Health & Medicine

Scents and Sensibility

Nobel Prize–winning molecular biologist Richard Axel ’67CC followed his nose to the mysteries of smell and cracked the two great problems of olfaction: how the nose recognizes thousands of odors and how the brain knows what it’s smelling.

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Slumping into the gray leather couch in his office, one leg draped over the armrest, Richard Axel admits that he was not the first to clone a nose. That distinction belongs to Woody Allen, who in 1973 regenerated a dead tyrant from a disembodied schnoz in the movie *Sleeper*. Axel, a University Professor of biochemistry, molecular biophysics, and pathology, shrugs and says, “Woody thought of it before me.”

Allen’s comic device has a whiff of scientific plausibility, as Axel recently demonstrated when he and others grew a mouse from a nose. To be accurate, the mouse was a clone, created by removing the genetic material from a nerve cell deep inside another mouse’s nose and injecting it into an empty egg. This elegant experiment was not really an homage to *Sleeper*, although Axel does refer to the zany movie in lectures on the science of smell. Nor was it a laboratory stunt. It was an important step toward unlocking the mysterious mechanisms of the mammalian olfactory system.

For his pioneering work explaining how humans make sense of the olfactory world, Axel shared the 2004 Nobel Prize in Physiology or Medicine with Linda Buck, a former postdoctoral fellow in Axel’s laboratory who is now a professor at the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle. Axel and Buck were recognized for their seminal 1991 paper describing a family of genes in mice that encode more than 1,000 different odorant receptors, the nerve cells in the back of the nose that interact with airborne molecules that waft into our nostrils. “Their work was among the most important biological discoveries of the past 50 years,” says Gerald Fischbach, executive vice president

for health and biomedical sciences, dean of the faculties of health sciences and medicine, and Harold and Margaret Hatch Professor of the University. “It opened up a field of sensory biology that didn’t exist before.”

Following His Nose

Axel was born in Brooklyn in 1946, the son of Polish immigrants, and attended Stuyvesant High School in Manhattan. Lanky and loose-limbed, he played starting center on the basketball team and once guarded a seven-foot-two opponent named Lew Alcindor, who later changed his name to Kareem Abdul-Jabbar. Alcindor dropped 54 points on him, and when Axel finally got the ball, “he looked at me and said, ‘What’re you going to do with the ball, Einstein?’ And the answer was, indeed, very little.”

Axel received a full scholarship to Columbia College in 1963, and reveled in his newfound freedom, eschewing academics for nights out at the opera and less-refined entertainment. “My classmate and friend, Kevin Brownlee [’67CC], now a professor of Romance languages at Penn, felt that there was substance to my mind,” he says, “but that I wasn’t using it and that I wasn’t taking advantage of the University in any way.” Brownlee convinced Axel to buckle down, and the two spent many long days studying in the reading rooms of Butler Library, often migrating to the “grubbery” to continue when the library closed at 11 p.m.

Axel at first had little interest in biology. An otherwise omnivorous student, he explored biochemistry while taking an English concentration with a focus on Faulkner. He needed to supplement his scholarship with a job (in part to support his opera habit) and found one washing glassware in the laboratory of I. Bernard Weinstein, now Frode Jensen Professor of Medicine and director emeritus of the Herbert Irving Comprehensive Cancer Center. “Frankly, he was a terrible glassware washer,” Bernstein said recently at a celebration honoring Axel. “The bottoms of beakers were murky, test tubes were broken, and pipettes were losing their tips. But in the midst of this, Richard was poking around, asking us why we were doing this experiment or that, or why we weren’t trying something else. So we fired him as the lab’s glassware washer and rehired him to do research.”

Axel was coauthor on several of Weinstein’s papers and was increasingly interested in the burgeoning field of molecular biology. “This was the time when the structure of DNA had been determined and the central dogma emerged in biology that DNA was the repository of all information,” he says. “I was absolutely fascinated by what was emerging in the new biology of the 1960s.” By his senior year, Axel was contemplating graduate school in literature or biology when he was drafted and “had the decision made for me.” He quickly applied to medical school (Axel opposed the war, and military deferments were given only for professional schooling) and went to Johns Hopkins.

Although he had graduated with honors and a Phi Beta Kappa key from Columbia, Axel admits that he was “a terrible medical student,” particularly during clinical rotations in his third year. “I found it very difficult and emotionally upsetting to spend time around sick people,” he says. “I spent most of my time in medical school in laboratories, and I owe Hopkins a tremendous amount of gratitude for tolerating me. I was extremely difficult.”

Indeed, after Axel’s third year, the dean presented him with an award for outstanding research and quietly gave him the option of not completing the final clinical year on the wards. “I opted immediately for that alternative,” he says, “with the understanding that I was never ever to practice medicine on live patients.” Instead, he returned to Columbia to intern in the pathology department. “I did 80 autopsies that year, and was given certification in pathology with the proviso that I never practice medicine on dead patients, either. For this and for many other things I also owe this University an enormous debt.” Axel was appointed professor of pathology and biochemistry in 1978 when he was only 32 and has been an investigator at the Howard Hughes Medical Institute since 1984.

How the Nose Knows

When Buck joined Axel’s lab in the late 1980s, little was known about the sense of smell. Researchers believed that small molecules excited neurons inside the nose, triggering activity in a region of the brain called the olfactory bulb. It was estimated that humans could identify 10,000 or more different chemicals as having distinct odors, but no one knew how the olfactory receptors discern a molecule of ripe banana, say, from a pear molecule when the two are almost chemically identical.

Even more baffling was the problem of discrimination: Once the thousands of different odorants dock with receptors in the nose, how does the nervous system make sense of all the electrical signals sent into the olfactory bulb?

Or as Axel often says, “How is it that the brain knows what the nose is smelling?”

Buck set out with Axel in 1988 to solve the first problem of recognition. They found more than 1,000 olfactory genes, each encoding a unique olfactory receptor. “We were quite surprised that up to 5 percent of the genome was taken up by odor receptors,” says Axel, who is also a member of Columbia’s Center for Neurobiology and Behavior. The human eye recognizes several hundred hues with only three different photo receptors in the retina that are encoded by three genes. Axel describes the visual genes as “promiscuous” because they interact with one another and many others to accomplish vision. The olfactory system, however, has evolved a large number of what he calls “chaste” genes that work independently.

Starting in 1991, Axel and Buck pursued the harder problem of discrimination. “The discovery of the olfactory receptors explained how mammals are able to detect a vast number and variety of chemicals in the nose,” Buck said in her Nobel lecture. “It also did something else important, however. It provided a set of molecular tools that could be used to begin to explore how olfactory information is organized and encoded in the brain.” Buck moved to Boston to study this question at Harvard, working independently and in parallel with Axel’s lab. They both found that odorant molecules are recognized by unique combinations of receptors, and the combinations activate specific areas in the brain’s olfactory bulb.

The vexing question, Axel says, is how an organism reads this olfactory map. Humans can look down at the olfactory bulb in a fruit fly or a mouse and see what patterns are activated in the brain, and thus what smell is perceived. But “the brain does not have eyes,” Axel says. “Who in the brain is looking down on an olfactory map? How are the spatially defined bits of electrical information in the brain decoded to allow the perception of an olfactory image?” This remains the ghost in the machine.

To the Grindstone

In the weeks leading up to the Nobel pageantry in December, Axel celebrated his achievement with friends, colleagues, and other Columbian laureates (there are 70 in total, 19 in the category of physiology or medicine). “The most useful advice I received from other colleagues who’ve been in this situation more deservedly in the past was to sit back, enjoy it, and as quickly as possible forget about it.”

Axel didn’t linger in Stockholm. Back in the lab, he thought about what to do with his half of the $1.2 million prize and began researching suitable charities. When asked how his life has changed post-Nobel, he frowns and crosses his long legs first one way, then the other. “I’m working extremely hard to ensure that there are no changes,” he finally says. “I’m really enjoying doing science, sitting here on this couch and talking with my students and fellows about our work.” He turns to the dry-erase board that takes up an entire wall of his office. It’s covered in scrawl, a week’s worth of diagrams and notes hashed out in red, blue, and green. “After all, I received a Nobel Prize for my efforts in the laboratory — more specifically for the efforts of my fellows and students — which is all the more reason to go back to what I really enjoy doing.”

This Is Not a Nose

When Axel describes olfaction, he often invokes the Belgian surrealist René Magritte. In lectures, Axel shows a spoof of Magritte’s famous “This is not a pipe” painting. It features a gigantic disembodied nose underneath the words Ceci n’est pas un nez, or “This is not a nose.” “It’s a particularly good representation of the problem of sensory perception,” Axel says of the painting. “There’s the tension between image and reality, the realization that a painting is not a physical image, but a portrayal of the artist’s brain’s representations of the image. The brain functions, then, not by recording an exact image of the world, but by creating its own selective picture, which is largely determined by that which is important to the survival and reproduction of the species.”

What about inside Axel’s brain? What do aromas mean to him after years of reducing olfaction to its component parts? Can he walk into a pastry shop, say, and simply inhale the riot of smells without thinking of the millions of cells in his nose that are sending electrical signals into his olfactory bulb? “Of course,” he says. “Having a reductionist view of the brain doesn’t in any way contradict the marvel

and joy of the translation of these physical principles into the final product: emotion, thought, awareness. The fact is that the mind is a marvelous entity, and the more one has a physical understanding of how it works, the more fascinated and romantic one is about how these physical events translate into experience, aesthetics, and feelings.”

Tim Stoddard writes about science for Bostonia *magazine.*

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