PART TWO

Origins of the Genome Project

5

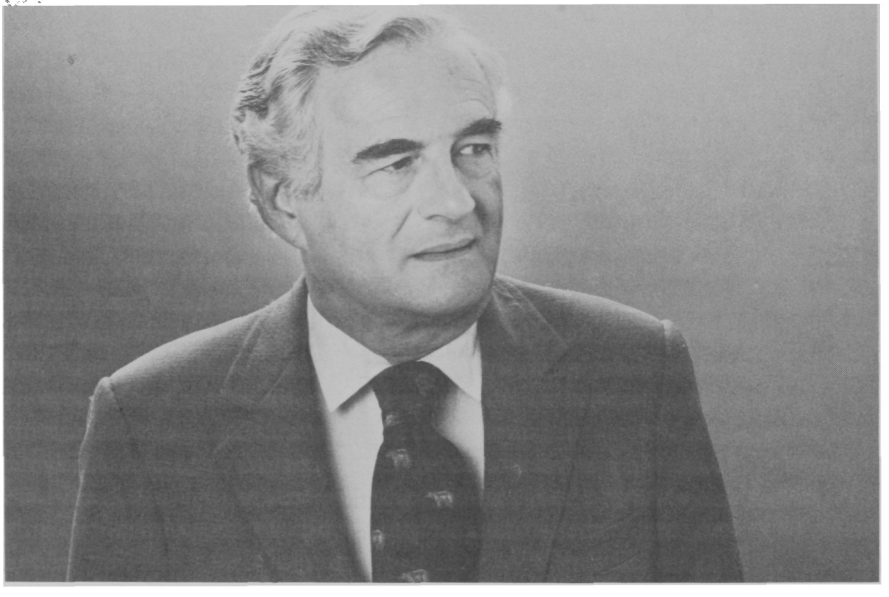
Putting Santa Cruz on the Map

THE FIRST MEETING focused specifically on sequencing the human genome was convened in 1985 by Robert Sinsheimer of the University of California at Santa Cruz. While the genome project did not grow out of the meeting, or even emerge as a topic of discussion, the 1985 Santa Cruz gathering did plant the seed.

Planning for Sinsheimer's May 1985 meeting at Santa Cruz began the previous October, when Sinsheimer called several faculty biologists—Robert Edgar, Harry Noller, and Robert Ludwig—into his office. Sinsheimer was then chancellor at UCSC. As such, he had been a participant in several major science planning efforts. These included relations with the three national laboratories managed for the Department of Energy (DOE) by the University of California (Los Alamos, Lawrence Berkeley, and Lawrence Livermore national laboratories), discussions of the California state proposal to house the Superconducting Super Collider, and, most directly, the Lick Observatory. The UCSC faculty in astronomy had an international reputation. As a biologist, Sinsheimer wanted biology to achieve similar stature. He wanted, he said, to "put Santa Cruz on the map."[1]

Others had previously conceived of large, concerted mapping projects and technology development, but these did not grow into the genome project.

The European Molecular Biology Laboratory had in 1980 seriously contemplated sequencing the entire 4,700,000-base-pair genome of the bacterium *Escherichia coli*,[2;3] but that project was judged technically premature. Norman Anderson, who had worked at several DOE-funded national laboratories during two decades, had a track record of devising instruments for molecular biology, including high-pressure liquid chromatography, two-dimensional protein electrophoresis, and zonal centrifugation.[4] He and his son Leigh lobbied during the late 1970s for a national effort to catalog genes and blood



Robert Sinsheimer, as chancellor of the University of California at Santa Cruz, convened the first meeting on sequencing the human genome in May 1985. Although the institute for human genome sequencing that he envisioned for the UC Santa Cruz campus never materialized, the impetus for such a project remained. *Don Fukuda photo, courtesy University of California, Santa Cruz*

proteins,[5] and Senator Alan Cranston pushed for a dedicated $350 million program in the early 1980s. Even then, there was talk of the need to collect DNA sequence data.[3] Father and son continued to urge adoption of their program in the national laboratory system and at DOE. Their efforts were known by DOE administrators, and may indeed have helped set the stage for the genome project, but they had not crystallized into a dedicated science program.

The inspiration for Sinsheimer's DNA sequencing proposal was a telescope.[6;7] A group of University of California astronomers wanted to build the biggest telescope in the world. The venture was ultimately successful, produc-

ing the Keck Telescope on Mauna Kea in Hawaii, which saw first light on November 24, 1990. This success came only after clearing several high hurdles.

In 1984, the costs of enlarging the giant telescope on Mount Palomar or constructing a facility of similar size were estimated in the range of $500 million, a large fraction of the expense associated with manufacturing an enormous mirror. Jerry Nelson of the Lawrence Berkeley Laboratory hit upon the idea of using thirty-six hexagonal mirrors to replace a single large one, reducing cost estimates eightfold. By computer adjustments of the hexagonal array, the complex of smaller and cheaper mirrors could provide the same resolving power. A piece about the telescope appeared in the *San Jose Mercury*. Soon after the article appeared, a Mr. Kane called the laboratory.[8] He thought he might know a donor interested in funding the telescope, the widow of Max Hoffman. Hoffman had made a fortune as the U.S. importer of Volkswagen and BMW automobiles, and had left an estate of several tens of millions of dollars, the Hoffman Foundation, whose trustees were his widow and two others. Mrs. Hoffman signed most of the papers for a $36 million donation for the Hoffman Telescope project the day before she died. It was the largest single gift in the history of the University of California, but it had to be returned. That $36 million return was the event that stimulated the DNA-sequencing idea.

The $36 million donation, generous as it was, fell $30 to $40 million short of what was needed to build the telescope. Further donors were needed, and the University of California was having trouble finding them. Since the telescope was already named for Max Hoffman, it was more difficult to entice further large donations. The University of California finally sought help from Caltech, a private university. The University of California got more than it bargained for. After finding several smaller donations, Caltech got an agreement from the Keck Foundation, built with Superior Oil money, to fund the entire telescope if the name was changed to the Keck Telescope. The Hoffman Foundation, having lost the glory of being the major donor and having lost its most interested trustee, was not interested in helping build a smaller sister telescope or in using its funds for other suggested alternatives.

Sinsheimer wondered if an attractive proposal in biology could recapture the interest of the Hoffman Foundation. He pondered whether there were opportunities missed in biology because of biologists' proclivity to think small, in contrast to their colleagues in astronomy and high-energy physics. Sinsheimer's laboratory had purified, characterized, and genetically mapped a bacterial virus, phi-X-174.[7] Its 5,386-base-pair genome was the first of any organism's to be sequenced, by Frederick Sanger in 1978.[9] Sinsheimer followed the progression of DNA sequencing to larger and larger organisms. As he thought about targets for a large biology project, Sinsheimer struck upon sequencing the human genome, fully a million times larger than the viral genome and ten thousand times larger than the biggest sequencing project to date. He sought

counsel of his colleagues at UCSC about establishing an institute to sequence the human genome, and in October 1984, he called the meeting with Noller, Edgar, and Ludwig.[10]

Edgar, Ludwig, and Noller were at first stunned by Sinsheimer's audacity, but as they began to think through the scientific approach that would lead to sequencing the entire genome, they decided that it would be a useful goal and would generate equally useful results along the way. In particular, the process of sequencing would entail physical mapping, a valuable enterprise in its own right. Edgar and Noller prepared a position paper for Sinsheimer on Halloween 1984, which became the basis for Sinsheimer's letter to University of California president David Gardner on November 19.[11] The Santa Cruz scientists proposed that the DNA sequencing institute could be

> a noble and inspiring enterprise. It some respects, like the journeys to the moon, it is simply a "tour de force"; it is not at all clear that knowledge of the nucleotide sequence of the human genome will, initially, provide deep insights into the physical nature of man. Nevertheless, we are confident that this project will provide an integrating focus for all efforts to use DNA cloning techniques in the study of human genetics. The ordered library of cloned DNA that must be produced to allow the genome to be sequenced will itself be of great value to all human genetics researchers. The project will also provide an impetus for improvements in techniques . . . that have already revolutionized the nature of biological research. . . .[12]

Sinsheimer urged Gardner to approach the Hoffman trustees with his new idea, asserting:

> It is a an opportunity to play a major role in a historically unique event—the sequencing of the human genome. . . . It can be done. We would need a building in which to house the Institute formed to carry out the project (cost of approximately $25 million), and we would need an operating budget of some $5 million per year (in current dollars). Not at all extraordinary. . . . It will be done, once and for all time, providing a permanent and priceless addition to our knowledge.[11]

Sinsheimer also discussed the idea with James Wyngaarden, director of the National Institutes of Health, in March 1985. Sinsheimer noted that Wyngaarden was "attracted by the idea," and he urged Sinsheimer to approach the National Institute of General Medical Sciences if the May meeting reached consensus on the project's feasibility.[13] Sinsheimer concluded he would have to find a source of funds. To do so, he would need the blessing of some internationally recognized scientists to lend the project credence.

The next phase was to call a meeting of experts from around the world. Noller wrote to Sanger, with whom he had worked several years earlier. Sanger's reply was encouraging: "It seems to me to be the ultimate in sequencing and will probably need to be done eventually, so why not start on it now? It's difficult to be certain, but I think the time is ripe."[14] Edgar, Noller, and Robert Ludwig convened the meeting on May 24 and 25, 1985, bringing together an eclectic mix of DNA experts. Bart Barrell was Sanger's successor as head of

large-scale sequencing at the MRC Cambridge laboratory. Walter Gilbert represented the Maxam-Gilbert approach to DNA sequencing. Lee Hood and George Church were Americans pushing sequencing technology, Hood through automation and Church (who had done his graduate work with Gilbert) through clever ways to extract more sequence data from each experiment. Those familiar with genetic linkage mapping were also invited, including David Botstein, Ronald Davis, and Helen Donis-Keller. John Sulston and Robert Waterston were invited to report on their efforts toward constructing a physical map of *C. elegans*. Leonard Lerman was a technologically oriented biologist from Boston, and David Schwartz had pioneered the techniques for handling and separating DNA fragments millions of base pairs in length. Finally, Michael Waterman of the University of Southern California was brought for his expertise in mathematics, DNA sequence analysis, and databases.

Over the course of an evening and a day, the group decided that it made sense systematically to develop a genetic linkage map, a physical map of ordered clones, and the capacity for large-scale DNA sequencing.[7] The first sequencing efforts should focus on automation and development of faster and cheaper techniques.[15] The workshop concluded, significantly, that a complete genome sequence was not feasible, as such an undertaking would require large leaps in technology. "In the meantime, one should concentrate on the sequencing of regions of expected interest (polymorphisms, functional genes, etc.). The first few percent should be of great interest."[15]

The idea of sequencing the human genome was out in the open. A later account of the meeting captured its modest aspirations as "Genesis, the Sequel."[6] Sinsheimer sent letters and a summary of the meeting to several potential funding sources, including the Howard Hughes Medical Institute (HHMI) and the Arnold and Mabel Beckman Foundation, but there were no takers.[16–18] Contacts with the Hoffman Foundation, while the initial impetus for the meeting, were not permissible. The University of California president's office now handled the foundation, so the Santa Cruz campus could make no direct approach. The NIH route was blocked by the need to ask for a facility in which to do the work and the large budget required. A major construction effort entailed approval from the UC system. NIH might be approached to fund the project, but not the facility in which to do the work, and not until the facility was built. These were formidable obstacles. Sinsheimer concluded the only solution was to find a private donor for the building first, but his access to large sources of private money also had to go through the UC president's office. The Hoffman funds were never recouped by the University of California.

Sinsheimer later reflected:

> I was certain of the value of the proposal. The human genome surely would someday be sequenced, once and for all time. The achievement would be a landmark in human history and the knowledge would be the basis for all human biology and medicine of the future. Why not now?[7]

Sinsheimer contemplated going directly to Congress. He discussed the institute idea with Leon Panetta, his congressman. Panetta was supportive, but indicated his awareness that proposals of such magnitude would have to go through the UC president's office.[19] Sinsheimer was frustrated in his attempts to cultivate interest in Gardner's office. As Sinsheimer neared retirement, prospects for a human genome sequencing institute at UC Santa Cruz quietly died. While he did not get his institute, the Sinsheimer Laboratory for biology was dedicated by UC president Gardner, Senator Mello of California, and Assemblyman Farr, with a public lecture by Charles Cantor, in February 1990.[20] The idea of sequencing the human genome moved on to other pastures, having acquired a life of its own.

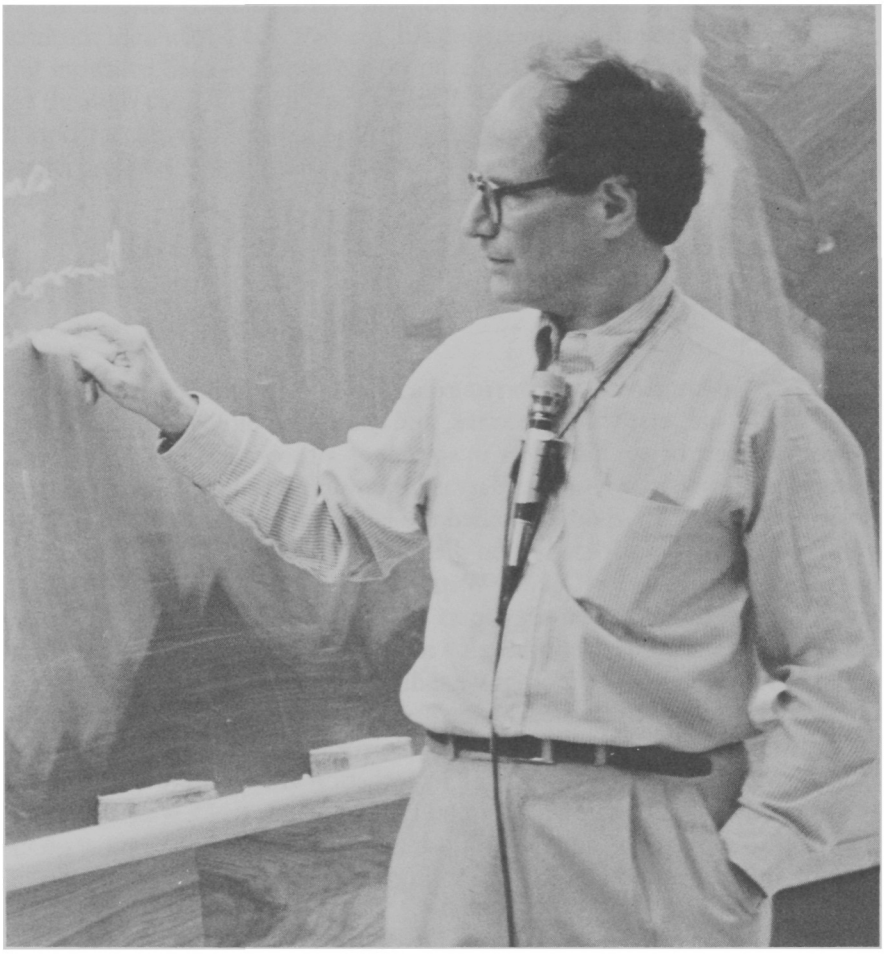
6

Gilbert and the Holy Grail

SINSHEIMER HANDED THE TORCH TO Walter Gilbert—Nobel laureate, erstwhile executive, and molecular biologist of legendary prowess. Gilbert began his career in science as a theoretical physicist. As an assistant professor in physics at Harvard, he wanted to learn about the new molecular biology. In 1960, he joined the laboratory of James Watson, who with François Gros was then hot on the track of messenger RNA. In a videotape taken of a meeting to celebrate Watson's sixtieth birthday in 1988, Gilbert described how he was given six papers to read when he first joined Watson and Gros, in contrast to the hundreds a new postdoctoral or graduate student would be handed today.[1] ("Things were different then.") Watson would hold a stopwatch while Gros sloshed a large flask of bacteria and Gilbert poured in ten to twenty millicuries of radioactive phosphate, to label the RNA in the bacteria. Messenger RNA was then a hypothetical entity, postulated to exist by some, but not yet a known commodity. Messenger RNA was, of course, eventually found to exist, and the group at Harvard joined those at the Pasteur Institute in Paris and the MRC Cambridge laboratory in the front ranks of molecular biology.

RNA is copied from stretches of DNA, then spliced, and finally transported out of the cell nucleus to serve as the code to assemble amino acids into proteins. Gilbert's career in molecular biology started with an extremely important problem. His reputation built even more on work that began in 1965 to find the repressor protein, an on-off switch for the gene that produced a bacterial protein. This was one of the most hotly contested races of its day in molecular biology. Gilbert commented on this phase of his work: "By the time the repressors were actually isolated, which was late in 1966, they had become a—Holy Grail?"[2] The mythic theme would return two decades later, by which time Gilbert was among the most respected thinkers in molecular biology.

Gilbert searched for the repressor protein with Benno Muller-Hill of Germany. The *lac* genes, involved in digesting sugars, were turned on and off in response to the presence or absence of sugars in the growth medium surrounding bacterial cells. The simplicity of the *lac* operon system made it a central target of molecular biology. Gilbert and Muller-Hill found the *repressor* protein



Walter Gilbert jots down his estimate of the cost and time it would take to sequence the entire human genome at a rump session of a symposium on the molecular biology of *Homo sapiens*, held at the Cold Spring Harbor Laboratory in June 1986. Gilbert left Harvard University in 1982 to become chief executive officer of the biotechnology firm Biogen; he returned to Harvard two years later and has been there ever since. *Victor McKusick photo, courtesy Cold Spring Harbor Laboratory Library*

that flipped this genetic switch in 1966.[3] It was a period of intense rivalry and cooperation with Mark Ptashne, who worked on a similar problem in a laboratory just down the hall.[4] Ptashne had come to Harvard to work under Watson and was trying to find a different repressor protein, one that turned genes on and off in the bacteriophage, or bacterial virus, named phage lambda.[5] Gilbert and Muller-Hill found their repressor just a few months before Ptashne found his. The next step was to study how the switch was thrown.

In the late 1960s and early 1970s, Gilbert isolated the DNA region that controlled the *lac* genes, called the operon, or genetic-switch region. This was the first segment of DNA isolated.[6] He chose to study the dynamics of the system by analyzing the structure of DNA in the region. This was the work that led to DNA sequencing, described in Chapter 4. Gilbert was thus a part of several landmark developments in molecular biology: the discovery of messenger RNA, the isolation of the *lac* repressor, and the technical miracle of DNA sequencing. It was not the end.

Gilbert joined a three-way race to isolate, study, and express the gene for insulin, one of the most studied proteins in all biology. Since its discovery in the 1920s, insulin had been used in treatment of diabetes. It was the first protein sequenced (by Sanger), and because of its therapeutic use, it was an obvious candidate protein to make using recombinant DNA technology as soon those methods were discovered in the mid-1970s. Gilbert threw his hat into the insulin ring in 1976. This and his past work took him on a short digression into commerce. Gilbert was among the founders of the Swiss-American biotechnology firm Biogen, created in 1978 while Gilbert's laboratory was working to clone insulin. Gilbert was enticed into involvement by a venture capital group hoping to establish the new company. At the scientific end, Gilbert's group at Harvard was the first to trick bacteria into producing the insulin protein, only the second mammalian protein ever so produced.[8]

Gilbert's star rose higher in 1980, when he shared the Nobel Prize for chemistry with Paul Berg of Stanford and Sanger. This was a special year for the Nobel, as these three scientists have a reputation as truly exceptional molecular biologists, even compared to other Nobel laureates. Each has not only left a significant personal legacy of science, but also left a trail of scientists trained in their laboratories and likely to travel to Stockholm themselves someday.

In 1982, Gilbert became chief executive officer at Biogen. Harvard forced him to choose between keeping his professorship and running a biotechnology company. He shook the academic world when he left his American Cancer Society chair at Harvard to direct Biogen. Biogen, however, did not fare well; it lost $11.6 million in 1983 and $13 million in 1984.[8] Gilbert resigned as CEO in December 1984 and returned to Harvard, where he became chairman of the department of biology. (Biogen continued to lose money after Gilbert left the helm.) In 1988, Gilbert was named Loeb University Professor at Harvard.

After leaving Biogen, Gilbert traveled to the South Pacific. The group organizing the Santa Cruz meeting sought him out, failing to locate him for many weeks. Robert Edgar finally reached Gilbert with a letter in March,[9] and Gilbert agreed to come. His addition was significant. After attending the Santa Cruz meeting, Gilbert became the principal spokesman for the Human Genome Project for the better part of a critical year.

Gilbert proved an articulate visionary, transmitting excitement to other

molecular biologists and to the general public. He translated the ideas at Santa Cruz into specific operating plans in a memo back to Edgar two days after the workshop. In it he offered a strategy for Sinsheimer's institute, although privately he was not convinced that it should be located in Santa Cruz:

> . . . In the early years the institute may want to be a sequencing resource—taking genes and probes from outside and returning sequences, cosmids [clones], and probes to the outside. . . . I expect that the most rewarding information scientifically will be in the first 1 percent of total sequence, if the work is focused, that most of the information, in the sense of interesting differences, will be in the next 10 percent, and the last 90 percent—of intron and intergenic regions—will be the least informative, but the increase in speed of sequencing should make each of these three phases take roughly equal times—or possibly make the last faster than the first.[10]

In this letter, he returned to a familiar motif, noting, "The total human sequence is the grail of human genetics—all possible information about the human structure is revealed (but not understood). It would be an incomparable tool for the investigation of every aspect of human function." Gilbert's Holy Grail proved an enduring rhetorical contribution to the genome debate. Indeed, it captured more than perhaps he intended. The Grail myth conjured up an apt image; each of the Knights of the Round Table set off in quest of an object whose shape was indeterminate, whose history was obscure, and whose function was controversial—except that it related somehow to restoring health and virility to the Fisher King, and hence to his kingdom. Each knight took a different path and found a different adventure.

Gilbert carried the ideas from Santa Cruz into the mainstream of molecular biology. He gave informal presentations on sequencing the genome at a Gordon Conference in the summer of 1985, and at the first international conference on genes and computers in August 1986.[11] Gilbert was extremely well connected, and he infected several of his colleagues with enthusiasm, including James Watson.

Gilbert gave the genome project much greater notice than it would otherwise have achieved. His role was featured in the *U.S. News & World Report, Newsweek, Boston* magazine, *Business Week, Insight,* and the *New York Times Magazine.*[12–17] He joined Watson, Hood, Bodmer, and others as the star of video documentaries on the genome project.[18] Gilbert and Hood wrote supporting articles for a special section in *Issues in Science and Technology* published by the National Academy of Sciences.[19;20] Gilbert and Bodmer promoted the genome project in editorials for *The Scientist.*[21;22] Gilbert thus stoked the genome engine, preserving the spirit of Santa Cruz.

Gilbert provoked a major controversy, however, when he decided to try to take the genome project private. He began thinking about establishing a genome institute himself in 1986. In January 1987, Michael Witunski, president of the James S. McDonnell Foundation, approached Gilbert with the idea of

foundation support to help create such an institute. This idea died when the foundation funded a study to assess the genome project at the National Research Council of the National Academy of Sciences. Gilbert participated in a spate of meetings convened to debate the genome project during late 1986, and he became a member of the NRC committee. In spring 1987, he decided to take the commercial plunge. He resigned from the NRC committee and announced plans to form Genome Corporation.

Gilbert's idea for Genome Corp. was to construct a physical map, do systematic sequencing, and establish a database.[6] The business objectives included selling clones from the map, serving as a sequencing service, and charging user fees for access to the database. The market would be academic laboratories and industrial firms, such as pharmaceutical companies, that would purchase materials and services from Genome Corp. The purpose was not so much to do things that others could not do at all, but rather to do them more efficiently, so that outside laboratories could purchase services more economically than they could perform the services themselves. In Gilbert's words, "Twenty years ago, every graduate student working on DNA had to learn to purify restriction enzymes. By 1976 no graduate student knew how to purify restriction enzymes; they purchased them. Historically, if you were a chemist, you blew your own glassware. Today, people simply buy plastic."[23] Genome Corp. could free biologists to focus on biology instead of wasting time making the things used in their experiments. These precedents fueled Gilbert's quest for funding from venture capitalists over the course of 1987 and into 1988. By late 1987, however, Wall Street's enthusiasm for biotechnology had turned to skepticism, and the stock market crash in October made capitalizing Genome Corp. all but impossible. The highly publicized efforts to start a genome project in the federal government made prospective investors leery of competing with the public domain. Genome Corp. could succeed only if Gilbert stayed so far ahead of academic competition that others would come to him for services, rather than waiting for the information and materials to be made freely available.

Gilbert was unabashed after the demise of Genome Corp. He remained a highly visible spokesman for a vigorous and aggressive genome project. He was consistently at the high end when making projections of what could be done in the way of mapping and sequencing. He was a technological optimist. Younger scientists balked at his enthusiasm for targeted, production-mode work and feared that he was publicly proclaiming goals too ambitious to attain. They loathed his almost monomaniacal focus on production-style DNA sequencing and bristled at his image of genome research as factory work. They complained bitterly that they would be held accountable for achieving impossible objectives set by policymakers listening to Gilbert; they felt they were being asked to climb Mount Everest after having only strolled a few miles along the Appalachian Trail.

If Gilbert was to blame for setting the sights too high, however, he would

at least be there on the firing line with the rest of genome researchers. Gilbert did not indulge in mere rhetoric, but committed his laboratory to be among the pioneers of large-scale DNA sequencing. In 1990, he proposed to sequence the genome of the smallest free-living organism, *Mycoplasma capricolum,* a small bacterium of goats.[24] This project was among the handful of sequencing projects intended to move sequencing from a theoretical possibility to a new way of understanding life. The genetics of the organism were not nearly so thoroughly studied as those of many other bacteria. Gilbert proposed to determine the DNA sequence of the bacterium's 800,000 base pairs, thought to contain five hundred or so genes. He hoped to reconstruct the biology of the organism by starting from its DNA sequence. The idea was not that sequencing would address all the questions of biological interest, but that starting from sequence would answer them faster.

Gilbert's project on *M. capricolum* joined other pilot sequencing projects on model organisms. These were among the grants given out in the first year's operation of the National Center for Human Genome Research at NIH.[24] A European consortium began a multicenter sequencing effort directed at yeast chromosomes. Botstein and Davis also proposed to start sequencing the yeast genome at Stanford (working from the physical map of yeast made by Maynard Olson). The groups working on the nematode *C. elegans* began systematic large-scale sequencing, in a transatlantic collaboration between John Sulston and Alan Coulson in England and Robert Waterston at Washington University in St. Louis.

Gilbert was not content to contribute only to the sequencing effort. His natural talents tended toward more theoretical generalizations. He was among the first to postulate an explanation of why genes were broken into different regions of DNA—with islands of base sequence to be translated into protein separated by long stretches of other sequences. In an article titled "Why Genes in Pieces?" he suggested that the role of fragmentation was to promote the shuffling of useful protein modules throughout the genome, enabling them to be used in different contexts.[25] Indeed, it was his terminology for DNA regions—"exons" for the parts that coded for protein and "introns" for the segments that separated exons—that eventually caught hold. Gilbert and, independently, Russell Doolittle postulated that the exon modules in DNA encoded protein substructures; these could be mixed and matched to serve similar functions in different proteins. They could be moved about in the genome over many generations, and the long intron sequences between the exons made this more feasible physically. Gilbert pushed the idea further a decade later, asserting in a controversial paper that nature had in fact settled on a relatively small set of structures to play with, several thousand or so, and built up the full complexity of existing organisms from a small fraction of the possible permutations.[26]

Gilbert also conveyed an ever enlarging vision of the role of molecular

genetics in biology, and the genome project in particular. He foresaw what science historian Thomas Kuhn had termed a "paradigm shift" in biology, with the science becoming driven more by theory. Molecular biologists would do experiments to test ideas first arising from the analysis of masses of information stored in computers. The cloning and sequencing that preoccupied the time of so many graduate students and postdoctoral fellows would be relegated to robots or specialized commercial services. "To use this flood of knowledge, which will pour across the computer networks of the world, biologists not only must become computer-literate, but also change their approach to the problem of understanding life. . . . The view that the genome project is breaking the rice bowl of the individual biologist confuses the pattern of experiments done today with the essential questions of the science. Many of those who complain about the genome project are really manifesting fears of technological unemployment."[27]

A genome program robust enough to sustain such a vision required a bureaucratic structure. The process of erecting this structure was at least as arduous as the science itself. At the beginning of 1987, as Gilbert formulated plans for Genome Corp., there was no center to support these and similar efforts in genome mapping and sequencing. Genome Corp. died, or rather was stillborn. While Gilbert despaired of federal leadership for the genome project, it was eventually two federal agencies that defined it. By the end of 1990, both the Department of Energy and the National Institutes of Health had genome programs with budgets totaling almost $84 million, and there were dedicated genome programs in the United Kingdom, Italy, the Soviet Union, Japan, France, and the European Communities. This remarkable bureaucratic transformation began late in 1985.

7

Genes and the Bomb

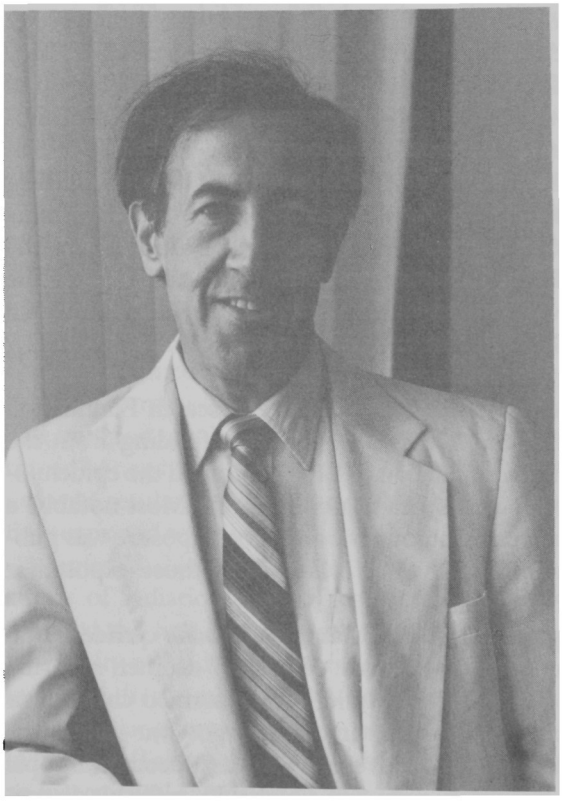
By proposing a Human Genome Initiative in the Department of Energy in 1985, Charles DeLisi thrust the Human Genome Project onto the public policy agenda. In so doing, he forced the ponderous bureaucracies at the Department of Energy (DOE) and the National Institutes of Health (NIH) into action. Several roots of DeLisi's genome research program can be traced back to the Manhattan District Project to build an atomic bomb. Some led through studies of the biological effects of dropping the bombs at Hiroshima and Nagasaki. Others led through the mathematicians who helped create the initial atomic bomb and, after World War II was over, the hydrogen fusion bomb.

In spring 1985, DeLisi became director of the Office of Health and Environmental Research (OHER) at DOE, the division responsible for funding the bulk of life sciences and environmental research for the department. The Nobel laureate physicist Arthur Holly Compton started the first biology project related to nuclear fission in 1942, at the University of Chicago, site of the first nuclear chain reaction.[1] He was aware of the dangers of radiation to workers, based on early experiences with X-rays and radium. Compton became one of the most important advisers to the federal government in the postwar period, chairing the Committee on the Military Value of Atomic Energy.[2]

Over the years, the mandate of the biological research program broadened considerably to include many biological effects of energy production, in addition to radiation biology. The bureaucracy underwent several reorganizations, from the Manhattan Project to the postwar Atomic Energy Commission (Public Law 79-585) to the Energy Research and Development Administration (Public Law 93-438). Jimmy Carter made a promise to create a Department of Energy in his 1976 campaign for President. The promise was made good in 1977 (Public Law 95-91), carrying with it the biology program that DeLisi later inherited.

In the period immediately after World War II, the Atomic Energy Commission (AEC) was a major supporter of genetics research. The AEC had a relatively large research budget at a time when the National Science Foundation was just coming into existence and the National Institutes of Health were quite small. Even the small fraction of the AEC budget devoted to genetics

dwarfed other genetics programs, and the national laboratories funded by AEC grew into centers on the forefront of research. This picture changed as the NIH budget increased steadily for three decades, leaving DOE in the dust. The National Institute of General Medical Sciences (NIGMS) became the principal funding source for basic genetics. Molecular biologists trained in the 1970s and 1980s were accustomed to thinking of NIGMS as the wellspring of genetics; older geneticists who might remember the AEC's role were smaller in number and generally separate from those who founded molecular biology.



Charles Delisi, as director of the Office of Health and Environmental Research in the Department of Energy, set aside the first funding for human genome research at DOE in 1985, in effect putting the genome project on the public policy agenda for the first time. *Courtesy Boston University*

DeLisi's idea for a DOE genome project spun off from an effort to study changes in DNA wrought in the cells of the atomic bomb survivors known in Japanese as the ***hibakusha*** ("those affected by the bomb"). They had been exposed to one of the most cataclysmic events of all time, but it was just the beginning of their collective nightmare.

The history of the genome project is linked to an attempt to determine if there would be a final, genetic wave of effects from bomb exposure. Specifically, investigators wanted to assess the frequency of inherited mutations caused by exposure to the atomic bombings. Those exposed to the bombings suffered

through many phases of radiation effects. Many people were vaporized, burned to death, or otherwise killed immediately by the bomb blast. Among those who survived the first hours, many died of radiation sickness that killed off cells in the immune system, skin, and intestinal lining. Fetuses *in utero* at the time of the bombing had an increased risk of microcephaly (small head and brain associated with mental retardation). Among burn victims, large deforming keloid scars formed in the months after exposure. A few years later, a wave of leukemias passed through the *hibakusha*. After a decade, they began to show somewhat increased rates of cancer in the breast, thyroid, gastrointestinal tract, bone marrow, and other tissues.

The *hibakusha* were severely stigmatized in the postwar period.[3;4] They were intensively monitored for decades with exhaustive medical follow-up of their health status, in one of the largest, most complex, and longest epidemiological studies ever attempted. In 1947, the U.S. National Academy of Sciences established the Atomic Bomb Casualty Commission (ABCC), with funding from the Atomic Energy Commission, to study the effects of the Hiroshima and Nagasaki bombs. The ABCC used legions of researchers to interview the *hibakusha,* eliciting details related to radiation exposure and health effects. The purpose of the ABCC was to gather information—not to provide treatment, a fact that aroused considerable resentment among the *hibakusha*.[3–5] Eventually, the Japanese government set up special health programs.

In 1975, the ABCC became the Radiation Effects Research Foundation (RERF), based in Hiroshima and Nagasaki, with joint funding from the governments of the United States and Japan. RERF continued the epidemiological investigations and conducted other related research. Most notably, a major reassessment of the nature and amount of radiation exposure was published in 1987, substantially changing dose estimates of those exposed at Hiroshima.[6]

One of the sources of stigma was a belief that the *hibakusha* carried mutations caused by the radiation they experienced. *Hibakusha* women reported they were rejected as mates because they would have deformed children or would pass on mutations and genetic disease. In the early postwar period, the extent of mutational damage to atomic bomb survivors was indeed a hot topic of controversy. H. J. Muller, fresh from receiving a Nobel Prize for his discovery that radiation could induce mutations, used his new fame to sound the alarms. Speaking of the *hibakusha,* he observed that "if they could foresee the results 1,000 years from now . . . they might consider themselves more fortunate if the bomb had killed them."[7] Alfred Sturtevant was even more apocalyptic about radiation exposure: in a letter to *Science,* he warned that atomic bombs already exploded "will ultimately result in the production of numerous defective individuals—if the human species itself survives for many generations."[8]

Such dire predictions were made by some of the most expert geneticists of the day. They fed a growing public fear of radiation that long predated atomic

bombs, but was greatly intensified by the mystery surrounding the Manhattan Project and its awesomely powerful products.[9] Nonetheless, the fears were products more of speculation than of observation. The speculations were not purely fabricated; they were based on animal studies, but in this case projections from other organisms proved errant, with distressing effects on the *hibakusha* and their children. The findings from extensive monitoring for three decades were contradictory: according to one expert, "the overwhelming impression that one gains from the analyses of the genetic data . . . is that there is not compelling evidence of genetic change in the offspring of exposed parents."[10] The children failed to show significantly higher rates of cancer or other disease, including birth defects and genetic disorders. If bomb exposure to their parents had produced inherited mutations, they were subtle and hard to detect among the DNA changes that normally occur between generations.[11]

The data were too sparse to drive choices among policies. While radiation clearly increased mutations, no one could say how many or what were the consequences in humans. Historian Susan Lindee concluded that "flexibility in the quantitative side of the argument contributed to flexibility in the 'acceptable' parameter."[5] One group of scientists noted that the species was unlikely to go extinct as a consequence of radioactive fallout, but this was small consolation to a public more interested in intermediate endpoints—the generations destined to live in the meantime.

An enormous range of interpretations was compatible with limited data. The question of whether the *hibakusha* suffered from heritable mutations continued to nag human geneticists. The ABCC studies were expected to produce negative results all along, an odd instance of a major commitment to a project fully expected to be inconclusive.[12]

James V. Neel and others devoted their careers to careful study of the effects of radiation on the genes of the *hibakusha* and their children. Neel founded the first department of human genetics in the United States, at the University of Michigan, based in part on funds to study the genetic effects of radiation. In the mid-1980s, a group sought to apply the emerging techniques of molecular genetics to the quantitative measurement of heritable mutations in humans. Taking the analysis down to the level of DNA sequence was merely an incremental extension of decades of work.

RERF convened a genetics study conference on March 4 and 5, 1984, in Hiroshima. Conferees recommended that cell lines be created from the *hibakusha,* and that "methods for direct examination of DNA should be introduced with all deliberate speed."[13] This recommendation could be interpreted any number of ways, and the International Commission for Protection Against Environmental Mutagens and Carcinogens elected to hold a meeting focused specifically on new DNA techniques. The Department of Energy funded the meeting. Mortimer Mendelsohn of Lawrence Livermore National Laboratory asked Ray White to organize the meeting.

White selected Alta, Utah, as the meeting site. At the same venue where

Botstein and Davis struck upon the idea of systematic RFLP mapping six years before, the masters of technology convened to discuss direct analysis of DNA. White invited an extraordinary mix of molecular and human geneticists to the meeting. The meeting, which lasted from December 9 to 13, 1984, took place in a blizzard. The skiing was memorable; the science was even better.

The 1984 Alta meeting planted the seeds for George Church's embellishments of the Maxam-Gilbert sequencing methods. Many of the young molecular biologists had never met Neel; indeed, some had never heard of him. Maynard Olson, destined to figure prominently in the genome story, was deeply impressed by Neel's commitment.[14] Olson was just beginning to get results on his physical mapping project of yeast. Charles Cantor presented some of the first data using the method he and David Schwartz described for separating million-base-pair fragments of DNA for mapping. The genetic linkage mappers, White foremost among them, had already found their first few RFLPs. Most of the participants had never met one another; as discussion heated up, the meeting became a boiling cauldron of ideas. The roiling broth within contrasted with the blizzard outside, isolating the participants from the world and lending intensity to the discussion.[15]

The conclusion of the meeting was, ironically, that the methods of direct DNA analysis were inadequate to detect the expected increase in mutation frequency from radiation exposure at Hiroshima and Nagasaki.[15–18] In attaining its specific end, the conference was a disappointment, but it brought together a welter of related ideas that would grow into the DOE genome project. The links were a congressional report and Charles DeLisi, a new face at DOE.

The congressional Office of Technology Assessment (OTA) was then doing a report on technologies to measure heritable mutations in man. Exposure to Agent Orange, environmental toxins, and radiation were coming before congressional committees as public policy problems.[19] Mike Gough, then an OTA project director, was present at the Alta meeting and discussed the various technologies in a draft report sent to the Department of Energy for review. The report was published in 1986 as *Technologies for Detecting Heritable Mutations in Human Beings*.

DeLisi had the idea for a project dedicated to DNA sequencing, structural genetics, and computational biology while reading the October 1985 preliminary draft of the OTA report.[20–23] DeLisi was then the newly appointed head of the Office of Health and Environmental Research at DOE. In a scene typical of Washington, he reflected on programs under his direction by reading about them in a report prepared by outsiders.

Once he had the idea, DeLisi moved quickly. He and David Smith, a scientist-administrator also working at DOE headquarters, barraged one another with notes and memos about how to plan this major new initiative. While most of the offices in and around Washington eased into the Christmas

lull, Smith and DeLisi were busy crafting a new science initiative. Smith and DeLisi asked the biology group at Los Alamos National Laboratory for comments on DeLisi's idea. The Los Alamos group replied with a dense, scattered, but wildly enthusiastic five-page memo just before Christmas, prepared by physician Mark Bitensky and others.[24] The memo bubbled over with enthusiasm about the potential technical and human health benefits that a structural approach to genetics would open up. The discussion centered on DNA sequencing and barely mentioned physical or genetic mapping. The Los Alamos group found another appealing argument for a concerted research program, arguing that such a project could become a "DNA-centered mechanism for international cooperation and reduction in tension."[24]

The memo saw the national laboratories emerging from the shadow of the atomic bomb. In Bitensky's words, "[J. Robert] Oppenheimer's statement 'I am become death, the Destroyer of Worlds' gives way to 'the National Laboratories are become the ultimate advocates for the understanding of human life.' "[24] He referred to Oppenheimer's quote from the *Bhagavad Gita,* uttered upon the explosion of the atomic fission bomb test at Alamogordo, New Mexico.[25–27] Los Alamos even checked with Frank Ruddle of Yale, to ensure that he would be willing to testify before Congress if called. With this initial encouragement, Smith and DeLisi began to pull the bureaucratic levers in Washington.

DeLisi outlined the political strategy to garner support from the scientific community, from their superiors at DOE, and from Congress.[28] Smith responded with a note about rumors of previous discussions, at a Gordon Conference and at the University of California the previous summer, but he did not know what had come of these.[29] Smith cautioned that criticisms would plague the DOE proposal for some time to come: it was not science but technical drudgery, directed research was less efficient than letting small groups decide what was important, and efforts should be concentrated on genes of interest rather than global sequencing. DeLisi bounced back: "Regarding the grind, grind, grind argument . . . there will be some grind; what we are discussing is whether the grinding should be spread out over thirty years or compressed into ten." He estimated that "we are talking about $100–150 million per year spread out over somewhat more than a decade," and he asserted that such a project certainly would rate as more important than the lower 1 percent of biology grants that funding of this magnitude would displace. The political effort, he argued, should focus not on whether it would displace other work, but instead on how to gain support for new funding.[30]

In order to reach out to the scientific community, DeLisi and Smith asked Los Alamos to convene a workshop: (1) to find out if there was consensus that the project was feasible and should be started; (2) to delineate medical and scientific benefits and to outline a scientific strategy; and (3) to discuss international cooperation, especially with the Soviet Union. A planning group at Los Alamos got together on January 6 to begin planning the workshop.[31] The

meeting was shaped in a series of notes and calls back and forth between DOE headquarters and Los Alamos.[32]

The workshop was held in Santa Fe on March 3 and 4, 1986, with "a rare and impassioned esprit."[33] Frank Ruddle chaired the meeting. Discussion at the Santa Fe workshop added an emphasis on integrating genetic linkage and physical maps and the process of making physical maps.[34;35] Participants agreed on the importance of the new venture and on part of what it should entail, but opinions failed to converge on how to organize the effort. Nobelist Hamilton O. Smith of Johns Hopkins University found that "perhaps the most impressive feature of the meeting was the unanimous consensus that sequencing the entire human genome is doable . . . [although] how to implement such a heroic and costly undertaking is less clear."[36] Anthony Carrano and Elbert Branscomb of Lawrence Livermore National Laboratory stressed the importance of clone maps and warned that "a program whose announced purpose was simply to 'sequence the human genome' might unnecessarily and incorrectly arouse fears of territorial and financial usurpation in the biomedical research community."[37] Events proved their political acumen; fears of a massive mindless sequencing operation became the major threat to scientists' support of the human genome project.

David Comings, a human geneticist from the City of Hope Medical Center in southern California, was further from the mark when he asserted that the whole physical mapping component might be funded "without any stirring up of any congressmen or other related creatures."[38] Those awful creatures proved altogether too alert and intrusive.

Beyond the first rationale, the study of heritable mutations, DOE had a second reason to mount a genome project. DOE managers wanted to capitalize on the resources of the national laboratories, with their ready access to exotic high technology, the best complex of supercomputers in the world, and multidisciplinary teams of scientists.

> The Genome Project also fit naturally within a broader DOE mission, and that is the utilization of the Labs to solve nationally important problems in areas that required their unique capabilities. In the case of Genome, the uniqueness was experience with large multidisciplinary projects, and a history of breakthroughs in applying engineering to the medical sciences (nuclear medicine being the paradigm). To the extent that large portions of the project could not be comfortably accommodated at most universities, this second rationale ultimately became as important as the first.[39]

This justification was liable to seem self-serving, however; the arguments sounded like a typical bureaucracy's merely expressing its proclivity for self-perpetuation. And so it was. David Botstein showed his knack for subtle understatement, calling the DOE genome initiative "DOE's program for unemployed bomb-makers."[40] Lee Hood was more diplomatic, noting:

> The argument they had enormous technological resources that could be focused on this problem was utterly irrelevant, unless they had the key individuals that could

integrate those in a focused and productive way, to take advantage of biology as well as the technology. So on all of those counts, I think DOE had not convinced the world in 1985 that they had the wherewithal to take on the Human Genome Initiative.[41]

The future of the national laboratories proved crucial to the DOE's genome effort. Mutation detection was the intellectual origin, but it was too weak a foundation on which to build a major new program. A new direction for the national laboratories, to channel their ample intellectual and technological energies, became a much more powerful drive once engaged. The laboratories were a natural political base with a well-developed support structure. Scientists at several of the national laboratories were enthusiastic about the idea and were already doing related research. DeLisi's idea started from a narrow base, mutation detection, but then grew to encompass a much larger political goal, the salvation of the national laboratories.

DeLisi discussed the possibility of a genome project with his immediate superior, Alvin Trivelpiece, who supported it and charged the DOE life sciences advisory committee (the Health and Environmental Research Advisory Committee, or HERAC) to report back to him about it. Trivelpiece and DeLisi had discussed why DOE did not have the same high stature in biology that it had in high-energy physics, and they aspired to lift DOE to the forefront of biology on the wings of a genome project. Trivelpiece, as director of the Office of Energy Research, reported directly to the Secretary of Energy (then John Herrington), who in turn reported directly to the President.

On May 6, 1986, six months after his initial idea, DeLisi produced an internal planning memo to request a new line-item budget. This went to Trivelpiece and up through the DOE bureaucracy. DeLisi argued for a two-phase program. Phase I had three components. The first, physical mapping of the human chromosomes, the central element, would take five or six years. The other two components were development of mapping and sequencing technologies and renewed attention to how computer analysis could assist molecular genetics (especially sequence analysis). As physical mapping progressed, parallel efforts would proceed, to prepare for Phase II, the sequencing of the entire genome. High-speed automated DNA sequencing and enhanced computer analysis of sequence information were both essential to making the transition from Phase I to Phase II. DeLisi's background in computational biology, his previous experience in interpreting DNA sequence information at the National Cancer Institute, came to the fore here. Phase II, contingent on success in all three parts of Phase I, was to sequence the banks of DNA clones that constituted the physical map.

DeLisi spoke of a project analogous to a space program, except that it would entail the efforts of many agencies and a more distributed work structure, with "one agency playing the lead, managerial role. . . . DOE is a natural organization to play the lead."[42] A six-year budget of $5, $10, $19, $22, and $22 million was proposed for fiscal years 1987–1991.[43] Plans survived the

internal DOE review, and a series of meetings was scheduled, beginning in July 1986, with Judy Bostock, the DOE life sciences budget officer in the presidential Office of Management and Budget (OMB), and with her boss, Thomas Palmieri.

OMB perches atop the federal bureaucracy, with responsibility to oversee management and prepare the President's budget request to Congress each year. Mention of OMB sends shivers of fear down the spines of most who work for the federal government. OMB is the dank home of malicious obstructionists and ax-toting budget officers. The genome project charged into the dark castle—the New Executive Office Building a block from the White House—to face the naysayers and dream-stealers. As the exception that proves the rule, the genome project got a major boost from OMB.

DeLisi's genome meetings with Bostock were focused on planning for fiscal years 1988 and beyond. Bostock was an erstwhile physicist from MIT, intrigued by prospects of improving the speed and efficiency of biological research, who believed that better instrumentation could improve the quality of biology.[44;45] She saw molecular biology as an extremely inefficient process with postdoctoral and graduate students doing mindless manual work that would be better done by robots or automated instruments. DeLisi was proposing a program to analyze DNA faster and with less human effort, a laudable goal that capitalized on the resources of national laboratories. Bostock bought DeLisi's plans, clearing a major obstacle from the road to Congress.[46]

DeLisi succeeded in his dealing with the DOE and OMB bureaucracies, but he also needed an endorsement from scientists. The OHER advisory committee, the Health and Environmental Research Advisory Committee (HERAC), endorsed the plan for a DOE genome initiative in a report from its special *ad hoc* subcommittee. The subcommittee was a blue-ribbon scientific group chaired by Ignacio Tinoco, a highly respected chemist from the University of California at Berkeley, then on a sabbatical year at the University of Colorado. The HERAC report urged a budget of $200 million per year and made a case for DOE leadership of the effort. The introduction to the report laid out the rationale:

> It may seem audacious to ask DOE to spearhead such a biological revolution, but scientists of many persuasions on the subcommittee and on HERAC agree that DOE alone has the background, structure, and style necessary to coordinate this enormous, highly technical task. When done properly, the effort will be interagency and international in scope; but it must have strong central control, a base akin to the National Laboratories, and flexible ways to access a huge array of university and industrial partners. We believe this can and should be done, and that DOE is the one to do it.[47]

Budget projections made by the committee were not directly coupled to the multiyear DOE-OMB budget agreement. The HERAC report was issued in April 1987, at least seven months after DeLisi began to reprogram funds,

and four months after the budget agreement with OMB.[48-51] The process of formulating a budget began with DeLisi's notes to David Smith in December 1985 and continued more broadly at a genome conference hosted by the Los Alamos National Laboratory in Santa Fe, New Mexico, in March 1986. In letters sent to the organizers after that meeting, budget estimates covered a wide range and generally focused on only one or two components. By the second Santa Fe conference in January 1987, planning had become more systematic. Several of the participants met over lunch at that conference to discuss what the budget should be. David Padwa, who had previously been involved with founding an agricultural biotechnology company, Agrigenetics, noted some political constraints on the budget. It had to be large enough to command congressional attention, so it would have to be at least $50 million to $100 million per year, but it could not be so large it threatened other research interests. The discussion continued at a meeting of the HERAC subcommittee at the Denver Stouffer's Hotel, February 5 and 6, 1987, a month before their report was to be considered by the full HERAC. Generating cost estimates was delegated to Lee Hood. The second day's meeting started at nine in the morning, and Hood's plane was delayed, so the group began to discuss what could be done within the range of budgets thought to be reasonable for OHER to request. There was discussion of how much physical mapping and sequencing could be done with $20 to $40 million, the maximum thought politically feasible.

Hood entered the meeting at ten o'clock, armed with some handwritten notes, including a menu of technologies and attendant costs. The proposal included technology development, physical mapping, mapping and sequencing of model organisms (yeast and bacteria), and regional sequencing of interesting chromosomal regions (e.g., those packed with genes). His estimates were $200 to $300 million per year for a full program. Someone asked if that was at all possible, since it was a full order of magnitude higher than earlier discussions. Hood did not wait for an answer, and asked passionately whether the budget would drive the vision or the vision would drive the budget. With this, the group deliberated over some technical details of how to make the projections and settled on a figure of $200 million. This brought the budget projection into the range judged politically attractive over the course of previous discussions.

The HERAC subcommittee did not discuss which agency should lead the Human Genome Project at its final meeting to draft its report. This was pointed out to HERAC when it met to consider the subcommittee report in March 1987. By April, when the report was released, Tinoco as subcommittee chairman and Mort Mendelsohn, a member of the subcommittee and chairman of HERAC, had canvassed the members. They wrote the language favoring DOE leadership. Later interviews with members of that subcommittee revealed that at least seven of the fourteen had reservations about giving DOE a blank check, but agreed to the suggested language because they feared inac-

tion on the part of NIH; it was more important to them that the project proceed than that NIH direct it.

Despite the go-ahead from his superiors at DOE, from OMB, and from the scientific community as represented by HERAC, DeLisi's job was still not complete. There was a two-step process in each house of Congress. Before a federal agency can fully implement a major new initiative, Congress has to authorize it and separately appropriate funds for it. These twin processes are interdependent but distinct.

Appropriations committees in the two houses are parallel. They allocate funds according to the executive department expending the funds and follow a relatively stable annual routine. The President's budget proposal is prepared, first by each department and then by OMB. In January the President's budget goes to Congress, where it is referred to the appropriations committees. Except in unusual circumstances (as occurred once during the Reagan years, violating the spirit, and probably also the letter, of the Constitution), the House takes action first, and the Senate works from the House figures. The appropriations committees cannot authorize new programs, but can only fund activities authorized by other committees. The interpretation of these distinctions can be tight or loose, depending on the circumstances. (One of the nation's first large science agencies, the U.S. Geological Survey, for example, was created and operated for years under a rider to an appropriations bill, without an authorization statute.)[52;53]

To get the genome program started, DeLisi took $5.5 million in funds from the preexisting fiscal year 1987 budget and reallocated them to the genome effort. Such limited "reprogramming" was standard fare, permitted by the appropriation and authorization committees within reasonable limits. For 1988 and later budgets, however, DOE needed support from its authorization committees. DeLisi noted the need for congressional action in his first personal note to David Smith,[28] and he began to hold meetings with congressional staff in 1986. This was unfamiliar territory for DeLisi, who was given to shyness and new to defending a program on Capitol Hill. There was little problem in the Senate, as DOE could in all likelihood count on strong support from Senator Pete Domenici and tacit approval of Senator Wendell Ford, the key figures on the authorization committee. Domenici also sat on the appropriations and budget committees. The problem was in the House.

Staff of the relevant DOE authorization subcommittee in the House were getting mixed signals about the DOE genome initiative. Congressman James Scheuer chaired the subcommittee with jurisdiction over DeLisi's program. Scheuer's staff read the generally negative response to DOE's plans in *Science* magazine; phone calls to biologists elicited both support and opposition. Eileen Lee, the biologist on staff, was uncertain what tack to take. She called on OTA staff, including me, to help plan a hearing, in hopes of penetrating the network of scientists concerned with the genome project.

DeLisi's problem was complicated by the politics of his other programs. Scheuer's staff was generally supportive of DOE staff initiatives, but DeLisi had problematic relations with Eric Erdheim, staff for Claudine Schneider, the ranking minority (Republican) member on the subcommittee. It was unclear to Scheuer's staff whether they should expend the political capital to defend DeLisi against Erdheim on the genome project. Claudine Schneider was generally suspicious of DOE's record on research into environmental health hazards, although she eventually decided DeLisi's program was good. As the hearing approached, the genome project became the battleground for a skirmish between Democrats and Republicans on the subcommittee staff.

About a week before the hearing, I was invited to meet with subcommittee staff from both parties. I could sense the tension in the room, but was blithely unaware of its origin,despite the fact that my wife, Kathryn, worked in Claudine Schneider's office at the time. As we were drifting apart after the meeting, Eileen Lee whispered to me that she thought Erdheim had asked James Watson to testify against the DOE genome program. A few minutes later, as I was preparing to leave the subcommittee's rabbit warren of offices, Erdheim took me aside to tell me he was thinking about calling the Delegation for Basic Biomedical Research to seek testimony from Watson or David Baltimore. Erdheim "had problems with what DeLisi was doing in his programs,"[54] and he was skeptical of the genome proposal. What did I think of that? I suggested that he had better find out what Watson or anyone else from the delegation would say before he invited him.

Eileen Lee arranged for Leroy Hood to testify before the committee. Hood agreed, oblivious to the political maelstrom swirling around him. At the March 19 hearing, he delivered an impassioned plea for the genome project.[55] Hood asserted a role should be found for DOE, NIH, and NSF. He thus deftly if unwittingly ducked the troublesome question of which agency should hold the reins. Scheuer's staff had agonized about the possibility of a Hood-versus-Watson contretemps, but Watson did not show. (Watson later said he was never asked to testify.)[56]

Rep. Schneider's latent distrust broke the surface in a series of questions about forthcoming DOE reports on health effects of radiation among submarine workers, radiation effects among the *hibakusha,* health effects in nuclear plant workers, and "least cost" energy. (DeLisi later noted that Schneider praised these reports when she got them.)[39] Despite the dramatic warning signals, the genome program coasted through the hearings unscathed. The DOE program was probably more vulnerable at this hearing than at any other point in its evolution. DeLisi, unaware of the backroom shenanigans, had cleared his highest hurdle.

The appropriations process was less troublesome than authorization and presented no major obstacles once the genome project had OMB approval. The DOE budget process for fiscal years 1988 and 1989 held true to the initial agreement with OMB—seeking $12 million and $18 million, respectively. It

began to exceed the initial agreement only in 1990, when it sought $28 million instead of the original $22 million.

After the March authorization hearing before Scheuer's subcommittee, I escorted Hood (who did not know me then) to the elevators and out to catch a taxi, through the labyrinthine Rayburn House Office Building. He asked, "Is that it?" I asked what he meant. He replied, "Do we get the money?" I was struck, not for the first time, by how much of the process that went into federal research funding was unknown to even the most sophisticated of its recipients. I said something about this being just the first of many steps toward DOE's budget. It was far from a done deal. Hood dashed into a cab and headed for National Airport. He was a long way from home.

DeLisi's ideas found fertile soil in the U.S. Senate, but for reasons different from his own. Senator Pete Domenici was a staunch supporter of the national laboratories in his home state of New Mexico, although he believed that they produced far less long-term benefit for the local economy than they should. He convened a panel of influential policymakers to discuss the future of the national laboratories one Saturday morning, May 2, 1987, in the U.S. Capitol. The meeting featured Barber Conable, a former New York congressman and head of the World Bank; Donald Fredrickson, former director of the National Institutes of Health; Ed Zschau, former California congressman and successful entrepreneur; Jack McConnell, director of advanced technologies for Johnson & Johnson; and the directors of several national laboratories.

In the midst of the meeting, Domenici asked, "What happens if peace breaks out?"[57–60] The bulk of the work supported at the two laboratories in New Mexico was focused on nuclear-weapon production and defense-related research and development. Domenici wanted to know how the immense research resources of the national laboratories could be better integrated into the national economy.[61] He also sought a new mission for national laboratories that did not depend on Cold War rhetoric and that might move them into the growth areas of science, including biology. Domenici knew that sooner or later the Reagan defense spending juggernaut would lose steam.

Donald Fredrickson, then president of the Howard Hughes Medical Institute, asked if the national laboratories might play a role in the human genome project. After the meeting, Jack McConnell helped draft legislation that resulted in Senate bill 1480. By that time, Los Alamos was already beginning its genome program, a year and a half after DeLisi's initial idea. This show of strong support from the Senate nonetheless helped secure the DOE program's future at a time of potential vulnerability.

DeLisi and Smith anticipated many of the arguments that would be made for and against the genome project. But what was missing from their thoughts proved just as important—competition with NIH and acceptance among molecular biologists and human geneticists proved even more important than they might have thought. DeLisi remarked later that "moving unilaterally was

not my preference, nor did I consider it optimal."[62] He had a strong potential ally in Vincent DeVita, director of the National Cancer Institute, where DeLisi had worked before. DeVita's power was waning, however, and he was soon to leave the NCI directorship. NIGMS was the NIH institute responsible for funding most basic genetics, but DeLisi's relations with NIGMS were more distant and there was a much greater difference in styles.

DeLisi saw a hole, put his head down, and ran. He put the genome project on the public agenda, but it was not a clean run for the end zone.

> The well-known NIGMS response was that if it were to be done, they should do it, but it should not be done. . . . One of my choices was to use the NIH style of cautious consensus building. At times, perhaps most of the time, that is the best procedure; but in my judgment, this was not such a time. I made a deliberate decision to move vigorously forward with the best scientific advice we could muster (HERAC). I am quite willing to take the criticism, rational or not, that such movement provokes. . . . I would have been far more timid about subjecting myself to . . . criticisms . . . if I saw my future career path confined to government.[62]

DeLisi decided to risk attack and push forward. His relations with NIGMS director Ruth Kirschstein, director of the most relevant scientific program at NIH, were intermittent and distant. Those of us observing the process could readily see that the two principal figures in genome politics at DOE and NIH were ill at ease with each other. DeLisi and Kirschstein were both, however, consummate professionals. They avoided direct conflict while encouraging staff exchanges and cooperation. Both later glossed over this period during which their objectives were at cross purposes and their roles inherently cast them in opposition, attributing the perception of conflict to science reporters covering genome politics. The reporters were telling the truth. The tension between DOE and NIGMS was real. The amazing feature of the genome project is that the conflict was contained. It never broke into destructive distrust or resulted in NIH and DOE taking positions that would force them into direct confrontation before Congress. Staff members on Capitol Hill were well aware of the potential for open conflict between NIH and DOE. Some even eagerly awaited the public theater it would provide. Had the battle lines been drawn, the genome project as a whole would almost certainly have been delayed or destroyed.

Several technical elements are remarkable by their absence from early consideration at DOE. There was very little discussion of genetic linkage mapping—the first and arguably the most important step toward making the project useful to the research community—and scant attention to the study of nonhuman organisms as either pilot projects or even scientifically important subjects to study. DeLisi explained these gaps as resulting from a *presumption* that RFLP mapping and work in other organisms would proceed apace, and that the genome program would merely augment the ongoing efforts in these related but distinct areas.[63] A memo from George Cahill corroborates that

DeLisi stressed the importance of comparative genome mapping in man, mouse, and other organisms at the initial meeting of the HERAC subcommittee.[51]

Genetic linkage maps and work on other organisms were, however, clearly subsidiary to the main goals of the initial DOE program: DNA sequencing technology, computation, and physical mapping. By 1990, the genome project was redefined so that genetic linkage maps and physical maps of model organisms and humans were accorded first priority, with sequencing to follow when (and if) it became affordable and sufficiently rapid. In the reoriented genome project, DNA sequencing was subtly removed from the top spot and subordinated to other goals.

The seeming neglect of genetic linkage mapping and nonhuman genetics drove a wedge between DOE and much of the biomedical research community. The enthusiasm driving the DOE human genome proposal proved sufficient to keep it going, but it was a rough ride.

8

Early Skirmishes

In a commentary introducing the March 7, 1986, issue of *Science,* Renato Dulbecco, a Nobel laureate and president of the Salk Institute, made the startling assertion that progress in the War on Cancer would be speedier if geneticists were to sequence the human genome.[1] For most biologists, Dulbecco's *Science* article was their first encounter with the idea of sequencing the human genome, and it provoked discussions in the laboratories of universities and research centers throughout the world. Dulbecco was not known as a crusader or self-promoter—quite the opposite—and so his proposal attained credence it would have lacked coming from a less esteemed source.

Like Sinsheimer, Dulbecco came to the idea from a penchant for thinking big. His first public airing of the idea came at a gala Kennedy Center event, a meeting organized by the Italian embassy in Washington, D.C., on Columbus Day, 1985.[2] The meeting included a section on U.S.–Italian cooperation in science, and Dulbecco was invited to give a presentation as one of the most eminent Italian biologists, familiar with science in both the United States and Italy. He was preparing a review paper on the genetic approach to cancer, and he decided that the occasion called for grand ideas. In thinking through the recent past and future directions of cancer research, he decided it could be greatly enriched by a single bold stroke—sequencing the human genome. This Washington meeting marked the beginning of the Italian genome program.[3]

Dulbecco later made the sequencing idea a centerpiece for his September 5 speech to dedicate the Sambrook Laboratory at Cold Spring Harbor on Long Island, New York.[4,5] Dulbecco sensed a transition in cancer biology: "It seems we are at a turning point in the study of tumor virology and oncogenes."[4] The well-known fact that cancers of certain cell types behaved quite differently in different species meant that "if the primary objective of our endeavor is to understand human cancer, we must study it in human cells."[4]

Dulbecco argued that the early emphasis in cancer was on exogenous factors—viruses, chemical mutagens, and their mechanisms of action. Cancer research had to change strategies, shifting its focus inward: "If we wish to learn more about cancer, we must now concentrate on the cellular genome."[1]

The article as published was considerably shortened from a draft that expanded on how sequence information might tease apart factors explaining the heterogeneity among breast cancer genes.[4] Understanding cancer came from focusing on animal models of cancer, especially tumor viruses. Studying viruses dramatically reduced the number of genes under study and permitted the isolation of individual cancer-associated genes (oncogenes) that would have been forever obscured by studying spontaneous cancers of humans. Molecular biology triumphed by studying the much smaller and more tractable set of genes contained in viruses causing cancer in animals. The study of cloned oncogenes in viruses permitted a reductionist dissection of individual genes contributing to cancer.

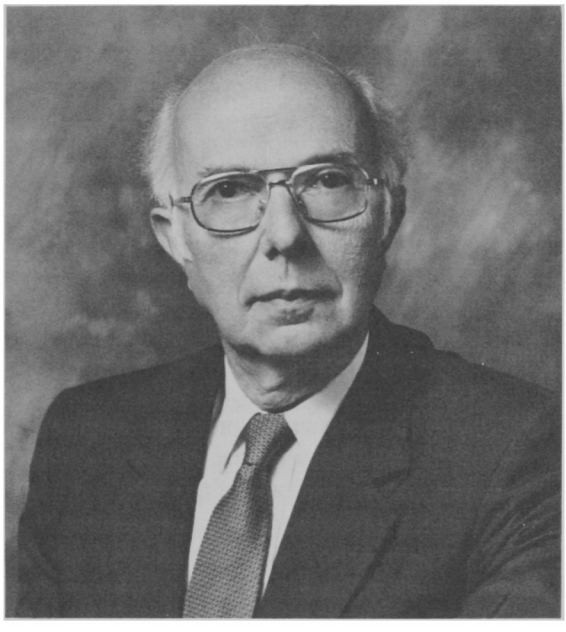
Studying oncogenes and tumor viruses could not, however, fully explain the "progression" of tumors—the multiple steps along the road from normal cell maturation to proliferation to cancer. Changes in genes were obviously taking place on this journey, but they could not be easily followed for lack of a road map. The point was not that experiments were impossible, but that they entailed making *ad hoc* maps; much less work would be necessary if there were good global maps of the genome. Dulbecco argued that cancer progression could only be understood once a map was prepared. The DNA sequence was such a map at its ultimate resolution.

While cancer was clearly not a purely genetic disease, in the sense that it was not inherited as a Mendelian trait except in rare families, it was equally clear that the steps leading to uncontrolled cellular growth involved changes in DNA. Changes *were* inherited by groups of cells within the body, even if such changes were not passed on to a person's progeny (since they took place in cells other than those giving rise to eggs and sperm). DNA mutations were thus inherited at the level of the cell, as cells from different organs continually gave rise to new ones. Dulbecco saw the DNA reference sequence as a standard against which to measure genetic changes taking place in cancer. He argued that some such reference was needed, because there was not then and never would be another standard. Human genetic variation was too great, and interbreeding to study specific mutations was unethical. In the mouse, 150 well-characterized, genetically homogeneous strains could be deliberately bred and studied. This well-controlled genetic environment was a vain hope in humans, however, and always would be. Dulbecco saw the sequence information as itself generating new biological hypotheses to be tested by experiment.[6]

Dulbecco envisioned DNA sequence as the lead actor in tomorrow's drama of cancer research. This vision issued from Dulbecco's intuition, more as an inchoate sense of the most productive research strategies for the future than as a concrete step-by-step argument. Indeed, he apologized for "hand-waving," but he did not apologize for his main conclusion, that DNA sequence data would be fundamental to understanding the central problems of biology—cancer, chronic disease, evolution, and how organs and tissues develop.[6] Dulbecco noted the need for biology to encompass some collective enterprises of

use to all, in addition to its extremely successful agenda of mounting small, narrowly focused inquiries.

In the *Science* commentary, these arguments for a standard genetic reference genome were given short shrift.[3] Many scientists were puzzled about the scientific rationale behind Dulbecco's proposal, but the *Science* article nonetheless became a catalyst for broader discussion. Sinsheimer convened the first meeting dedicated to discussing whether or not to sequence the human genome, and DeLisi laid the first stones in its bureaucratic foundation, but Dulbecco was the first to publish the idea in a large-circulation journal aimed at the entire scientific community.



Renato Dulbecco independently promoted the idea of a massive project to determine the sequence of nucleotides in the DNA of human chromosomes in 1985. Dulbecco, who was awarded the Nobel Prize in physiology or medicine in 1975, is president of the Salk Institute. *Courtesy Salk Institute*

By the summer of 1986, the rumor networks of molecular biology were buzzing with talk of the DOE human genome proposal. Dulbecco's proposal helped build the wave. News of the Santa Fe workshop was disseminated by those who attended it; those in the mainstream of molecular biology were beginning to discuss the idea of sequencing the human genome in their phone conversations and at scientific meetings. As is so often the case in molecular biology, Cold Spring Harbor Laboratory on Long Island, New York, became the focal point.

A landmark symposium modestly titled "The Molecular Biology of *Homo sapiens*" took place at Cold Spring Harbor in June 1986, bringing together the giants of human genetics and molecular biology. More than one hundred

speakers addressed an audience of 311, reviewing the astonishing progress in two decades of human genetics.[7] The various proposals to sequence the genome were by then hot topics, and they took center stage.

Walter Bodmer, a British human geneticist of broad view, familiar with both molecular methods and mathematical analysis, was the keynote speaker. He emphasized the importance of gene maps and the advantages of having a DNA reference dictionary. He concluded his talk by urging a commitment to systematic mapping and sequencing, as "a revolutionary step forward." Bodmer argued that the project was "enormously worthwhile, has no defense implications, and generates no case for competition between laboratories and nations." Moreover, it was better than big science in physics or space because "it is no good getting a man a third or a quarter of the way to Mars. . . . However, a quarter or a third . . . of the total human genome sequence . . . could already provide a most valuable yield of applications."[8]

Victor McKusick, dean of human genetics and keeper of *Mendelian Inheritance in Man,* the immense compendium of human genetic disease, was next at bat. He summarized the status of the gene map and finished his talk by urging a dedicated effort to genomic mapping and sequencing.[9] He argued that "complete mapping of the human genome and complete sequencing are one and the same thing," because of the intricate interdependence of genetic linkage maps, physical maps, and DNA sequence data. To find a disease gene and understand its function, one would need all three kinds of maps. He urged the audience to get on with the work, and pointed to the future importance of managing the massive flood of data to come from human genetics. Lee Hood enthused about successful early experiments with automated DNA sequencing.[10] The Cold Spring Harbor meeting was also the first exposure many young biologists had to the polymerase chain reaction and to the mix of systematic approaches to mapping and sequencing that were slowly becoming integrated into the Human Genome Project. The synthesis, however, was still a dialectic in transition.

Debate on the genome project came to a head at an evening session not originally on the program. Paul Berg, another Nobel laureate, was unaware of discussions at Santa Cruz and Santa Fe (or within DOE). He read Dulbecco's article and suggested to Watson that it might be useful to have an informal discussion of a genome sequencing effort.[11]

Watson, always well informed through an extensive network of contacts, was aware of the Santa Cruz and Santa Fe meetings. He had talked with Dulbecco and with Walter Gilbert. He called Gilbert at Harvard, asking him to co-chair a genome project discussion with Berg.[12] Berg arrived at Cold Spring Harbor to find himself co-chair of a June 3 rump session intended to ventilate the proposals for a genome project.

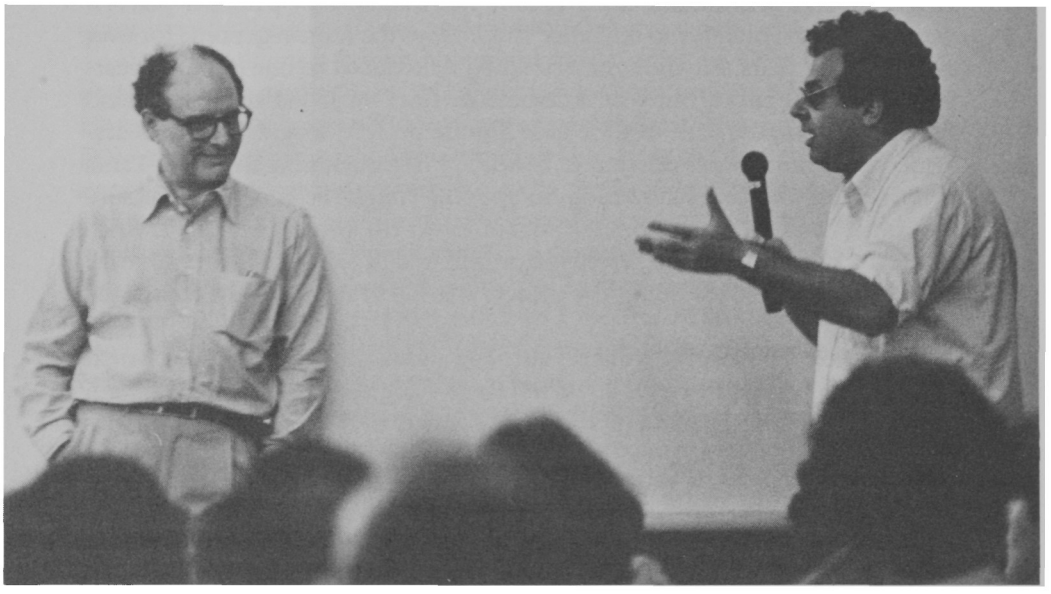
Berg led off by trying to channel discussion into the scientific merits of mapping and sequencing, and what technical approaches might make the effort feasible. Gilbert briefly described the Santa Cruz and Santa Fe meetings

and then went to the essentials of his post–Santa Cruz missives. He noted that DNA sequence was accumulating at only two million base pairs per year. At that rate, there would be no reference sequence of the human genome for over one thousand years. He thought that could be reduced to one hundred years with no special effort, but that a dedicated effort involving thirty thousand person-years, on the scale of the Space Shuttle project, would produce a dramatic acceleration with enormous benefits. His conclusion from the Santa Cruz meeting was that sequencing the genome "might be doable in a reasonable time," and "it would be inadvisable to do the project in a way which competed with R01 grants [investigator-initiated projects]. . . . the only way in which one could see doing the project was to do it with some structured funding."[13]

Berg took the floor for a short time, and raised the question "Is it worth the cost?" Gilbert had written down numbers—large numbers—large enough to unleash the pent-up fears of younger scientists in the audience. At $1 per base pair, there could be a reference sequence of the human genome for about $3 billion. The audience was stunned. Gilbert's cost projections provoked an uproar. Gilbert seemed to be urging a commitment to a $3 billion project. Sensing a loss of control, Berg called for discussion about whether it would be worthwhile to have the DNA sequence of the human genome, setting aside the cost issue. Berg's white flag was ignored, as the fusillades became too intense to restrain.

David Botstein rose to the podium when he could no longer contain his volcanic energy. Botstein stated that "there are two components to this. One is political, and we shouldn't forget about the political, because we hope to get something, right? And another is scientific, because we hope to learn something. And the question is: How much is it going to cost?" Catching his stride, he moved for the kill, "if it means changing the structure of science in such a way as to indenture all of us, especially the young people, to this enormous thing like the Space Shuttle, instead of what you feel like doing . . . and we should be very careful." He cautioned that "we should not go forward under the flag of Asilomar, okay, because we are amateur politicians and we're about to be dealing with professionals." This was a swipe at Berg, who played a prominent role in the recombinant DNA debate, including a famous meeting at Asilomar on the California coast. Botstein derided the notion of genome sequencing, noting that if Lewis and Clark had followed a similar approach to mapping the American West, a millimeter at a time, they would still be somewhere in North Dakota. Botstein closed by pleading that molecular biologists "maybe accept the goal, but not give away our ability to decide what is important because we have decided on the Space Shuttle."[14]

This broke the dam, and applause resonated through the audience. Gilbert responded that Botstein was basically right, and that the initial efforts should concentrate first on the 1 percent of the genome containing biologically known function, then do the next 10 percent, and only then finish the job, devoting



equal resources to each phase. A Gilbert-Botstein-Berg exchange then went on for several more minutes, reaching consensus on an important point when Gilbert cautioned that "we shouldn't confuse, let's say, sequencing the human genome with a total knowledge of all science." And Botstein responded, "That's what I hope will not happen." Gilbert then stated the main goal of the project: "essentially the total speeding up of all the things that laboratories [now have to do one gene at a time]."

The exchange went on until Maxine Singer of the Carnegie Corporation (a nonprofit foundation) broke it off by focusing on the notorious failure of science to predict its future. Several speakers followed, including many prominent scientists who reiterated Botstein's sentiments. Others supported the notion of a sexy proposal that could attract public support but were ambivalent about its impact on science. David Smith from DOE spoke on the focus of the DOE proposal, which did not embody a commitment to DNA sequencing per se, but only developing the technologies and infrastructure necessary to a future commitment, but he was clearly on the defensive, ceding in response to one question that perhaps DOE should not lead such an effort. His comments were largely swept away as the dam broke, although he noted that many people in the audience later came forward privately to indicate their support. Berg struggled intermittently and unsuccessfully to contain the flood, pleading for a discussion of the technical and scientific aspects. The emotional torrent was simply too strong, however. Molecular biologists were not enthused by the DOE Human Genome Initiative, perceiving it as a misguided bureaucratic initiative and, more important, as a direct threat to their own research funding.

At the time, the Cold Spring Harbor symposium seemed to stall the momentum toward a massive DNA-sequencing effort. DOE's effort, in particular, was under heavy fire. The symposium, however, proved merely a short losing battle in a longer war from which the genome idea emerged triumphant. That hardly seemed the likely outcome in June 1986, however. The symposium proved to be the opening event in an international tour culminating in a restructured genome project that commanded worldwide consensus. It marked a transition from emphasizing the sequencing of the human genome to a broader plan for genetic linkage mapping, physical mapping, and the study of nonhuman organisms.

Prospects for the Human Genome Project reached a nadir in June 1986, at a special rump session of a Cold Spring Harbor Laboratory symposium on the molecular biology of *Homo sapiens*. In the upper photo on the facing page, David Botstein, a geneticist from Stanford University, attacks the notion of mindlessly sequencing the entire human genome, as Walter Gilbert listens. In the lower photo, Paul Berg, who chaired the session, attempts to quell the unruly crowd following Botstein's remarks. Berg, also from Stanford, shared the 1980 Nobel Prize for chemistry with Sanger and Gilbert. *Victor McKusick photos, courtesy Cold Spring Harbor Laboratory Library*

The goals of the Sinsheimer, Dulbecco, and Gilbert formulations were simple and clear: a complete reference DNA sequence of the twenty-four human chromosomes (X, Y, and the twenty-two nonsex chromosomes). DeLisi's program was justified primarily as the first step toward that goal. In the genome project that began to emerge in the wake of the Cold Spring Harbor meeting, however, the goal was a useful set of chromosomal maps, not only of humans but also of some other organisms. DNA sequencing—particularly the technology to make it faster, cheaper, and more accurate—was still important but no longer dominant. Sequencing dropped from being the primary or only goal to a goal subsidiary to these more general objectives. In the redefined genome project, the goal of the project was to bring the new techniques of molecular genetics to bear on a massive scale, to enable approaches to human genetics analogous to those long employed to study yeast, nematodes, fruit flies, and other organisms.

The DNA-sequencing goal continued as a source of controversy, with many equating the project to the initial sequencing goals. Sequencing the genome became the butt of jokes. A letter to *Nature* suggested that "sequencing the genome would be about as useful as translating the complete works of Shakespeare into cuneiform, but not quite as feasible or as easy to interpret."[15] Robert Weinberg of the Whitehead Institute was surprised that "consenting adults have been caught in public talking about it. . . . it makes no sense"[16] and worried that geneticists would be "wading through a sea of drivel to merge dry-shod on a few tiny islands of information."[17; 18]

Joseph Gall of the Carnegie Institute noted that DNA sequencing might be an inefficient way to study genetics, since complex organisms like nematodes and fruit flies could get by with only 3 to 6 percent as much DNA as humans, while salamanders and many plants had ten times as much.[19] More DNA did not necessarily imply greater complexity, and deciphering the information content of DNA was more than simply reading off the order of base pairs. Gall suggested a two-pronged attack, expanding on the work on nematodes to construct physical maps on one front, and sequencing of individual genes of interest on the other front. The sequencing part might be expedited by a large-scale project to catalog and sequence those parts of DNA directly coding for proteins. A letter to *Nature* pointed out that the pace of gene cloning and sequencing could not continue to explode without displacing all other biology, but noted tongue-in-cheek that "Man's feeling of self-importance will probably not be satisfied until the last bit of his genome has been sequenced and filed somewhere."[20]

The first reports of the *C. elegans*– and yeast-sequencing projects began to make sequencing look like a more efficient way to ferret out and study the function of large numbers of unknown genes, but the results took five years of scientific effort. By then, it began to seem that more traditional projects directed at individual genes and genome-scale sequencing were not interchangeable strategies. Gene analysis and "the sequencing of entire genomes are not

alternatives, but are rather complementary approaches. . . . [Studying expressed genes] cannot by definition throw much light on regulatory processes, on the reasons why some genes [are interrupted] and others are not . . . and on how the genome got like that, anyway."[21] But securing the future of the genome project required a broadening of the political and scientific base, building bridges to both genetic linkage mapping and more traditional genetics.

The originators of the genome idea differed in their assessments of whether the redefinition of the genome project resulted more from political pressures than scientific ones. Gilbert stuck to his guns at many public forums, stating his views that sequencing was still the ultimate goal, and the faster the better.[22;23] He viewed the redefinition as a step backward, while committing a part of his laboratory to original project of large-scale sequencing. Dulbecco believed he presented the "most extreme case" in 1985 and was merely watching a normal scientific reformulation of the sequencing idea as it met with the need for realistic goal-setting.[6] Sinsheimer believed that genetic and physical mapping remained only stepping stones to the true objective, added to the agenda of the project mainly to gain political support.[24] DeLisi felt the program was unfolding more or less as he anticipated.[25]

The initiators thus viewed the new project as only slightly changed, in that the physical mapping, genetic linkage mapping, and study of other organisms were always part of the process of moving toward genome-scale sequencing. The explicit redefinition, however, enabled those who did not view genome-scale sequencing as the end goal to fall in line to support a genome project with broader goals. This was a subtle but important transition. If the originators were correct that DNA sequence would in the end be the most important objective, then the project could rededicate itself to that goal in the future, but the redefined project made room for them to be wrong and nonetheless produce something quite useful. Sequencing moved from the primary to a subsidiary goal. The broader definition of mapping extended the political support base within science, enhanced the scientific integrity of the project by increasing the likelihood of attaining at least some of its goals, and hedged bets on exactly which kinds of genetic maps would ultimately prove most important. Without such support, the funding to make the massive sequencing projects possible, and the biology to make them meaningful, would not have been in place.

The disputes at the June 1986 Cold Spring Harbor symposium were covered by Roger Lewin for *Science,* the first signals of the debate to come for many in science and in government.[26;27] These articles highlighted Gilbert's quest for the "Holy Grail" in a call-out quote and introduced the history of the idea for a DNA sequencing project: "During the past twelve months there have been half a dozen separately organized small gatherings scattered across the country, each one discussing the prospect of obtaining a complete nucleotide sequence of the human genome."[27] Lewin chronicled the shift in objec-

tives, quoting Ray White—"Humans deserve a genetic linkage map. It is part of the description of *Homo sapiens*"—and elaborating on the utility of physical maps. But Lewin captured the confused mix of issues and supposed goals of a genome project, ending his piece on an ambivalent note by quoting Nobelist David Baltimore—"The idea is gathering momentum. . . . I shiver at the thought."[27]

At the June 3 Cold Spring Harbor session, Carnegie Institute biologist Maxine Singer observed, "Of course we are interested in having the sequence, but the important question is the route we take in getting it."[27] A consensus was forming, but it had not jelled and could not yet be articulated. The process of building a consensus reconstructed the genome project and resulted in a dedicated program of map-making with new organizational bases in the federal government. As the goals shifted, the debate moved from the scientific Mecca, Cold Spring Harbor, to the political Gomorrah, Washington, D.C.