Igniting the Spark

BY IAN MCCLUSKEY

What lessons can we learn from outstanding scientists in our region? The path to a career in science—and even a Nobel Prize—is often guided by a curious nature, the ability to seek out challenges, and willing mentors—with a dash of serendipity. Some leading Northwest researchers share their stories and suggestions for teaching tomorrow's scientists.

FRANKLIN STAHL—
Construct Your Own Hurdles

James Watson was chatting with Francis Crick and some colleagues, when he pointed out the window, toward a lawn across the street, where one of his new summer students was mixing, selling, and drinking gin and tonics. "See that," he said, "That's Frank Stahl. He thinks he's pretty hot stuff."

The year before, Watson and Crick had published their seminal paper on the replication of DNA. That summer, in 1954, Watson and Crick were visiting researchers at the Woods Hole Laboratory in Massachusetts. Watson was teaching a physiology course, and the young man across the street, Franklin "Frank" Stahl, was his new student. Watson continued, "Why don't we give him a really tough experiment and see what he can do with it?"

"The poor guy," thought Matthew Meselson, who was working as Watson's assistant and was standing with the group. He wondered, *"Who was this student who had caught the eye of the world-famous Watson and Crick, and why would they want to throw him such a 'hot potato?'"* So Meselson decided to go down and meet Stahl. The two struck up a conversation about Watson and Crick's new theory on the proposed double helix structure of DNA, and the possibility of designing an experiment to learn how DNA replicates.

Previous ground-breaking studies had focused on organisms such as garden peas, fruit flies, and mice. Stahl became interested in bacterial viruses. With a countable number of atoms, bacterial viruses demonstrate all the basics of genetics, such as mutation, replication, and recombination. "People said it was just a fad, not something for professional biologists to study," recounts Stahl. His advisors told him there was no future in microbiology. "It wasn't just unexplored, but flat out denied," Stahl insists. "I saw a door. It wasn't clear to many, but it was to me."

Though Watson and Crick had cracked open the door with their landmark 1953 paper on the structure of DNA, the double helix model did not gain wide acceptance until Stahl and Meselson published the results of their experiment in 1958. Their experiment gave physical validity to a model that many scientists saw as speculation. Today, the double helix is an internationally recognized symbol of modern science. For his lifetime of work in DNA research, Stahl was awarded a MacArthur Fellowship, also known as a "genius award."

"The whole point of science is to overthrow conventional understanding to reach a deeper understanding," states Stahl, now an emeritus professor of biology at the University of Oregon. Reflecting back on his career, he has some strong advice for today's students: "Pursue your interests without regard to what others think you should do. Construct your own hurdles and jump them, rather than the ones placed in front of you. Question a teacher to the point you can understand a concept in your own terms. If you don't understand, keep questioning."

Stahl feels teachers can help start the process by getting students to ask questions. If he could offer one piece of advice to today's teachers, it would be to show students the experiments that fell apart, not just the successes. "The failed ideas are valid," he says. "Many failed ideas sounded promising when they were put forth. An experiment showing that a 'good' idea was, in fact, wrong frees us to look for a better one."

LINDA BUCK—
Encourage Obsessions

When Linda Buck's pet hamster died, the young girl buried it. She then tried to dig it back up to "see what it looked like." When her cat miscarried, she fetched her microscope from the basement. "I was always curious," the 57-year-old scientist explains.

Her father, an electronics engineer, was always trying to get his three girls to put down their dolls and build toy motors, operate amateur radios, and learn Morse Code. Her mother was a homemaker who loved puzzles, especially crosswords. Not surprisingly, Buck is known today for her analytical skills. "My mother used to complain I had a one-track mind," Buck recalls.

When Linda Buck was a teenager, she knew she wanted to help people, but she didn't know if science was the way to achieve that goal. When she graduated from Seattle's Roosevelt High School in 1965, her high school biology teacher wrote in her yearbook that she would make a "fine biologist one day."

Little did that teacher know how prescient her prediction was: This past December, Buck flew to Sweden to receive a 2004 Nobel Prize in the category of physiology or medicine. Buck, along with her colleague Richard Axel, has helped unlock the science of smell.

In 1991, Buck—who was then a postdoctoral fellow working in Axel's laboratory—discovered a family of genes that encode the odorant receptors of the olfactory epithelium, a patch of cells on the wall of the nasal cavity. Made up of some five million olfactory neurons, the olfactory epithelium sends messages directly to the brain, where they are processed as distinct scents, tastes, emotions, and memories. The discriminatory power of the olfactory system is immense; even a slight change in the structure of an odorant can alter its perceived odor, for example, from a hibiscus flower to sea salt.

Instead of hunting for the receptor proteins directly, Axel and Buck looked for genes that contained instructions for proteins found only in the olfactory epithelium. Their efforts produced nothing at first. Finally, Buck came up with what Axel calls "an extremely clever twist." She made three assumptions that drastically narrowed the field, allowing her to zero in on a group of genes that appear to code for the odorant receptor proteins.

Based on scattered evidence from other labs, Buck made the decision to narrow her search to a family of proteins called G protein-coupled receptors (GPCRs). Making use of a recently developed gene amplification technology, Buck then decided to conduct an exhaustive search for GPCRs in the olfactory epithelium. Further analysis narrowed the search to one candidate and Buck had found precisely what she had been looking for. Buck's cut-to-the-chase instincts obviated the need to sort through thousands of genes and, according to Axel, "saved several years of drudgery."

"I had tried so many things and had been working so hard for years, with nothing to show for it," explains Buck, who is a member of the Fred Hutchinson Cancer Research Center and an affiliate professor at the University of Washington in Seattle. "So when I finally found the genes in 1991, I couldn't believe it! None of them had ever been seen before. They were all different but all related to each other. That was very satisfying."

Having persisted in her quest to unlock the secret of scent for so many years, Buck tells students: "Pick a problem that you're extremely interested in. That sounds kind of simplistic maybe, but it's not, because you don't want to just do a problem because it's easy to solve, you want to do something that you're obsessed with, that you just have to understand."

Since making the first discovery in the olfactory epithelium, Buck has unlocked the complex mapping of the olfactory balls and the olfactory cortex—at each step, placing one more piece in a larger, more complex puzzle. She's been pursuing the path of scent and perception for the past 16 years, and says she's "just scratched the surface" so far.

"That's where the joy comes from," says Buck, "and that also, I think, is where the great discoveries come from—from people who are really trying to figure out things that they don't understand. And they don't necessarily know how to do it, but they try very hard and then they succeed." ■

Meet cancer researcher Grover Bagby, marine biologist Brenda Konar, microbiologist Peter von Hippel, and nurse-scientist Jeanne Quint Benoliel in the Web exclusive.

Igniting the Spark: Another Look