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David C. Page, M.D.



The snow was gently falling as a young David Page hopped onto his bicycle, a rolled-up poster describing his latest results tucked securely under one arm. In a few hours Page would be off to his first scientific meeting, having worked half the night to assemble his poster, pasting together the bits and pieces—text and figures—that would tell the story of his research. Even the plows had not yet been through, and Page, a medical student in love with life in the lab, found himself alone with his

thoughts. Surrounded by the hushed beauty of the snowy landscape, he felt energized and excited by his life and his work. "I remember feeling really good," Page smiles. "I was happy."

With that late-night bike ride, Page would embark on his lifelong career in scientific research—and on his relationship with the Y chromosome. But he wasn't always a science junkie. Page grew up on a farm in central Pennsylvania, in a town so small that it didn't even have a stoplight. Like many boys, he received his share of chemistry sets and microscopes for Christmas. "I remember using them," he says. "But I certainly didn't know in high school that I wanted to be a scientist. I didn't even know what a scientist was."

That changed when Page went to Swarthmore, where he got his first taste of what research was all about. Page landed a summer job at the National Institutes of Health in the laboratory of Robert Simpson. There, studying the histone proteins that help package DNA in the cell nucleus, he learned how to design experiments to answer scientific questions. "I became obsessed," Page remembers, "running off at the mouth to anyone who would listen." His girlfriend that summer withstood endless scientific monologues as Page paced around Simpson's basement (his home away from home), dreaming of the next experiment—and what it might reveal. "I was finally coming to grips with the fact that scientists are the first people in the world to know things," he explains. "And I found it absolutely intoxicating."

But it was David Botstein, the famous yeast geneticist, who first introduced Page to the Y chromosome. After

Swarthmore, Page entered an M.D. program run jointly by Harvard and the Massachusetts Institute of Technology (MIT). Students in this program were encouraged to do small research projects, and Page found himself in Botstein's lab at MIT, where he was recruited to work on a not-so-small project—mapping the human genome. In the course of this work, Page identified a genetic probe—a small DNA sequence—that he could use as a marker to find his place on the Y chromosome. The DNA probe could also be used to tell whether you were looking at the Y chromosome or the X.

What could one do with such a probe? That's where the late-night bike ride—and, more importantly, that first poster—came in. When Page presented his discovery of the sex chromosome probe at the conference, a distinguished-looking gentleman came over to introduce himself. That conferee turned out to be Albert de la Chapelle, the researcher who had described the first case of an XX male nearly 20 years before. These sex-reversed individuals lack a Y chromosome—so their chromosomes "look female," but they develop as males. How can that be?

To find out, de la Chapelle suggested a collaboration. Using Page's probe (and other probes they found jointly), the researchers examined the patients' sex chromosomes. And they soon discovered that many XX males actually harbor a tiny piece of the Y chromosome. What's more, the finding suggested that by using genetic techniques to study these sex-reversed males, the researchers might be able to determine which part of the Y chromosome makes a male.

"I was hooked," admits Page. And this enthusiasm sustained him—which is fortunate because these were lean years, financially, for the young scientist. Although he was scientifically productive, Page was not officially enrolled in a Ph.D. program. Instead, he conducted his studies as a "medical student on leave of absence"—a job that came with a very small stipend. It was "enough to keep me in peanut butter by day" and macaroni and cheese—the generic brand—by night, says Page. "I couldn't afford Kraft," he laughs. "So it was generic mac-and-cheese with generic tuna and generic peas for me."

Although he received his M.D. degree in 1984, Page chose not to embark upon a career in medicine. "If there's anything I don't like about medicine, it is the sort of hierarchical spirit of things and the formalism and paper credentials. In science, it's still a meritocracy. There's a deep recognition that if you've got the goods, you've got the goods," he says. "Of course, the flip side in science—and a large part of the excitement and challenge—is that ultimately it's, 'What have you done for me lately?' You can't just publish the same paper every day."

When he joined the Whitehead Institute for Biomedical Research at MIT as a fellow in 1984, Page broadened his study of how genes on the Y chromosome influence male development and fertility—and how these genes found their home on the Y over the course of evolution. The Institute, a nonprofit, independent research and training institution, had been founded in 1982 to "identify and support the finest

young minds in science." Page's efforts soon won him a MacArthur Fellowship—which recognizes "exceptional creativity" and promise for important future advances. "It was very exciting but also frightening," says Page. "I was all of 30 and still learning what it meant to be on my own as a scientist." The MacArthur prize helped Page pay off his medical school debts. (Had he chosen to get a Ph.D., he would have received free tuition and a stipend to cover his living expenses.) "The MacArthur funders must have realized that they had to help this poor fool who couldn't be trusted to make even the most basic financial decision," he jokes.

Now a full faculty member at the Whitehead, Page has come a long way since that bike ride through the snow. But in some ways he hasn't changed. "I was first taken in by the beauty of the questions," he says. "Now I realize that the closer I can stay to that original romantic, idealistic beginning, the happier I am and the more satisfied I am with what I'm doing.

"I've learned, over the years, what in hindsight is so completely obvious," he adds. "Happiness in science amounts to working on questions you think are important with people you like to work with." So Page selects his projects and his collaborators with care. "Life is short, energy is finite, and I want to have fun doing what I'm doing."

Photo: Stanley Rowin

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