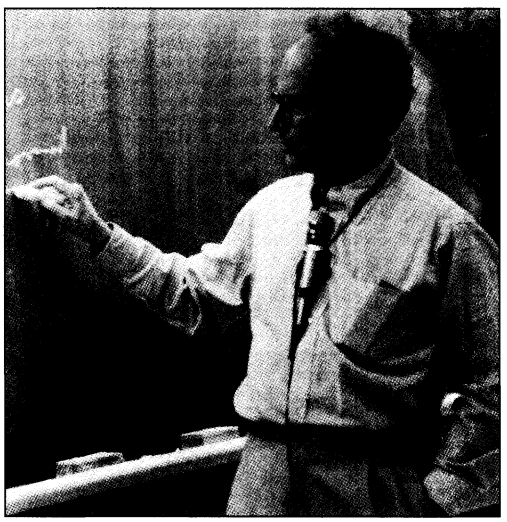
Controversial From The Start

The human genome: the crown jewel of 20th century biology, heralded at the White House, plastered on the covers of countless magazines—and at last spelled out today in intricate detail in both *Science* and *Nature*. Deciphering this string of 3 billion A's, T's, G's, and C's is being hailed as an achievement that will usher in a new era of biology and even alter our understanding of who we are.

That's a far cry from how the idea was greeted when it was first proposed 15 years ago. "Absurd," "dangerous," and "impossible," scoffed numerous critics, who noted that the technology did not exist to sequence a bacterium, much less a human. And even if the project's starry-eyed proponents could by some miracle pull it off, who would want the complete sequence data anyway?

It turns out a lot of people did. This once-ludicrous proposal became one of most hotly contested—and contentious—races in recent scientific history. Although the race has been dominated in the past few years by the acrimonious feud between the public and private teams, tensions go way back. And no wonder, with a prize this great and a project that has transcended and transformed traditional ways of doing biology. "The change is so fundamental, it is hard for even scientists to grasp," notes geneticist Maynard Olson of the University of Washington, Seattle, who ranks decoding the human genome as one of the biggest accomplishments ever in biology.



Walter Gilbert. A crucial early proponent, he later tried to set up a company to produce and sell genome data.

An impossible dream

One of the first to grasp that potential was Robert Sinsheimer, a biologist who was then chancellor of the University of California (UC), Santa Cruz. UC astronomers were already angling to build the world's biggest telescope, and Sinsheimer was looking for a project of similar magnitude in biology. Unraveling the sequence of the human genome might be just the ticket—if he could rally the scientific support and, of course, money. At the time, the largest genome yet sequenced was the minuscule Epstein-Barr virus—and that feat had taken several researchers years to complete. To apply such tools to the human genome, nearly 20,000 times bigger at 3 billion bases, was audacious beyond belief.

In 1985, Sinsheimer assembled some of the best minds in the nascent field of genome analysis to hash over the proposal at his idyllic campus, nestled in the hills above the sleepy beach town of Santa Cruz. John Sulston of Cambridge University and Robert Waterston of Washington University in St. Louis, who were already trying to map the genome of the nematode *Caenorhabditis elegans*, were there, as was Bart Barrell, head of large-scale sequencing at the U.K. Medical Research Council (MRC). So were genetic mappers David Botstein, then at the Massachusetts Institute of Technol-

Objection #1: Big Biology Is Bad Biology

The human genome project was biology's first foray into "big science," and many scientists abhorred the idea at the outset. Researchers feared that a massive sequencing project would siphon precious dollars from investigator-initiated research, destroying the cottage industry culture of biology in the process. And just as bad, the project didn't even amount to hypothesis-driven science at all. Rather, critics charged, it was no more than a big fishing expedition, a mindless factory project that no scientists in their right minds would join. Were they right?

Not exactly, says David Baltimore, president of the California Institute of Technology (Caltech) in Pasadena, who raised some of the early concerns. "One of the things I didn't fully anticipate was the state of progress in automation," he says. In the mid-1980s, gene sequencing was done by hand. Baltimore and others feared that it would take an army of "worker bees" to carry out sequencing on a genomewide scale. But sequencing machines pioneered by Leroy Hood and colleagues at Caltech changed that equation forever. Today, sequencing is nearly completely automated.

The genome project was still a fishing expedition, of course. But the enormous haul of genomic data it netted has changed most minds about such "discovery" research. This once-maligned type of research has enabled teams around the world to explore newfound genes and their links to health and disease. "Discovery science has absolutely revolutionized biology," says Hood, now director of the Institute for Systems Biology in Seattle, Washington. "It's given us new tools for doing hypothesis-driven research," maintains Hood, and these tools help rather than hinder individual investigators.

The biggest objection to the audacious proposal was that funding for the genome project would come at the expense of other quality science. "There was a worry that it was a zero-sum game," says Maynard Olson, a genome center leader at the University of Washington, Seattle. "Frankly, it was a gamble that we'd be able to expand the pie [of research dollars]." But the gamble paid off. In a 1998 National Research Council report, a committee led by Bruce Alberts, a former professor at the University of California, San Francisco, recommended that the human genome project be funded separately from traditional science budgets. And Congress happily went along, giving the Department of Energy $10.7 million and the National Institutes of Health $17.2 million for the new project in fiscal year 1988.

By voicing the early concerns, "I think we did what we hoped we would do," says Baltimore. "It helped develop a debate, which set us on a productive course." –ROBERT F. SERVICE

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