Persistence and Intensity

By Daniel Grossman

Mark Ptashne '61, chairman of Harvard University's biochemistry and microbiology department, stands near the summit of the United States's scientific establishment. Before turning 30, he solved molecular biology's most important problem. He's since published stacks of scientific papers and been heaped with awards for scientific achievement—including Columbia University's Louisa Gross Horwitz award, often the precursor to a Nobel Prize. He's a member of the prestigious National Academy of Sciences. And his 1986 book, *A Genetic Switch,* is widely read by biology majors and graduate students. Yet on a recent visit, Ptashne is neither tabulating research results nor composing copy for a grant application. Head swept back, he places a violin between his chin and his left shoulder. Pursing his lips and lowering his eyes to the instrument's bridge, he launches into Brahms' C-major trio.

"I couldn't live without this violin," says Ptashne. The instrument, built by the 18th-century Italian craftsman Giuseppe Guarneri del Gesu, is one of the world's finest violins. "It has a warmth and expressiveness" says Ptashne, "that has never been equaled." Ptashne's collection includes five prize "fiddles" as he calls them— including another Guarneri and a Stradivari. His two "second-tier" instruments are often on loan to deserving conservatory students. He practices every day on the others, although he's reluctant to admit how long. "It's just not like an adult," he says, to be spending so much time occupied learning a new skill.

Ptashne usually listens to classical music as he works, and he says orchestral music is often on his mind. But he doubts any profound relationship exists between his passion for music and his scientific achievement, although he says both inspire the same ardor: "What drives the scientist is no different than what drives the artist." Ptashne himself is driven by the challenge of unsolved scientific riddles. He was first struck with a thirst for dis-

Ptashne used this method to do something Gilbert had not been able to do: to work out the details of how the lambda repressor binds to DNA and governs the genetic code.

In the decades since the frantic early days, Ptashne has worked toward one single goal: "to turn gene regulation into a problem of chemistry." After cutting his teeth on molecular machinery of the primitive phage lambda, he turned to higher organisms. Meselsen says that Ptashne's research has been "seminal, leading to much work of others." Ptashne himself "hasn't touched a test tube in years." Now his experiments are carried out with the help of a small army of researchers in a sprawling laboratory covering half a floor of a modern brick building. The war room is the staff lounge. And every Wednesday Ptashne holds court there to discuss research results around a large conference table.

At one recent session, Ptashne listens intently while Aseem Asari, a postdoctoral fellow from India, presents results from an experiment. Ptashne puts his feet on the table and leans back in a swivel chair. His argyle socks show below his cuffs, and a handful of change tumbles from his pockets. "Is this the main point, or are you just filibustering?" he asks, interrupting Asari's explanation of a transparency projected on the wall. Some of Ptashne's former students complain that the researcher is arrogant and unsupportive. But others, such as Nancy Hopkins, consider themselves lucky to have trained under the scientist. "When I teach," says Hopkins, "I hear Mark."

For over a hour at the Wednesday gathering, Asari presents results and answers questions. Ptashne seesaws between inquisitor and mentor—ribbing one moment, quizzing the next. Asari is studying the genes in yeast that control the organism's use of sugar. Yeast, one of the simplest of the higher organisms, or eukaryotes, is this laboratory's favorite research subject. By 5:30, it's getting late and stomachs are beginning to growl. By coincidence, yeast is an important ingredient of tonight's dinner. "Where's the pizza?" says Ptashne, closing the conference. A student plants a tall stack of pizza boxes on the table. "Zowie," Ptashne says. "Anyone get Diet Coke?"

Ptashne's research has had important practical applications. The same techniques he used to turn lambda into a factory to produce the repressor, for instance, can also trick bacteria into manufacturing drugs and other products. And Ptashne has not been shy about exchanging his lab coat for a corporate suit and tie. In 1980, then Harvard president Derek C. Bok announced a proposal to set up a corporation to bring to market commercial applications of recent advances in recombinant DNA research—including techniques discovered by Ptashne. Ptashne says it was Bok who thought up the venture, which would have guaranteed the university a stake in the lucrative new biotechnology industry. The *New York Times* reported at the time that faculty insiders said privately Ptashne himself initiated the idea. In any event, the proposal provoked an intense debate at Harvard and elsewhere about the effect of grafting research firms to universities. Several weeks later, Bok called the plan off. Such arrangements encouraged conflicts of interest that "could confuse the university's central commitment," said Bok in a public statement.

It is not a time Ptashne remembers fondly. "They stabbed me in the back," he says, adding that in the intervening years many universities have launched similar joint ventures. Harvard itself founded Medical Science Partners less than a decade later to commercialize the research of faculty members with $36 million in venture capital money. Ptashne persevered without Harvard's help, and today the firm he helped to establish, the Genetics Institute, is a major pharmaceutical manufacturer with a staff of 1,000 employees and revenues topping $70 million. He has since cut his ties to the firm, though not without receiving generous compensation for his contributions. The industry newsletter *Genetic Engineering News* included Ptashne on its 1994 list of "molecular millionaires," with $9 million in Genetic Institute stock. Referring to his collection of virtuoso musical instruments he says, "I had a reason to make a lot of money."

In the decades since his first dramatic discoveries, Ptashne has never veered from the course he first set. Today his lab is still ironing out the details of how genetic controls work in higher organisms, including humans. Jonathan Beckwith, Harvard Medical School's American Cancer Society Research Professor, praises Ptashne's long-standing commitment to understanding the genetic switches so critical to the life of the cell. "He has had the persistence to pursue a small area," says Beckwith, "with profound applications."

"Things are much messier in people than in bacteria and viruses," acknowledges Ptashne, but "the groundwork has been laid." There are still of problems to solve, but Ptashne says he's frequently conflicted over how to spend his time. He says frankly he'd often rather be practicing the violin or working on his golf swing. But, he adds, "I can only do that if I have something percolating in the lab." ■

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