least mutated genome. And like a ratchet wheel that only moves in one direction, this process can never be reversed: Once mutants replace healthy genes, the good genes don't come back without recombination to replace them, while other bad genes continue to accumulate. Charlesworth hypothesized that a similar ratcheting effect could operate on a nonrecombining Y chromosome, given a sufficiently high mutation rate in a finite population over hundreds and thousands of years.

Rice verified this by speeding up time. He made two chromosomes in a line of fruit flies (*Drosophila melanogaster*) behave as if they were one large Y, and he kept the population size small. These "microevolutionary tricks," as he calls them, together sped up the rate of decay. "The bigger the Y, the more chances there are for errors to occur," Rice explains, and in a small population, the errors would spread rapidly. He ran five 35-generation experiments, and in all five found the Y degenerated. This accounts for the functional losses, although there's uncertainty about the mechanisms behind actual physical shrinkage. Once a gene doesn't work anymore, Rice suggests, there's no selective pressure to maintain it, and physical deletions can occur.

But was Muller's ratchet the reason that big Ys accumulated the deleterious genes? Rice argues that it was, and Charlesworth agrees—with one caveat. "Muller's ratchet is probably going on [in Rice's experiment]," he says, "but there is no way to sort out how much of the decline is due to it and how much is because of chance fixation." Fixation refers to genetic mistakes that accumulate because of random genetic drift, a process which occurs in both sexual and asexual populations; Muller's ratchet operates only in asexual populations. "Still, the implication of his experiment suggests that the parameters required for Muller's ratchet to work do come within the ball park even in a very large population," Charlesworth says.

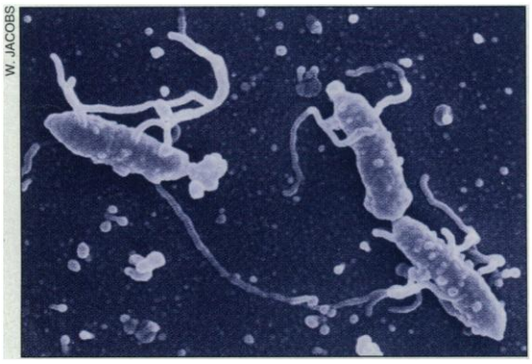
Evolutionary geneticists now hope that Rice's work, coupled with Charlesworth's hypotheses, may one day add up to a universal evolutionary law. "It might be something on the order of: 'Once a Y chromosome stops recombining it is doomed to lose all, or virtually all, of its genetic activity,'" suggests Rice. Eventually, the law might even be extended to asexual species, since there is a curious parallel pattern. "What intrigues me about this phenomenon of the Y not recombining and degenerating is how closely it mirrors what happens to asexual species," Rice says. "We know that most asexual species are at the tips of the tree of life; that they are doomed to extinction, apparently because of the lack of genetic recombination. It may be that the same mechanism that causes the Y to degenerate also causes asexual species to die out." Researchers consumed by physics envy might even consider expressing that in terms of an equation.

–Virginia Morell

INFECTIOUS DISEASES

Unveiling a Tuberculosis Drug Target

When an age-old scourge learns some new tricks, the results can be deadly. And the plague of tuberculosis, rising dramatically around the world, comes with some dangerous new ploys: strains of the disease that can resist many previously effective drugs. Yet knowledge of the molecular mechanisms behind drug resistance is emerging almost as fast as the resistant strains themselves. On page 227, a collaboration of U.S. and New Zealand investigators identify a new gene in *Mycobacterium tuberculosis*, the TB agent, that is implicated in resistance to isoniazid, one of the most popular anti-TB drugs.



W. JACOBS

Bugs say no to drugs. A mutation in one gene can make mycobacteria resist tuberculosis drugs.

This gene, they suspect, makes the protein that is the drug's primary target; when the gene is overexpressed or mutated, it frustrates isoniazid's effectiveness. Collaring it should allow scientists to develop quicker ways of identifying TB patients who carry isoniazid-resistant strains. Perhaps even more important, the discovery promises to aid the search for isoniazid-analogs that sidestep resistance.

Given that potential payoff, it's not surprising that the medical community is excited. "They still haven't answered exactly how isoniazid resistance works, but it's an important step along the pathway to that understanding," says Joseph Bates, a bacterial geneticist at the University of Arkansas in Little Rock.

Isoniazid has been in use against tuberculosis since 1952, but investigators have never quite understood how it works. Excitement mounted in 1992 when a group reported in *Nature* that the deletion of a different gene—one that codes for an enzyme called catalase—conferred resistance on some strains of the TB microbe (*Science*, 21 August 1992, p. 1038). But the discovery didn't solve the mystery of isoniazid's action; researchers believe the enzyme merely concentrates or activates the drug inside the bacteria. The best hypothesis on isoniazid comes from indirect evidence indicating the drug blocks synthesis of mycolic acid, a fatty acid that's part of the cell wall of all mycobacteria.

Investigators now believe they have the genetic smoking gun to back up these biochemical clues: The new suspect gene codes for a protein that probably plays a role in mycolic acid synthesis. The U.S.-New Zealand research group, led by William Jacobs, a Howard Hughes investigator at Albert Einstein College of Medicine, came across it while analyzing the genomes of two species of mycobacterium, related to but faster-growing than the slow-growing TB organism, and thus easier to study. From some isoniazid-resistant microbes, investigators isolated a mutated fragment of DNA that could transform normal mycobacteria into drug-resistant strains. After examining normal copies of that fragment, Jacobs' team found that it held a specific gene, labeled *inhA*, coding for a protein that strongly resembles several bacterial proteins implicated in fatty acid synthesis.

Jacob's group and others are now analyzing TB bacteria from patients harboring isoniazid-resistant strains and have found *inhA* mutations in many of them. If alterations in *inhA* and the catalase gene do account for the large majority of drug-resistant strains that turn up in patients, and ongoing studies may determine that within the year, physicians could use a DNA-based diagnostic test to find out quickly whether a patient is infected by isoniazid-resistant microbes and alter treatment accordingly.

The gene will also give a boost to drug development against all mycobacterial infections. Investigators hope to create a new generation of more effective isoniazid-like drugs that disrupt the construction of mycolic acids. "What's required now is a concerted effort to understand the biosynthesis of mycolic acids," says Colorado State University microbiologist Patrick Brennan. "[This discovery] gives us the academic background for an onslaught of new chemotherapies." And as the incidence of drug-resistant strains of TB rises, those weapons are desperately needed.

–John Travis