behavior to an emotion?

"Emotions just didn't pop up out of nowhere. When did they begin? What are the building blocks?" He pauses. The corners of his mouth turn up. He smiles. "There is a rich vein to be mined in fruit flies. And in the end, I'm convinced that, if nothing else, fruit flies are going to teach us about the evolution of emotions." ■

WEB EXTRA: For details of Anderson's studies on fear and pain, visit the *Online Bulletin*.