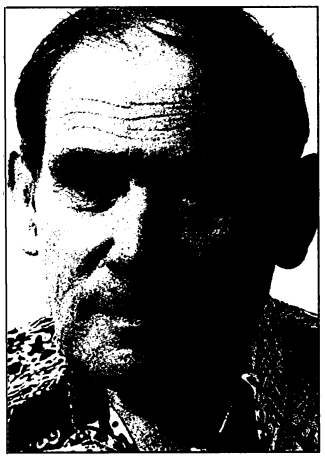
UNSUNG HERO: PHIL GREEN

Phil Green, a mathematician and software designer, wrote the phred and phrap programs at Washington University in St. Louis, Missouri. These became essential tools for evaluating the quality of raw DNA sequence and linking up assemblies. He's now at the University of Washington, Seattle, creating new programs.



Sydney Brenner. Joked that sequencing was so boring it should be done by prisoners.

ogy (MIT), Helen Donis-Keller, then at Collaborative Research Inc., and sequencing aficionados Walter Gilbert and George Church of Harvard University and Leroy Hood of the California Institute of Technology in Pasadena. Their collective conclusion: bold, exciting—but simply not feasible. Sinsheimer's proposal for a genome institute at Santa Cruz died, but not before it had captured Gilbert's imagination.

Gilbert soon became the proposal's biggest champion, and his support meant the idea could no longer be blithely dismissed. A decade earlier, Gilbert and Allan Maxam, also at Harvard University, had invented a brand-new technique that enabled scientists for the first time to determine the genetic sequence of an organism. (Gilbert went on to share the Nobel Prize with Fred Sanger of Cambridge University, who independently invented a similar technique.) And he soon won over another giant of molecular biology: James Watson, who shared a Nobel Prize with Francis Crick and Maurice Wilkins for their 1953 discovery of the double helical structure of DNA.

The ambitious idea had also captivated Charles DeLisi, a cancer biologist who was then head of the Office of Health and Environmental Research at the Department of Energy (DOE). To DeLisi, the genome project was a logical outgrowth of DOE's mandate to study the effects of radiation on human health. Another equally compelling rationale—but one DeLisi did not openly tout—was that a massive new endeavor could provide new focus for DOE's national labs, whose bombmaking skills were in diminishing demand.

At the urging of DeLisi and DOE colleague David Smith, the Los Alamos National Laboratory hosted a workshop in Santa Fe, New Mexico, in March 1986 where the excitement was palpable. The idea quickly gained momentum, dominating discussion at a June meeting at Watson's Cold Spring Harbor Laboratory in New York. By then, biologists were beginning to think the project just might be doable. But whether it was worth doing was another matter (*Science*, 27 June 1986, p. 1598).

To many, like Botstein and Nobel laureate David Baltimore, then at MIT, the project ran counter to the way biology had been conducted for decades. The best work, the mantra went, came from investigator-initiated studies in small labs, not from some massive, goal-driven effort. Moreover, this was technology development, not experimental biology, and it would be mind-numbingly dull. Sydney Brenner of the MRC facetiously suggested that project leaders parcel out the job to prisoners as punishment—the more heinous the crime, the bigger the chromosome they would have to decipher. What was truly horrifying was the price tag, which was quickly estimated at $3 billion—a number that stuck through countless reports ever since. If the National Institutes of Health (NIH) were to foot the bill, the megaproject would rob funds from the rest of biology, the critics asserted. "It endangers all of us, especially the young researchers," warned Botstein.

The scientific value seemed dubious as well. Although many biologists agreed that maps of the chromosomes would be useful for finding genes, what good would come from deciphering every A, T, G, and C, especially since most of them were "junk" that did not code for genes. The sequence might be handy to have, but "was it worth the cost, not in terms of dollars but in terms of its impact on the rest of biological science?"

CREDITS: (TOP TO BOTTOM) HHMI; MRC; ILLUSTRATION: CAMERON SLAYDEN

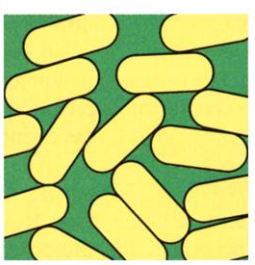
NEW SCIENCE:

Finding the Talismans That Protect Against Infection

Since 1995, the minigenomes of dozens of pathogenic microbes have been sequenced, including those that cause tuberculosis, cholera, and ulcers. Many others are almost in the bag, including the much larger genome of *Plasmodium*, the malaria parasite. That data flood is helping researchers understand how nefarious microorganisms work—and how they might be stopped.

The giant human genome promises to help solve another poorly understood problem: why some people get sick and die when they encounter a pathogen, whereas others stay healthy as an ox. Such information could eventually help put more people in the latter category.

Researchers have long known that differences in disease susceptibility are partly genetic, the most famous example being the



gene for sickle cell hemoglobin, which offers protection against malaria to those who inherit one copy of it. (Having two copies causes sickle cell anemia.) Several other susceptibility genes have been discovered for various diseases; malaria now tops the list with 14 genes. "We're just beginning to scratch the surface," says Adrian Hill, a geneticist at the University of Oxford in the United Kingdom.

To identify genes that might confer susceptibility or resistance, researchers try to find genetic differences between large groups of patients and healthy controls. Without the complete genome, they could only look for previously discovered genes. Now, they can theoretically take each and every gene into consideration. Eventually, such work will lead to a better understanding of the molecular interaction between a bug and its host. That, in turn, may reveal new drug or vaccine targets.

–MARTIN ENSERINK