



Sydney Brenner's hopes for understanding the brain — put on hold 30 years ago — are now revived, courtesy of advanced techniques and new insights about a humble but invaluable worm.

by Maya Pines

illustration by Aaron Smith



The Wise Man of Janelia





As soon as Sydney Brenner walked into the hall, leaning on his cane, several young scientists rushed toward him like bees drawn to nectar. They wanted to talk to him about many things—his current activities, their own work, even a recently published article by someone else. Brenner, 80 years old, answered their questions with gusto. He made it clear that he disliked the new article. “The only thing that’s worse than ‘bad’ is ‘boring,’” he quipped. They laughed.

Brenner doesn’t do boring. A Nobel Prize winner and one of the founders of molecular biology, he keeps opening up new fields of research. After solving some initial problems and attracting clever collaborators, he then moves on to try something different. On this occasion, last March at HHMI’s Janelia Farm Research Campus in Ashburn, Virginia, he was attending a conference on the nervous system. A senior fellow at Janelia, Brenner was making one of many stops on an ever-full itinerary. He spends much of his time flying around the world, giving talks and advice, running research projects, launching new alliances, stirring things up.

“I’ve been a rebel, or as I was once called, an *enfant terrible*,” he said in a series of interviews later published as an autobiography, *My Life in Science*, by BioMed Central Ltd. “Being a rebel has always appealed to me, largely because I’m convinced that the standard parts of any activity are already petrified at the core.”



A Most Worthy Worm

In the late 1960s, for instance, “after cracking the genetic code, Sydney decided he wanted to understand how genes control the development and function of the nervous system,” says Paul W. Sternberg, an HHMI investigator at the California Institute of Technology. “So he chose to work with the worm”—specifically, a tiny transparent nematode called *Caenorhabditis elegans*, that he seemed to pick out of obscurity.

“People thought I was crazy,” Brenner recalls.

But these worms are only 1 millimeter long—a good size to study under an electron microscope—and easy to grow in bulk. Ten thousand can fit onto one petri dish, where they feed on *Escherichia coli* bacteria. And they take only three and a half days to grow from egg to sexual maturity, when they produce about 300 progeny apiece.

Brenner liked them for all these reasons and also because of what he called their “beautiful sex lives.” *C. elegans* is usually “a self-fertilizing hermaphrodite,” he notes, and “each animal is the result of a cross of itself with itself.” This means the worms have a uniform genetic constitution, as if they are clones. Occasionally, some smaller, male *C. elegans* worms crop up, which researchers can use to move genetic markers from one animal to another in experiments.

Brenner hoped his worms would enable scientists to study how genes affect behavior “because there is no simple mapping that connects the two,” he explains. “The link between genes and behavior resides in understanding the structure of the nervous system”—partic-



ularly, the brain. So, in the early 1970s, he began to find mutant worms with behavioral abnormalities and to map the sites of their genetic mutations. Brenner also started a program of cutting up the worms into serial slices and examining each slice with an electron microscope.

Ultimately, in 1986, he and his colleagues John White, Eileen Southgate, and J. Nichol Thomson published the structure of the nervous system of *C. elegans*. (Some ten thousand electron micrographs from these studies are now archived and accessible for scientific review at the Albert Einstein College of Medicine. For more information, visit www.hhmi.org/bulletin/may2006/features/archives.html.)

Other results flowed in. By 1977, after years of doggedly staring into microscopes, John Sulston—who had joined Brenner’s group at the Medical Research Council (MRC) in Cambridge, England—produced the complete lineage map of an adult worm, from a single fertilized egg cell to the 959 cells in the fully organized animal. H. Robert Horvitz, doing a post-doctoral fellowship in the same lab, teamed up with Sulston in the later stages of this work, tracing the fate of each cell



during the worm’s growth from embryo to adult. Their research revealed that cell division produced 131 more cells than actually make up the mature worm. They learned that those extra cells died through an orderly process known as apoptosis, or programmed cell death, during which certain cells commit suicide for the benefit of the whole animal.

In a series of experiments that began in the 1970s, Horvitz, who is now an HHMI investigator at the Massachusetts Institute of Technology, identified a number of genes that regulate apoptosis in the worm. He also found that one of those genes had a similar counterpart in humans. Researchers subsequently found versions of other worm apoptosis genes in humans, where they play an essential role in normal development. Both Sulston and Horvitz eventually shared the Nobel Prize in Physiology or Medicine with Brenner in 2002 for their achievements.

Brenner, a short man with bushy eyebrows who has been known to wave his cane in the air during arguments with other scientists, has a low tolerance for delay. He became disappointed that the new findings did not make a dent in the much more complex problem he had started out with: how genes control the nervous system and behavior. Concluding that the right tools for this work were not yet available, he simply gave it up temporarily. “That’s why I like to have a lot of things to do,” he explains, “so that if one gets stuck, you can go on with the others.”

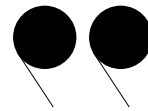
Now Is the Time

Now, 30 years later, Brenner is once again eager to tackle one of biology’s greatest challenges—“understanding how a complete brain works,” as he puts it. That is also the stated goal of the Janelia Farm Research Campus, whose work so far has focused on the brains of flies and mice. But Brenner pins his hopes on the worm, which has the simplest and best-known nervous system. “We will fulfill the program of Janelia in *C. elegans*,” he predicts.

Brenner helped organize the March conference at Janelia on “Neural Circuits and Behavior in *C. elegans*.” It was prompted by the fact that researchers have now obtained three types of information that Brenner considers crucial for relating brain to behavior, and all three are available in the worm.

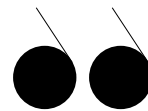
First, “we have the wiring diagram—we know exactly how many neurons are in the worm’s nervous system and how they are connected,” Brenner points out. Second, “we know the complete cell lineage of the worm”—how a single egg cell develops into all the other cells, and which cell comes from which progenitor. And third, researchers have established the complete DNA sequence of the worm’s genome, which was published in 1998.

With all this information, “you can make models of how some circuits work and test them,” says Brenner. But the key, he adds, is to use “the real structure of the worm’s neural circuits.” What needs to be done, he says, is “to think hard about how the worm solves a problem.”



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– Sydney Brenner





Exceeding All Expectations

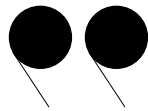
The 40 scientists who came to the Janelia Farm conference talked about their first efforts in this direction. Cornelia I. Bargmann, an HHMI investigator at The Rockefeller University in New York City (and co-organizer of the meeting), described her studies of how worms regulate their patterns of locomotion after they have been removed from food. She analyzed the hungry worms' search patterns, located the neurons involved in each pattern, and confirmed their activity by means of imaging. Jamie White, a postdoc in the University of Utah lab of HHMI investigator Erik M. Jorgensen, took a different approach: he analyzed the neuronal circuits that make male worms differ from hermaphrodites in their responses to pheromones, the chemical signals with which animals communicate. The males were attracted to pheromones released by hermaphrodites, while other hermaphrodites avoided them.

Other scientists used their expertise in imaging or computation to pave the

way for future experiments. Rex Kerr, a fellow at Janelia Farm, pointed out "there is no easy way to precisely monitor the activity of neurons, or to quantify behavior at the same time." To help solve this problem, Kerr is working with a new microscope that could provide three-dimensional views—even movies—of what goes on inside the worm's head, where half of the animal's 302 neurons are located.

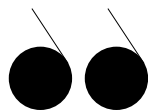
Brenner seemed thrilled by what he heard. "People are modeling all parts of the nervous system," he says. "This has exceeded all expectations. ... It will be seen as a turning point in our understanding of the nervous system.

"If we can simulate a behavior with a computer model of the nervous system," he adds, "then we have the capacity to predict how [the animal] will behave under circumstances that have not yet been tested. And if we can check it by experiment, then we have the basis for explaining the nervous system."



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Scientist-Citizen of the World

Brenner himself has influenced these and other results, directly or indirectly, and his insights and advice continue to be sought the world over. He and his wife have a house in Ely, England, a small town near Cambridge renowned for its cathedral, but they live there only a few months a year. In the winter they move to the Salk Institute for Biological Studies in La Jolla, California, where he collaborates with HHMI investigator Terrence J. Sejnowski at the Crick-Jacobs Center for Theoretical and Computational Biology.

He travels frequently to Singapore, where he says he's "been helping to build a new biomedical research program that now has several thousand people and is going very well." While in Singapore, he guides the program, gives lectures, supervises students, and even runs some research projects. A decade ago Brenner started a study of fugu, a pufferfish that he chose because it is a vertebrate with a tiny genome. The Singapore team played a big role in the international consortium that sequenced and published the fugu genome in 2002. Last October, Brenner received Singapore's top science award, the National Science and Technology Medal, and an orchid there has been named after him.

In addition, Brenner heads a planned Okinawa Institute of Science and Technology in Japan. He works with the Molecular Sciences Institute in Berkeley, California, which he founded a decade ago, and holds a variety of other positions, some of which, he says, "are secret."

A Precious Asset to Janelia

Gerald M. Rubin, director of Janelia Farm, recruited Brenner during the earliest planning stages of the research campus. Rubin remembered the stimulating environment he had found at the Medical Research Council in Cambridge where he did his graduate studies with Brenner, beginning in 1971, and he wanted to reproduce some of its best features at Janelia—in particular, having people like Brenner to talk to.

“I could hardly think of a single person who could do more for the intellectual environment,” says Rubin. Just consider some of Brenner’s early work. He was a co-discoverer of messenger RNA and he collaborated with Francis Crick, the co-discoverer of DNA’s double helix, to show that the genetic code consists of nonoverlapping triplets of nucleotides, with each triplet specifying a particular amino acid. “He did work worthy of a Nobel Prize even before he got into *C. elegans*,” says Rubin.

“And Sydney has a combination of wit and insight that is very rare. He was so entertaining when he taught at Cambridge



Sydney Brenner (right) with Gerry Rubin at Janelia Farm.

that students would bring their nonscientist friends to his lectures just to listen to him. So for me,” says Rubin, “it would be enough if Sydney just came here and sat at a table in the pub and talked to all comers, happily giving advice on people’s experiments and careers.”

As Brenner describes it with a smile, “My function is to be decorative, ornamental ... to talk to the young people, tell them stories, and keep the conversation going—about science, its puzzles, and its problems.”

Such conversations have already produced results. During a recent talk

with Brenner, Janelia group leader Gene Myers, a computer scientist famous for developing the whole-genome shotgun technique that his team used in sequencing the human genome, became very interested in the problem of the brain. “It’s a little surprising to me,” he says, “but I started thinking about some experiments, which I described to Sydney, and he made some astute comments. We had a period of a day or so when the conversation was really intense.”

Myers finds Brenner’s attitude particularly impressive. “Very often, scientists look for reasons why something can’t be done,” he says. “But Sydney’s response is, ‘Let’s have a go!’ Especially since I’m not an experimental scientist, I’ve found that liberating. So we’ve now got a very interesting project going in which we’re literally watching the neurons firing in transgenic constructs. It’s fairly high risk, yet easy and inexpensive, and there’s a nice little computational problem involved. Sydney and I have got ourselves all worked up in a lather about it and we’ve infected everyone else at Janelia. We’re going to have a go!” ■

ALL IN THE FAMILY

The number of people in the “worm community,” as *C. elegans* researchers call themselves, is growing rapidly. Once regarded as a joke organism, the little worms have become a powerful experimental system, with more than 3,000 scientists working on them in some 400 labs. “Somebody told me a new nematode lab is opening every week—I believe that’s the same rate as McDonald’s!” says Sydney Brenner. ○ ○ ○ Actually, most members of this community can trace their scientific lineage to Brenner. They are either his direct professional offspring, such as Robert Horvitz, who was a postdoctoral fellow of his at the MRC, or they were trained by people whom Brenner

has trained. Paul Sternberg, who joined Horvitz’s lab as a graduate student, considers himself “second generation,” or F₂ in the jargon of genetic researchers. So does Cornelia Bargmann, who joined Horvitz’s lab as a postdoctoral fellow. Rex Kerr, an F₃, was trained by William Schafer, an F₂ who was trained by Cynthia Kenyon, who was a postdoctoral fellow in Brenner’s lab. ○ ○ ○ They share a kind of family feeling for Brenner. When a new species of nematode, closely related to *C. elegans*, was officially named “*Caenorhabditis brenneri*” in April of this year, Sternberg and his “relatives” rejoiced. He says, “It made everyone in the field very happy.” — M.P.