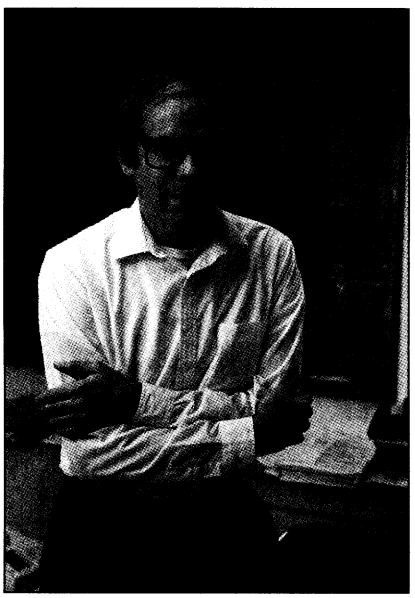
congressional hearing. NIH was so impressed with his progress, Venter said, that it was filing patent applications on the partial genes he was identifying—at a rate of 1000 a month.

Watson erupted, denouncing the patenting scheme as "sheer lunacy" and noting that "virtually any monkey" could do what Venter's group was doing (*Science*, 11 October 1991, p. 184). What irked him was that Venter and NIH had no clue about the function of the genes from which these fragments came. If the patents held, that meant anybody could lay claim to most of the human genes, undercutting patent protection for biologists who labored long and hard to identify whole genes and figure out what they did. "I am horrified," Watson told Congress.



**Maynard Olson.** Helped pave the way with work on mapping the yeast genome.

Watson also went to war on this issue with his boss, NIH Director Bernadine Healy. The fight cost him his job. In April 1992 he returned to Cold Spring Harbor Laboratory, muttering that no one could work with that woman (*Science*, 17 April 1992, p. 301).

Venter, too, left NIH in 1991 when he was offered $70 million from a venture capital company to try out his gene identification strategy at a new nonprofit, The Institute for Genomic Research (TIGR).

**From tools to medicine**

After Watson's sudden departure, NIH picked gene hunter Francis Collins of the University of Michigan, Ann Arbor, to take the helm. Fresh from the heady success of finding several elusive genes—including those involved in cystic fibrosis, neurofibromatosis, and Huntington's disease—Collins was then in a highly competitive race to find the gene involved in a form of inherited breast cancer.

A physician by training, Collins brought a different perspective to the genome project, placing its medical applications front and center. Collins charmed Congress and the media by riding to work on his motorcycle and playing guitar in a pick-up rock band. Whereas Watson and his advisers had spoken of creating a tool, Collins talked about saving children's lives. "The reason the public pays and is excited—well, disease genes are at the top of the list," he explained.

It was a heyday for gene hunters. The early investments in the genome project paid off as increasingly sophisticated maps of the human and mouse genomes were compiled (*Science*, 1 October 1993, p. 20). With these maps in hand, the time it took to track down most disease genes dropped from a decade to perhaps 2 years. Every week, it seemed, another deadly disease gene was discovered. Lost in the hoopla, however, was the fact that finding a gene was a far cry from having a treatment, much less a cure. The consortium was growing as well, fueled by an infusion of funds from the Wellcome Trust, which in 1993 set up a major new sequencing lab, the Sanger Centre near Cambridge, with Sulston as its head.

But sequencing overall was lagging behind. At the existing rate and cost, Collins lamented when he took on the job, there was no chance they could finish the sequencing by 2005. None of the "blue sky" sequencing technologies that had been imagined at the outset materialized, and with U.S. funding tight and much of the money concentrated on mapping, Collins was worried that "we have mortgaged part of our future."

Steady, incremental advances were enabling scientists to spew out longer "sequence reads," and the cost was slowly dropping. Even so, reassembling the DNA fragments in correct order was tricky. To do so, the sequencers looked for similar patterns in the fragments—much like assembling a jigsaw puzzle—but one with lots of missing pieces. Some pieces just wouldn't fit, some "fit" in the wrong place—others "got lost" in the cloning process. Still others refused to be sequenced.

Sequencing clearly needed a shot in the arm—and soon got one, but from an unlikely source. In 1995, Venter surprised the community by announcing that along with Hamilton Smith, then at Johns Hopkins, and TIGR colleagues Rob Fleischmann and Claire Fraser, they had sequenced the first entire genome of a free-living organism, *Haemophilus influenzae*, at 1.8 megabases (*Science*, 28 July 1995, p. 496). What's more, they had done it in just a year using a bold new approach, whole-genome shotgun sequencing, that NIH had insisted wouldn't work and wouldn't fund.

Sequencers in the publicly funded project had adopted a conservative, methodical approach—starting with relatively small chunks of DNA whose positions on the chromosome were known, breaking them into pieces, then randomly selecting and sequencing those pieces and finally reassembling them. Eventually, larger pieces called contigs would be hooked together. By contrast, Venter simply shredded the entire genome into small fragments and used a computer to reassemble the sequenced pieces by looking for overlapping ends.

CREDIT: HERB WEITMAN/WASHINGTON UNIVERSITY

## Objection #3: Impossible to Do

**Perhaps the most surprising thing about the human genome project is that it was begun at all. In the mid-1980s, the technology for decoding DNA's sequence of chemical bases was in its relative infancy. State-of-the-art labs could sequence only about 500 bases a day, working day in and day out. And the computer technology that came to play such a vital role in the project wasn't even invented yet. "In retrospect, the optimism that the project could be done on a 15-year timetable was striking," says Maynard Olson, who directs a sequencing center at the University of Washington, Seattle.**

**Unexpectedly, however, says Stanford University geneticist David Botstein, sequencing technology didn't need a revolution to make the leap in speed. "In the early days, it was believed that a radical new technology would be required" to sequence the full human genome, says Botstein. "But it didn't turn out that way."**

**Incremental but vital improvements in manipulating DNA and chemical probes enabled researchers to switch from identifying bases with radioactive probes to fluorescent ones. That eased the way for detectors to read and catalog the sequence of bases automatically. That automation was then honed with the advent of high-speed machines that pushed snippets of DNA through dozens of capillaries, reducing the sequencing time and cost of reagents. "It was definitely evolution," says molecular biologist David Baltimore, president of the California Institute of Technology in Pasadena. "But you can go a long way with evolution."**

**–R.F.S.**