PROFILE

Shirley Tilghman: Princeton's Unconventional New Chief

Next month, this expert on gene silencing and advocate of women in science will become the first woman president of Princeton University

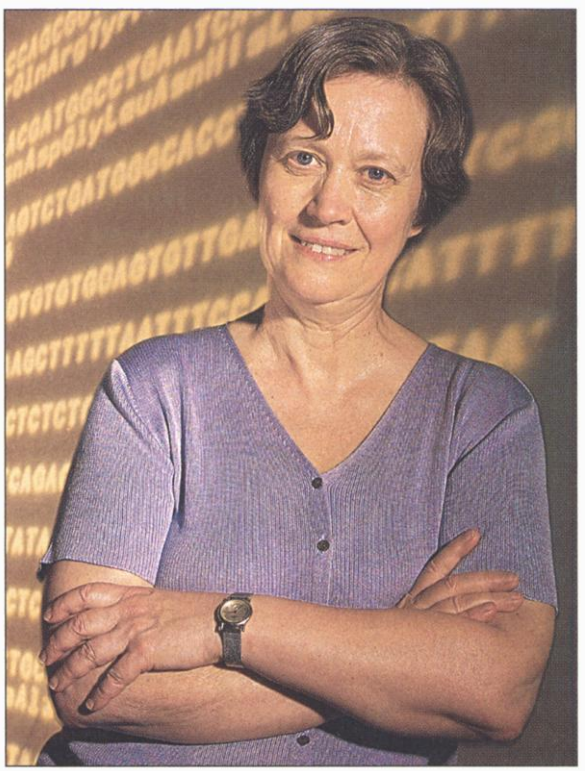
Fifteen years ago Shirley Tilghman, then a single mother with two young children, was working at the Institute for Cancer Research of the Fox Chase Cancer Center in Philadelphia. Battling traffic, "I spent hours every day driving between work and kindergarten and home," she recalls. Life was getting "impossibly complicated." At the same time, "I had a feeling I was becoming very narrow" academically.

Everything got simpler in 1986 when Princeton University offered her a job in the biology department. The university seemed "perfect," she recalls, not only because it enabled her to start afresh in basic biology (she had been a biochemist at Fox Chase), but also because there was no commute. To her delight, she discovered she could drive "anywhere in 3 minutes," leaving her more time for research, family, and students. Tilghman says: "I knew I was a good teacher; I wanted to teach, and I liked the fact that Princeton considered teaching a really serious part of the job."

Tilghman's move in 1986 was a boon for the university as well. Two years after arriving she became a Howard Hughes Medical Institute investigator. Her work in mammalian genetics won recognition and honors, including membership in the National Academy of Sciences (NAS). In 1998, Princeton asked her to head a new interdisciplinary institute, endowed with $70 million, that would integrate biology, physics, mathematics, and engineering. And this spring, just as bulldozers began digging a foundation for the institute, Princeton made another offer: Would she like to run the university? She decided she would. On 15 June, Tilghman will become Princeton's first woman president.

Scientists on and off campus applaud the choice. Tilghman "never shies away from asking the kinds of questions that turn things topsy-turvy; questions that make you realize that, just because we've always done it this way, doesn't mean we should continue doing it," says Maxine Singer, a biologist and president of the Carnegie Institution of Washington in Washington, D.C. This openness, Singer says, "makes her a wonderful scientist."

Singer first met Tilghman 2 decades ago when she arrived as a postdoc at the National Institutes of Health (NIH) to work in Philip Leder's lab. There, Tilghman helped clone the mouse beta-globin gene, the first mammalian gene cloned, revealing its complex structure. Tilghman continued working on mammalian genetics at Fox Chase and Princeton. Today she's best known for studies of imprinting, the process by which genes from the mother or father are "silenced" to allow expression of the other parent's genes. Researchers had observed the phenomenon earlier, Singer notes, but "a lot of people didn't take it very seriously."



Just asking. Tilghman has a knack for turning assumptions "topsy-turvy" with her questions, says Carnegie's Maxine Singer.

CREDIT: KAY CHERNUSH, FOR HHMI

Tilghman's research "put it on a sound molecular basis ... and made people sit up and realize that this was important—that epigenetic effects are much more prevalent than we had realized."

Gene silencing can occur in many different ways, Tilghman notes. Recently, her lab and Gary Felsenfeld's group at NIH have been studying how a protein called CTCF plays a reciprocal role with methylation to permit or block expression of a gene, depending on the gender of the gene's source. The intricacy of this system—and new information about the number of different proteins that can come from a single gene—suggests that DNA may be extravagantly variable in the way it functions. Tilghman says: "I am taken these days with the idea that cells program in sloppiness as a diversity-generating mechanism—that they are not nearly as precise a machine as we thought."

Leaving behind this research is "the most difficult part" of becoming Princeton's president, Tilghman says. She plans to keep her lab "active and open" until the current trainees are through in a few years. Another hard task, she says, will be to find a new chief for the Lewis-Sigler Institute for Integrative Genomics, which she has been developing since its inception 2 years ago. She has recruited several faculty members, looking for scientists who can collaborate easily and are willing to merge fundamental theory with precise observation. Two of her early recruits, for example—physicist Stanislas Leibler and biologist Saeed Tavazoie—bring their different disciplines to bear on the effects of gene transcription and regulation. Both scientists, she says, identify fundamental problems and "take both global and quantitative approaches to studying them." Tilghman hopes the institute will have an educational role as well, and she had recruited Harold Shapiro, Princeton's current president and chair of the U.S. National Bioethics Advisory Commission, to the faculty to cover ethics. Now she's assembling a search committee to find her successor.

Outside her field, Tilghman is known as a critic of graduate education and, in a newspaper's phrase, "a fervent advocate of women in science." She accepts the label, but notes that she has written and talked about problems more than she has taken "concrete" actions. One of her bold proposals is that the tenure system be dropped because it is "no friend to women." It makes huge demands at a time when women are already stressed out with young families, she asserts. She's also not impressed by the method of rating tenure candidates—counting publications. Would she scrap tenure at Princeton? "It's something that's worth looking at," she says. "Princeton has a short tenure clock compared to other institu-

tions, about 6 years, but there's nothing here that wouldn't benefit from scrutiny."

As chair of a 1998 NAS study, Tilghman pushed a controversial recommendation that graduate programs in the life sciences cut back on enrollees to curb a perceived glut of biology Ph.D.s. According to Tilghman, the data showed that too many young scientists were ending up in a holding pattern, employed as cheap laboratory workers with little chance of becoming university teachers. She still feels that way. Others are uneasy with the proposal, which the NAS panel endorsed, because it raises issues that "no one wants to talk about"—proper pay for laboratory staff and how to allocate growth among competing institutions, according to one colleague. One of Tilghman's fellow NAS panel members, biologist William Brinkley of Baylor College of Medicine in Houston, Texas, has now backed away from the panel's conclusions. The economy has changed, he says, and graduates can now find good jobs in the private sector. But he admires Tilghman for her "tremendous leadership ... and the way that she hasn't wavered—I respect that."

Like many others, Brinkley also praises Tilghman as a teacher and interpreter of science: "Young people flock around her." When she gave a talk recently at Baylor, the students "bombarded her the moment she stepped off the stage. ... There wasn't that boundary that often exists between great scientists and students. They felt an identity with her."

As president of Princeton and its chief emissary to alumni and donors, Tilghman may have to learn to "speak in generalities," Brinkley says. But he's certain she'll do well.

–ELIOT MARSHALL

INFECTIOUS DISEASES

West Nile Researchers Get Ready for Round Three

West Nile virus, now entering its third summer in the U.S., is straining public health labs to their limits—and triggering a research renaissance

GUILDERLAND, NEW YORK—For all the misery the West Nile virus has caused since it arrived in the United States—from the cancellation of one of New York City's beloved concerts in Central Park to nine deaths—the virus has also been a source of opportunity. In this small town, 10 kilometers outside Albany in upstate New York, it has enabled virologist Laura Kramer to assemble a new research group. Although the team is still housed in a small, cramped brick building that once served as a horse stable, Kramer has been showered with money, equipment, and the possibility of hiring more people.

Kramer's group, 12 members strong and growing, is part of the Wadsworth Center, the laboratory of the New York State Department of Health. Its main—and rather tedious—task is to test thousands of bird and mosquito samples from all over the state for traces of the West Nile virus. (Just last week, neighboring New Jersey reported finding the first two dead crows infected with West Nile this summer, marking the beginning of the 2001 West Nile season.) But Kramer, who arrived here a year ago from the University of California, Davis, hopes to do her share of basic scientific research as well. "We're ambitious," she says. "I think we've gathered an exceptional group, and we'll be able to do some very nice studies." (The group plans to publish the harvest of the first year of research in several papers later this year.)

Kramer's lab is one of the most prominent examples of how federal and state agencies have rallied to the threat of West Nile. In New York, Governor George Pataki's administration is spending more than $20 million on surveillance, control, and research this year, while the U.S. Centers for Disease Control and Prevention (CDC) is giving the state another $3.9 million to deal with the outbreak. In a sense, the new effort marks a return to the past. In the 1960s and '70s, New York had a strong research program for mosquito-transmitted diseases, such as Eastern equine encephalitis and LaCrosse encephalitis. As those diseases waned in New York, skilled staff members retired, and more pressing public health concerns such as AIDS emerged, the program dwindled over the next 2 decades. By 1998, "the state had run the lab into the ground," says Kramer's predecessor, Jack Woodall, who retired that year. "In the end, I had one half-time animal helper and no technicians, nothing."

The 1999 outbreak has changed all that. "We're now seeing a renaissance, and I think that's terrific," says Thomas Monath, a former CDC virologist and vice president at Acambis, a vaccine company in Cambridge, Massachusetts. Kramer, who spent much of her life studying a West Nile cousin called St. Louis encephalitis, "is excellent for the job," adds Woodall, now a professor at the Federal University of Rio de Janeiro. "She knows viruses and birds, she recruited all these enthusiastic people—she's got this lab buzzing!"

CREDIT: WADSWORTH CENTER, PHOTOGRAPHY AND ILLUSTRATION GROUP

New team on the block. Kristen Bernard, Laura Kramer, Gregory Ebel, and Elizabeth Kauffman study the West Nile virus at New York state's health lab.

Counting dead crows

Two years ago, the West Nile virus caught researchers and public health authorities completely by surprise. Never before seen in the Western Hemisphere, the virus sickened 62 mostly older people in its first year and killed seven, all of them in and around New York City. Last summer, the virus made disconcerting geographic advances, killing birds—its primary hosts—as far north as New Hampshire and as far south as North Carolina. The good news, however, was that only 21 human cases were reported, with just two fatalities. Again, most of those infected lived in New York City, although the "hot zone" had shifted from the borough of Queens to Staten Island.

This year, experts think the virus will once more rage through bird populations along the East Coast. Expect crows, by far the most susceptible species, to die in droves, they say. They also expect the virus to keep spreading, perhaps into Canada, the Midwest, and the Deep South. But the most crucial question—how many humans will get sick—is also the most difficult. "It's anybody's guess, really," says Kramer.

Part of the problem is that viral presence in birds alone clearly doesn't signal an impending human outbreak. Researchers think that the transmission level in birds must be very high for the epidemic to spill into humans. Recently, New York State Department of Health epidemiologist Millicent Eidson found what may be a simple way to predict human risk: the "dead crow density" factor. Throughout the state, citi-