The notion of the Y sex chromosome as a genetic wasteland still entices biologists. David C. Page has spent a good part of his career knocking down that myth. By GARY STIX

An English literature student called up David C. Page a few years ago and told him she was thinking of doing a thesis that would rebut feminist criticism and bring back a measure of respectability to him and his work. “I didn’t know I was in need of rehabilitation,” Page remarks one late September afternoon in his fourth-floor corner office at the Whitehead Institute on the Massachusetts Institute of Technology campus. He retells the incident while resting his “Save the Males” coffee cup on a circular conference table.

Ever since he picked up and inspected a random piece of DNA in 1979 as a young researcher and later learned that the glob contained a piece of the Y chromosome, Page has devoted much of his working life to the study of the genetic package that confers maleness. The very idea of investigating the Y chromosome offends those feminists who believe that it serves as nothing more than a subterfuge to promulgate an inherent male bias in biology. And, in Page’s view, some reputable scientists have even pandered to these sentiments by writing books and papers that predict the extinction of men—or the Y’s disappearance.

Page has sometimes found himself defending the genome’s smallest chromosome against preconceptions that do not necessarily jibe with the science that comes from the 20 researchers in his laboratory. He has helped dispel columns such as that the Y chromosome is a decaying, unintelligible mess—the Animal House of the human genome—or that because the Y has a very limited capacity to exchange genetic information with the X chromosome, it is sickly and dying out, a victim of its own masculine social incompatibility.

Bemused and unrehabilitated, Page can point to a long list of scientific papers with his name on them that demonstrate that the Y is an infinitely richer and more complex segment of the genome than ever imagined and one that does not fit neatly into the prejudices of gender-based interpretations of science.

Page seems to be an unlikely candidate to defend maleness. The slim and youthful 48-year-old does not cut a macho figure. At home he is surrounded by females: his wife, three daughters, and a female cat and guinea pig. He only developed an interest in the world of science when he arrived at Swarthmore College in 1974 and spent a few summers doing internships at the National Institutes of Health and Brookhaven National Laboratory. While training in the early 1980s under David Botstein, an M.I.T. geneticist, Page developed a molecular probe that he later used to track down what appeared to be the gene that codes for a protein...
triggerring an embryo to develop into a male. Published with great fanfare in 1987—just after he had received a MacArthur “genius” award and the offer of a tenure-track professorship at Whitehead—the results catapulted him onto national television and the front pages. “The wave of publicity that accompanied that period was something I wasn’t quite ready for,” he says. And then the discovery turned out to be in error. Two British groups issued their findings in 1990 about the correct gene on a part of the chromosome just adjacent to the one Page had identified. At the age of 34, the same as some postdoctoral students, Page was cast adrift. In retrospect, the experience had an upside. If he had been the one to discover the sex-determining gene, or SRY, he might have spent way too much time researching just that one gene. For a few years, he struggled with the question of whether more work remained on the Y. Then, in 1995, his laboratory discovered a mutation on the Y chromosome that causes the most common genetic form of male infertility, accounting for about 13 percent of cases in which men do not produce sperm. “We were on our way again,” he says. “We came out of a period of wandering around in the wilderness.”

Last year Page’s team, along with investigators from Washington University School of Medicine, published the complete sequence of the gene-containing portion of the human Y. It has proved to be the most challenging chromosome to decipher. The other 45 chromosomes, including the X, lent themselves to high-powered industrial reading of the nucleotides of DNA. “It turns out that the one-size-fits-all Wal-Mart approach works everywhere, but not on the Y chromosome,” Page explains. The Y poses such a hurdle because its endlessly repetitive series of nucleotides were expected to be nothing more than a collection of garbage DNA. Sequencing required what Page characterizes as “extreme genomics,” a search for landmarks among the millions of nucleotides on the chromosome. These guideposts consisted of minute differences among the repeat sections of nucleotides. “It would be as if you had two virtually identical copies of Manhattan, but they differed by the precise placement of some mailboxes and fire hydrants. And if you had been transported from copy A of Manhattan to copy B of Manhattan, the likelihood that you knew you had been moved would be very small. That was the problem we faced,” he elaborates.

The sequencing effort tallied about 80 genes; 20 years ago the prevailing wisdom suggested only a scattering of genes, maybe just one. Both the Y and the X began to evolve from an autosome (a non-sex chromosome) some 300 million years ago. Unlike every other chromosome that comes with a matched pair, including the X in females, the Y has scant ability to trade good genes for defective ones. Over time, most of its 1,000 or so genes that had started in the autosome withered away.

But perhaps the most interesting result attests to the survival prospects for the Y. The myth of the Y as weak and irrelevant has led to ponderings about what will happen in the event that males become extinct. Musings by some biologists have projected the Y’s demise anywhere from 125,000 to 10 million years from now. But Page’s work shows that the Y may have staying power. The male chromosome contains stretches of DNA that are virtually identical mirror copies of each other, creating huge genetic palindromes (the equivalent of the sentence “MADAM I’M ADAM”). If one of these sections makes a hairpin bend in the middle, it appears capable of donating an intact gene to fix a defective copy on the neighboring section. In essence, the Y seems to have its own self-repair mechanism, a process called gene conversion, making reports of its impending demise highly premature.

Because it is the male chromosome, the seat of human recklessness to some observers, controversy may never fully abate. Biologist Jennifer A. Marshall Graves of the Australian National University in Canberra argues that gene conversion in the palindromes represents a form of “genetic masturbation” that may not only fail to inhibit deleterious mutations but may even speed the process of the chromosome’s decline. Page’s terse response: “Ah, rhetoric and theory unburdened by experimental data.”

At this point, Page has found most or all of the protein-coding genes on the Y—he even shows at conferences a graphic of a whimsical version of the chromosome dotted with genes for channel flipping (FLP), spitting (P2E) and selective hearing (HUH). He is now turning to other questions. He has begun studies of the role of germ cells (egg and sperm) in initiating the process by which an embryo becomes anatomically female.

Yet he still has not lost his affection for the Y. The specialized expertise gained by Page’s group may now be used to target other genomes. “To date, hundreds of bacterial genomes and more than a dozen animal genomes have been sequenced, but at present there’s only one Y,” he says. Page may or may not have rehabilitated himself. But he has gone a long way toward restoring the status of the so-called rotting chromosome.