has been finalized. But he suggests that he will cast a wide net, telling *Science* that "TIFR must engage the public in its vision of the future of science in India and India's role in the global science enterprise."

Whereas the TIFR appointment has generated considerable discussion, the Department of Atomic Energy caused barely a ripple last year when it chose an Indian-born U.S. citizen to lead another prominent institute within its fold, the Harish-Chandra Research Institute in Allahabad. Ravi Kulkarni, a mathematics professor at the City University of New York, says he had to demonstrate his Indian roots before being picked for the job. "I think that they wanted to make sure I was not a CIA agent," Kulkarni told an audience of Asian-American scholars this summer at a symposium in New York. In the end, he says, his extensive knowledge of Indian philosophy and the Sanskrit language won over his future employers.

The slim pickings within the domestic ranks have meant longer tenures for those at the top. With the exception of Anil Kakodkar, secretary of the Department of Atomic Energy, the secretaries of seven major scientific departments have exceeded their scheduled terms, including those at the departments of science and technology, biotechnology, space, and ocean development; the Council of Scientific and Industrial Research; the Indian Council of Medical Research; and the Defence Research and Development Organisation. When they do step down, warns Pavagada Venkata Indiresan, a former director of the Indian Institute of Technology in Chennai, their successors might be career bureaucrats, as has already happened at two ministries.

Given the magnitude and duration of the shortage of senior talent, Indian scientists are not expecting any quick fixes. But they agree that the problem can no longer be ignored. "All the government agencies should have a discussion and arrive at an action-oriented program," says Rao. "This is a matter of serious concern."

—PALLAVA BAGLA

MEETING THE INSTITUTE FOR GENOMIC RESEARCH

Gene Researchers Hunt Bargains, Fixer-Uppers

BOSTON, MASSACHUSETTS—Technology buffs, bioinformaticists, and hard-core experimentalists rubbed elbows here 2 to 5 October at TIGR's 14th International Genome Sequencing and Analysis Conference. They met to discuss better ways to gather and use genomic information, a vast array of which is now at their fingertips. Highlights included discussions of chromosome evolution and new low-cost sequencing approaches.

Do-It-Yourself Repair Kit

Men have a reputation for trying to fix things without asking for help from others. The same might soon be true of the Y chromosome, that knobby piece of the human genome that makes men men, says David Page, a geneticist at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts.

Some biologists have theorized that the Y chromosome is destined to decay because it lacks a twin to help it keep its genes intact. Other chromosomes come in pairs that intertwine during meiosis. This allows matching genes, or alleles, in one chromosome to change places with their doubles. This recombination sheds faulty DNA and keeps each chromosome pair well matched. Females carry two X chromosomes, enabling X's to recombine, but males carry an unmatched X and Y. "If a piece [of DNA] does not participate in crossing over, then its genes begin to rot," Page explains.

But now Page and his colleagues have discovered that the Y chromosome does have matching genes—within itself. These repeated genes might allow the Y chromosome to somehow fix problem DNA. It seems this chromosome has "taken out an insurance policy," says Stanley Letovsky, a bioinformaticist at Boston University.

The new find might improve the Y chromosome's reputation. "For centuries, the Y chromosome has been called a junk heap," Page points out. A few genes at its very tips are similar enough to genes at the tips of the X chromosome to successfully recombine. Researchers have proposed, though, that with no apparent way to swap out harmful mutations on most of its length, the Y chromosome has become ever more dysfunctional, full of dead or dying genes. Indeed, some geneticists have gone so far as to predict that the Y chromosome will one day self-destruct, perhaps taking males with it. A superficial view of the chromosome seems to confirm this dire warning: More than half of its 59 million bases are apparently meaningless sequence.

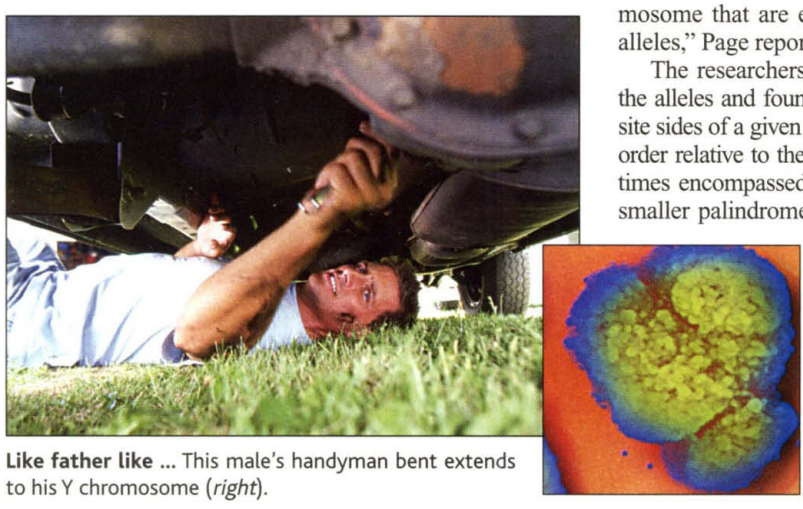
But when Page and his colleagues sequenced 24 million Y chromosome bases that do contain genes, they found a surprise. About one-third of that DNA consists of complex blocks that are repeated two or more times along the chromosome, Page reported at the meeting. Furthermore, the blocks tended to be arranged in eight huge palindromes. Each is composed of coding regions that are mirror images of each other, separated by small spacers.

The few Y chromosome genes that are shared with the X chromosome, in contrast, tend to exist as single copies. They are active in many types of cells, carrying out a variety of housekeeping functions. The genes in blocks thus far appear to be active only in the testes.

Page and his colleagues chopped DNA from these palindrome blocks into small segments and found that one-third of the pieces had almost perfect matches to other parts of the Y chromosome. And 18% had perfect matches that stretched as far as 2000 bases. "There are sequences on the Y chromosome that are effectively functioning as alleles," Page reported.

The researchers mapped the positions of the alleles and found that they were on opposite sides of a given palindrome, one in reverse order relative to the other. Palindromes sometimes encompassed multiple genes and even smaller palindromes. The large palindromes spanned upward of 3 million bases, Page reported. In contrast, pseudogenes—genes that had ceased to function—were outside these blocks of DNA.

Although 2 years ago Page and his colleagues suggested that



Like father like ... This male's handyman bent extends to his Y chromosome (*right*).

CREDITS: (LEFT TO RIGHT) TOM STEWART/CORBIS; BIOPHOTO ASSOCIATES/PHOTO RESEARCHERS

genes with multiple copies might be predisposed to errors, they now propose that in many cases this arrangement sets the stage for the Y to work out kinks in its genes without help from another chromosome. Good genes might replace bad neighbors down the line. "It's not that anyone has seen this happen," cautions Svante Pääbo, a geneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, "but it seems that one copy on one part of the palindrome [fixes] another without getting changed itself."

This apparent solution to the Y chromosome's lack of a recombinatorial partner might be ancient. Page's team has analyzed parts of the chimpanzee Y chromosome and found similar palindromes. "That puts [this DNA structure] back 5 million years," says Letovsky, one of many male researchers pleased to see his DNA redeemed.

Bargain-Basement Sequencing?

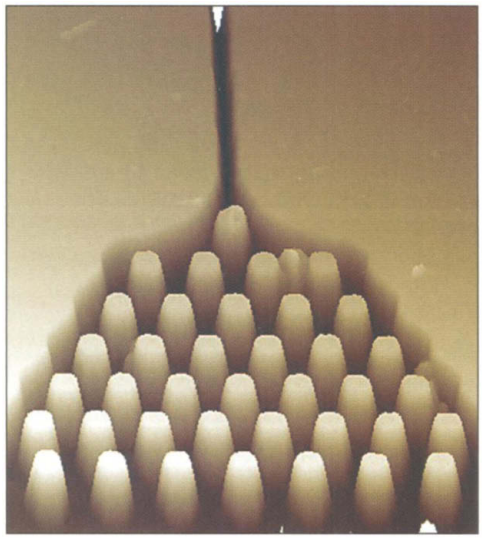
There's a certain amount of bravado among genomics researchers about how far the cost of sequencing genomes has dropped—from $1 a base in 1985 to 10 cents a base this year. But with today's grand total running from tens to hundreds of millions of dollars for one genome, the price needs to get cheaper for sequencing's full potential to be realized. At the TIGR meeting, researchers debated how to achieve their new goal: the $1000 genome. "What is exciting [now] is how quickly this notion is gaining momentum," says George Church, a biophysicist at Harvard University.

There's strong motivation to trim sequencing costs to the bone, allowing more researchers to spell out more genomes, says J. Craig Venter, president of the Center for the Advancement of Genomics in Rockville, Maryland. The newly deciphered human genome and the rapid unraveling of the genomes of a half-dozen other vertebrates have whetted researchers' appetites. Sequencing the genomes of additional species would make evolutionary studies stronger and improve the understanding of DNA outside genes.

In addition, geneticists are hoping that the genomes of thousands of people will be deciphered, making it easier to track down genetic risk factors for diabetes, heart diseases, and other disorders. Other researchers foresee using cheap DNA sequencing technologies to monitor the environment for specific microorganisms, including biowarfare agents.

Dozens of corporate and academic research groups are working feverishly to satisfy the hunger for bargains. In some cases, researchers are finding ways to squeeze every base they can from current sequencing technology. Others are trying new ways to decipher genetic codes. All are moving toward reducing the amount of chemicals used in sequencing reactions, which represent sequencing's biggest cost. This approach often entails shrinking DNA samples, sometimes going down to just a few molecules (*Science*, 12 March 1999, p. 1669).

But getting down to bargain-basement prices won't be easy, says Trevor Hawkins, a sequencing expert at Amersham Biosciences in Sunnyvale, California. Pushing existing techniques to the limits "will get us down to $30,000 genomes in the next few years, but taking that next leap is going to take a new technology." There are good new technologies in the wings, but Hawkins worries that, even if they work, developers may not have the know-how or resources to bring their products to market.



Nanocomb. DNA is straightened as it moves through this lattice prior to sequencing.

One new technology that researchers are nevertheless excited about "reads DNA like a ticker tape," claims Eugene Chan, head of U.S. Genomics Corp. in Woburn, Massachusetts. The traditional approach, in comparison, sequences bits of DNA and then pieces them back together. The basis of the U.S. Genomics approach is a lattice built of closely packed, nanometer-sized posts. The lattice acts as a comb: DNA's spirals straighten out as they squeeze between the posts. The DNA emerges as a linear molecule—the ticker tape—whose fluorescently labeled bases can be read as they exit.

Currently, the U.S. Genomics technology can't read every base. And although Chan boasts that 3 billion bases can stream through the lattice in 45 minutes, his team has yet to come up with a way to handle all that data. The technique can now process DNA molecules of about 200,000 bases, but he hopes it will be able to take care of whole chromosomes and whole microbial genomes by next year.

The equipment will be quite expensive, says Chan. But once the system is in place, the $1000 genome should be a breeze. "We think we can do it for much less," he predicts.

Lower-tech approaches can also make genome sequencing cheaper, says Church. Since 1999, he and Robi Mitra, also of Harvard, have been working out a sequencing system that uses off-the-shelf equipment. All they need are slide racks commonly used in histology labs, microarray scanners that are now part of most genomics operations, and machines that control chemical reactions by cycling between warm and cool temperatures. "From scratch, [the equipment] currently costs about $40,000," Church says. Once in place, he calculates that the cost for a quick pass across the human genome could come down to about $750.

Church, Mitra, and their colleagues start by mixing up a gel containing the DNA under study, chemicals that promote DNA replication, and short DNA sequence tags needed for the polymerase chain reaction. They deposit the gel as a thin layer on a microscope slide. The primer tags capture random bits of the DNA to be sequenced, which then multiply and form piles of DNA called polonies.

To determine the order of the bases, the researchers add fluorescently labeled bases, one base at a time, to the polonies. The polonies' single-stranded DNA builds up a matching strand using the newly added bases, whose order the researchers record. Over the past month they've made great progress on the software needed to streamline this process, Church notes.

Church's and Chan's are but two of about a dozen groups pushing back the sequencing frontiers. At the meeting, Susan Hardin, president of VisiGen Biotechnologies Inc. in Houston, Texas, described progress she's made in exploiting the natural chemistry of DNA replication to distinguish one base from another more efficiently. Others, such as Michael Weiner of 454 Corp. in Branford, Connecticut, are working out ways to do many thousands of sequencing reactions in parallel.

All of the teams must still surmount technical problems, says Hawkins, and for the time being, he thinks improvements upon sequencing machines now in use—including the one his company makes—hold the key to bringing down sequencing costs. But Venter says it's possible there will be "a radical change" in how people sequence within 5 years. Either way, Church says he's poised for exciting times: "Like the World Wide Web in 1993, this project may zoom forward."

—ELIZABETH PENNISI

CREDIT: U.S. GENOMICS